Systematic review and/or Meta-analysis

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Prognostic impact of resection margin status on survival after neoadjuvant treatment for pancreatic cancer: systematic review and meta-analysis

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Background: A greater than 1 mm tumour-free resection margin (R0 > 1 mm) is a prognostic factor in upfront-resected pancreatic ductal adenocarcinoma. After neoadjuvant treatment (NAT); however, the prognostic impact of resection margin (R) status remains controversial.

Methods: Randomised and non-randomised studies assessing the association of R status and survival in resected pancreatic ductal adenocarcinoma after NAT were sought by systematic searches of MEDLINE, Web of Science and CENTRAL. Hazard ratios (HR) and their corresponding 95% CI were collected to generate log HR using the inverse-variance method. Random-effects meta-analyses were performed and the results presented as weighted HR. Sensitivity and meta-regression analyses were conducted to account for different surgical procedures and varying length of follow-up, respectively.

Results: Twenty-two studies with a total of 4929 patients were included. Based on univariable data, R0 greater than 1 mm was significantly associated with prolonged overall survival (OS) (HR 1.76, 95% CI 1.57–1.97; $P < 0.00001$) and disease-free survival (DFS) (HR 1.66, 95% CI 1.39–1.97; $P < 0.00001$). Using adjusted data, R0 greater than 1 mm was significantly associated with prolonged OS (HR 1.65, 95% CI 1.39–1.97; $P < 0.00001$) and DFS (HR 1.76, 95% CI 1.30–2.39; $P = 0.0003$). Results for R1 direct were comparable in the entire cohort; however, no prognostic impact was detected in sensitivity analysis including only partial pancreatoduodenectomies.

Conclusion: After NAT, a tumour-free margin greater than 1 mm is independently associated with improved OS as well as DFS in patients undergoing surgical resection for pancreatic cancer.

Keywords: neoadjuvant treatment, pancreatic cancer, resection margin status, surgical resection

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is nowadays regarded as a systemic disease even in its early stages[1,2]. A multimodal treatment concept comprising complete surgical resection of the primary tumour and effective systemic therapy therefore offers the only potential chance for cure[3]. Despite the significant improvement in survival times achieved by upfront resection followed by modern adjuvant chemotherapy protocols, prognosis remains dismal due to recurrence within the first

HIGHLIGHTS

- This first meta-analysis on the prognostic impact of the R status in pancreatic ductal adenocarcinoma patients after neoadjuvant treatment summarises critically appraised data from 22 recently published studies including 4929 patients.
- Results show that R0 greater than 1 mm resections are significantly associated with prolonged overall and disease-free survival in meta-analysis of data from both univariable and multivariable analyses.
- R0 direct resections were also significantly associated with prolonged overall and disease-free survival, but the statistical significance diminished in the sensitivity analysis including only partial pancreatoduodenectomies.
- The findings confirm that similar to upfront resection, a wide margin greater than 1 mm is associated with prolonged survival after neoadjuvant treatment: this emphasises the importance of radical surgical resection, potentially guided by intraoperative evaluation of frozen sections.

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2 years after surgery in more than 65% of cases[1]. Neoadjuvant multiagent treatment strategies have recently become increasingly implemented in PDAC treatment and are now well established in locally advanced and borderline resectable PDAC based on level I evidence[4,5]. Even in resectable PDAC, neoadjuvant chemotherapy with or without chemoradiotherapy is an emerging concept with potential advantages such as better tolerability and higher likelihood of completion of systemic treatment in the preoperative setting[4]. As a result of considerable research on the benefit of neoadjuvant treatment in PDAC patients, pathology-based predictors of survival after neoadjuvant treatment and resection have been extensively documented in recent years[6]. Neoadjuvant treatment results in extensive cancer cell death and increased fibrosis, as well as subsequent dispersion of tumour cells with potential impact on the clinical relevance of resection margin (R) status and its definition[7]. In upfront-resected PDAC, it was shown that R status is a predictor of survival. In particular, R0 defined as tumour-free margins with greater than 1 mm clearance is associated with significant survival benefit[8–10]. After neoadjuvant treatment, however, results from studies regarding the prognostic impact of R status are inconclusive. Some large studies have reported a significant association of R status with prolonged survival after multivariable adjustment[11–14], whereas other studies have not identified R status as an independent prognostic factor[6,13,15–20]. Besides variation in pre-treatment resectability status among studies, different definitions for the R status were utilised[17–19]. Furthermore, some studies detected an independent association for overall survival (OS), but not for disease-free survival (DFS)[18,20].

This systematic review and meta-analysis aimed to summarise the available evidence on the association between R status and survival in PDAC patients who have undergone neoadjuvant treatment, taking into account the various definitions of R status.

Methods

This systematic review and meta-analysis is reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[21], Supplemental Digital Content 1, http://links.lww.com/JS9/B88 and AMSTAR 2 (Assessing the methodological quality of systematic reviews 2) Guidelines[22], Supplemental Digital Content 2, http://links.lww.com/JS9/B89. The a priori defined study protocol conforms with the recommendations of the Cochrane Collaboration and was registered with the Research Registry. The UIN is reviewregistry1688[23].

Data sources and search strategy

Systematic literature searches were conducted to identify all published and unpublished randomised and non-randomised studies investigating the prognostic impact of R status on survival in patients with PDAC undergoing pancreatic resection after neoadjuvant treatment. Due to the challenges of randomised study designs in oncologic surgery, we expected to find only a small number of randomised studies involving low numbers of patients[24]. For this reason, prospective and retrospective cohort studies were also eligible for inclusion. Case reports, register studies, meeting abstracts, letters, comments, editorials, and narrative and systematic reviews were excluded. The following electronic bibliographic databases were surveyed: the Cochrane Central Register of Controlled Trials (CENTRAL) from the Cochrane Library, MEDLINE (via PubMed) and Web of Science All Databases. The search strategy for MEDLINE, using a combination of medical subject headings (MeSH) terms and free text words, is shown in Appendix S1 (supplementary information), Supplemental Digital Content 3, http://links.lww.com/JS9/B90. The search strategy was adapted as appropriate for each of the databases. In MEDLINE, the similar articles function was used to search for additional relevant studies. Additionally, a hand search of the reference lists of relevant articles and related systematic reviews was performed. Further, experts in the field were consulted. The search was not restricted by language. To limit study heterogeneity, the search was restricted to studies published no earlier than 2010 due to changes in pathological work-up[25–27]. The search was last updated on 5 March 2023.

Study selection

Two reviewers (U.K. and C.S.L.) independently screened all records identified by the search. Studies meeting the following criteria were included for review: statement of hazard ratios (HR) for the association of the R status and median OS and/or DFS in PDAC patients undergoing any type of formal pancreatic resection (e.g., partial and total pancreatoduodenectomy or distal pancreatectomy) with curative intent after neoadjuvant treatment. Studies with patients undergoing upfront resection were excluded, as were patients suffering from other tumour entities, recurrent or metastatic disease or unresectable tumours. Patients undergoing resection after neoadjuvant treatment without macroscopic tumour clearance (R2 resection) were also excluded. Furthermore, studies that did not provide separate HR for the association of the R status and survival and those that failed to specify the respective margin definition were excluded. If the title and abstract suggested relevance, the full article was assessed for eligibility. Any disagreements between the two reviewers were discussed within the working group to reach a consensus and to decide which studies to include for qualitative and quantitative analysis. In the case of two or more publications with critical overlap of included patients, only the most recent study was included.

Data extraction

For data extraction, specific forms were constructed and pilot tested using representative studies. Subsequently, data from the included studies were extracted by two reviewers independently (U.K. and C.S.L.). Any discrepancies were discussed within the working group until a consensus was reached. The following items were extracted from each study: title, authors' names and institutions, year of publication, journal, duration of follow-up, study design and sample size. The baseline data extracted were age, sex, underlying disease, resectability status, type and duration of neoadjuvant treatment, adjuvant chemotherapy regimen, type of surgical procedure, extended (e.g. vascular) resections, pathology protocol, definition of R status, type and number of margins examined and median OS and DFS. Furthermore, HR based on Cox proportional hazards regression models investigating prognostic factors of OS and DFS were extracted from eligible studies. Additionally, factors other than the R status included in the multivariable models were documented.

Outcomes and definitions

Hazard ratios and their 95% CI from univariable and multivariable analyses assessing the prognostic impact of R status on OS and DFS, respectively, were used to generate estimates of log HR and standard errors. Data were grouped depending on the definition of the R status as follows.

"Wide margin" *group:*

R0 >1 mm = circumferential resection margin negative (CRM –): defined as tumour-free margin greater than 1 mm (R0 wide)

R1 ≤1 mm = circumferential resection margin positive (CRM +): defined as presence of tumour cells less than or equal to 1 mm distance from the margin (R1 wide)

"Narrow margin" *group:*

R0 direct: defined as absence of tumour cells at the resection margin (R0 narrow)

R1 direct: defined as presence of tumour cells infiltrating the resection margin (R1 narrow)

For each group, data from univariable and/or multivariable analyses for OS and DFS were extracted.

Assessment of methodological quality

The methodological quality of the included studies was assessed using the ROBINS-I tool for non-randomised studies[28]. Due to the low number of randomised studies included, no additional tool was used. The seven domains "bias resulting from confounding", "selection of participants", "classification of interventions", "deviations from intended interventions", "missing data", "measurement of outcomes" and "selective reporting" were evaluated by two independent reviewers (U.K. and C.S.L.) for each study. Within each domain, the risk of bias was judged to be low, moderate, serious, critical or non-assessable (no information). Subsequently, the overall risk of bias was assessed for each study. Any disagreements were resolved by discussion with a third reviewer.

Statistical analysis

To generate pooled HR using R0 as reference parameter, extracted HR were recalculated if necessary. Subsequently, log HR and standard errors were meta-analysed using generic inverse-variance methods and illustrated by forest plots. Meta-analysis was performed if data from at least two studies were available. A random-effects rather than a fixed-effects model was used due to variability in clinical factors such as pathology protocols and type and duration of neoadjuvant treatment[29,30]. Statistical heterogeneity among studies was evaluated by the use of forest plots and the I^2 statistic[31]. Meta-regression was performed with the median duration of follow-up as a covariate and was limited to categories including greater than or equal to 10 studies. Predefined subgroup analyses were conducted to account for study heterogeneity owing to reported statistics. Moreover, sensitivity analyses were performed to account for substantial differences in clinical variability arising from different surgical procedures or resectability status. Funnel plots were created for each outcome to evaluate the risk of publication bias. In the case of funnel plot asymmetry, Egger's test was performed[32]. Meta-analysis was carried out using RevMan Version 5.4.1 (The Cochrane Collaboration, The Nordic Cochrane Centre). All other statistical analysis was performed using the R programming language (R Foundation). A p value less than 0.05 was considered to show a significant difference.

Results

Study selection

A total of 2745 records were retrieved using the search methods (Fig. 1). After exclusion of duplicates, the titles and abstracts of 2552 records were screened. The full texts of 157 articles were assessed for eligibility. After exclusion of 134 articles that did not meet the inclusion criteria, 23 studies remained. The study by Sekigami *et al.*[33] was further excluded because no confidence intervals were provided. Hence, 22 studies with a total of 4929 patients were included in both the qualitative and quantitative analyses.

Trial characteristics and study population

Study characteristics are presented in Table 1. All study results were published between 2012 and 2023, with the majority of studies (14/22) published within the last three years, reflecting the current state of the art therapy in pancreatic cancer. Sample sizes ranged from 29 to 468 patients. Nineteen of the 22 studies were retrospective and three were prospective, one of them a randomised controlled trial[34]. The neoadjuvant treatment regimens were predominantly FOLFIRINOX ($n=1916$, 38.9%) or gemcitabine-based ($n=1712$, 34.7%), with other or unspecified regimens accounting for 1301 patients (26.4%) (Table 2). In total, 3550 patients (72.0%) underwent partial pancreatoduodenectomy, 740 patients (15.0%) distal pancreatectomy and 326 (6.6%) total pancreatectomy, while for some patients the exact procedure was not specified ($n=313$, 6.3%). In 8 of 22 studies (36.4%), R0 was defined as absence of tumour cells at the resection margin (R0 narrow = R0 direct) with R1 corresponding to presence of tumour cells directly at the resection margin (R1 narrow = R1 direct)[13,15,17,34–38]. In the remaining 14 studies (63.6%), R0 was defined as tumour-free margin greater than 1 mm (R0 wide = R0 >1 mm) and R1 as tumour cells less than or equal to 1 mm from the margin (R1 wide = R1 ≤1 mm)[6,11,12,14,19,20,39–46].

Quantitative analysis of included studies

Table 3 summarises the statistical findings of meta-analyses comparing HR of R0 and R1 resections in PDAC patients after neoadjuvant treatment under consideration of the different definitions used and the surgical procedures performed.

Narrow margin definition: meta-analysis of HR for median OS and DFS

Eight studies including a total of 1463 patients reported HR for median OS after R0 direct versus R1 direct resection[13,15,17,34–38]. Proportional meta-analysis yielded an *R1 direct* rate of 15% (95% CI 4–54) across these studies. Seven studies presented HR for OS based on univariable regression analysis[11,15,34,35,37,38,41]. The pooled HR was 1.67 (95% CI 1.24–2.23; $P=0.0007$) with low statistical heterogeneity (I^2 = 31%), demonstrating a statistically significant prognostic impact of R0 direct versus R1 direct (Fig. 2a). Eight studies presented HR for OS based on multivariable regression analysis. The pooled HR was 1.47 (95% CI 1.04–2.09; $P=0.03$), showing an independent association of R0 direct resection and prolonged OS. I^2 was 63% (Fig. 2b). Subgroup analyses of studies reporting only univariable or multivariable data, respectively, did not show a

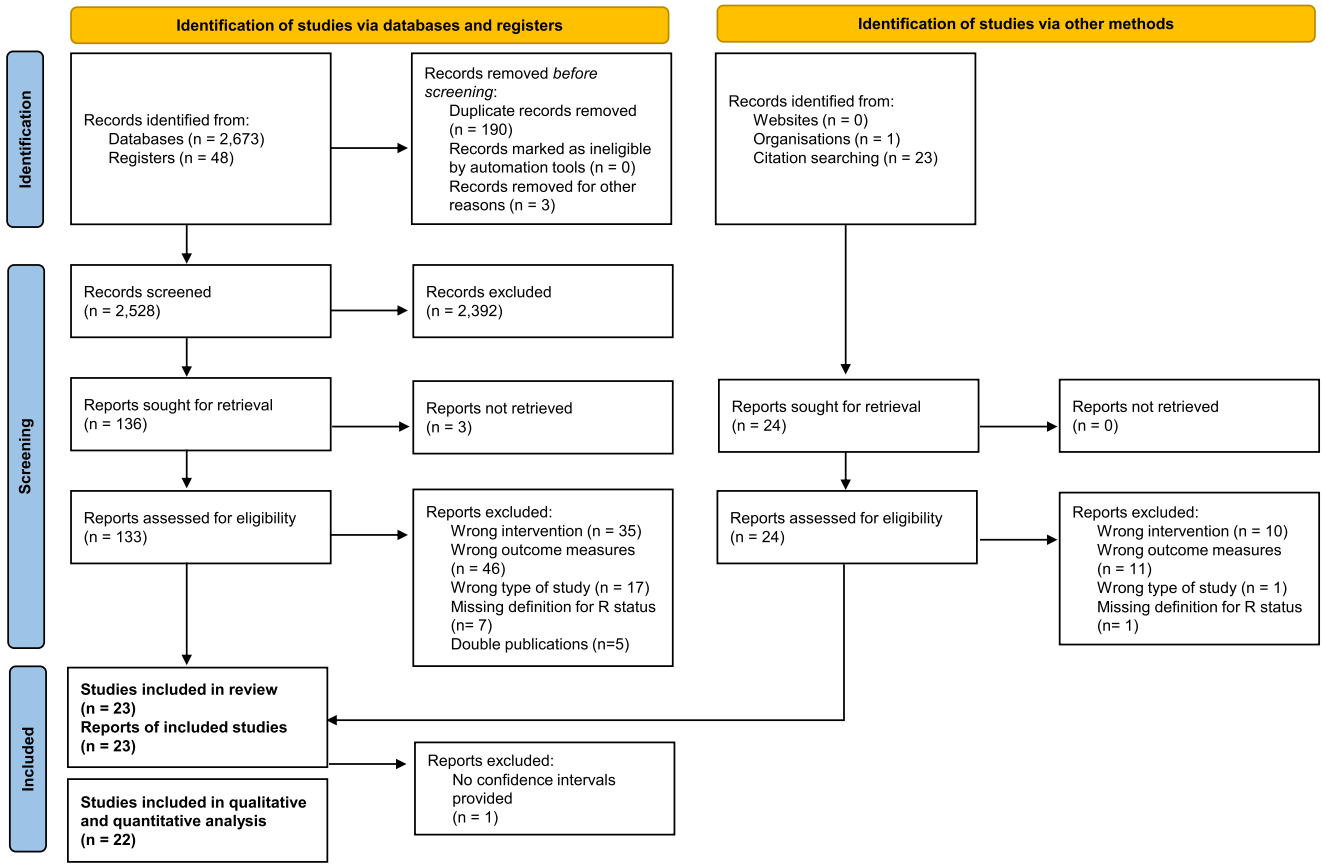

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram.

statistically significant association between narrow margin and OS (Fig. S1, Supplemental Digital Content 4, http://links.lww.com/JS9/B91)[13,34,36,37].

Two studies including a total of 443 patients reported HR with associated 95% CI for median DFS after R0 direct versus R1 direct resection. For these studies, meta-analysis of HR from univariable regression analyses revealed a statistically significant association between *R0 direct* resection and prolonged DFS compared with R1 direct resection (pooled HR 1.56; 95% CI 1.15–2.11, $P = 0.004$; $I^2 = 0\%$) (Fig. S2, Supplemental Digital Content 5, http://links.lww.com/JS9/B92). HR from multivariable analyses could not be pooled due to the lack of sufficient data.

Wide margin definition: meta-analysis of HR for median OS and DFS

In 14 studies with a total of 3284 patients, HR for median OS after R0 greater than 1 mm versus R1 less than or equal to 1 mm resection were reported with a pooled estimate of 22% (95% CI 7–70%) for R1 resections[6,11,12,14,19,20,39–46]. Using univariable data from 13 eligible studies, meta-analysis revealed that R0 greater than 1 mm resection was significantly associated with prolonged OS compared with R1 less than or equal to 1 mm resection (pooled HR 1.76, 95% CI 1.57–1.97; $P < 0.00001$), with $I^2 = 0\%$[11,15,34,35,37,38,41] (Fig. 3a). Similarly, when pooling the HR of nine studies reporting data from multivariable analysis, R0 greater than 1 mm resection was significantly associated with prolonged OS compared with R1 less than or equal to 1 mm resection (pooled HR 1.65, 95% CI 1.39–1.97; $P < 0.00001$; $I^2 = 27\%$)[11,12,14,19,39–41,44,46] (Fig. 3b). Subgroup analysis of studies that only presented HR from univariable analysis confirmed this result[6,20,34,42,45] (Fig. S3, Supplemental Digital Content 6, http://links.lww.com/JS9/B93). Sensitivity analysis excluding the study by Klaiber *et al.*[6], which contained a small number of M1 patients among 280 patients with locally advanced PDAC, did not substantially alter the results (data not shown).

Univariable and multivariable HR investigating the association of DFS and wide R status were presented by nine studies with 2157 patients[6,14,19,20,39,40,42–44] and by five studies with 1164 patients[12,14,39,40,44], respectively. Meta-analysis of HR from univariable regression analyses revealed a significantly increased likelihood of shortened DFS after R1 less than or equal to 1 mm resection compared with R0 greater than 1 mm resection (pooled HR 1.66, 95% CI 1.39–1.97; $P < 0.00001$; $I^2 = 31\%$)[6,14,19,20,39,40,42–44] (Fig. 4a). Correspondingly, the pooled HR from multivariable regression analyses indicated a statistically significant association between R1 less than or equal to 1 mm and reduced DFS (pooled HR 1.76, 95% CI 1.30–2.39; $P = 0.0003$; $I^2 = 58\%$)[12,14,39,40,44] (Fig. 4b).

Sensitivity and meta-regression analyses

Planned sensitivity analyses including only those patients who underwent partial pancreatoduodenectomy showed that there is no statistically significant difference between the prognostic

Table 1

Study characteristics.

First author	Year	Country/region	*N* (patients)	Study design	Procedure	Margin definition	Follow-up (months)
Maeda[17]	2020	USA, Japan	305	Retrospective	PD	Narrow	13.4
Pietrasz[15]	2019	France	203	Retrospective	PD, DP	Narrow	45.1
Ren[39]	2021	China	83	Retrospective	PD	Wide	35.4
Schmocker[11]	2021	USA	468	Retrospective	PD, DP, TP	Wide	18.5
Takahashi[45]	2013	Japan	207	Prospective	PD, DP	Wide	N/A
Truty[20]	2021	USA	194	Retrospective	PD, DP, TP	Wide	22.4
Zhang[13]	2022	USA	134	Retrospective	PD, DP, TP	Narrow	23.8
He[12]	2018	USA	182	Retrospective	PD, DP, TP	Wide	27.0
Ahn[35]	2022	South Korea	38	Retrospective	PD, DP, TP	Narrow	37.0
Alva-Ruiz[19]	2022	USA	429	Retrospective	PD, DP, TP	Wide	29.5
Aoki[36]	2019	Japan	240	Retrospective	PD, DP	Narrow	21.3
Cloyd[37]	2019	USA	258	Retrospective	PD, DP, TP	Narrow	44.4
Delpero[41]	2017	France	29	Prospective	PD	Wide	83.0
Estrella[38]	2012	USA	240	Retrospective	PD	Narrow	29.8
Groot[42]	2019	USA	231	Retrospective	PD, DP, TP	Wide	44.9
Klaiber[6]	2021	Germany	280	Retrospective	PD, DP, TP	Wide	18.0
Leonhardt[14]	2023	Austria, USA	357	Retrospective	PD, DP, TP	Wide	27.0
Igarashi[43]	2023	Japan	41	Retrospective	PD, DP, TP	Wide	35.2
Sohn[44]	2023	USA	398	Retrospective	PD	Wide	114.1
Van Veldhuisen[46]	2023	Europe	423	Retrospective	PD, DP, TP	Wide	32.0
Hartlapp[34]	2022	Germany	45	Prospective	PD, DP, TP	Narrow	28.1
Choi[40]	2022	South Korea	144	Retrospective	PD, DP, TP	Wide	23.9

DP, distal pancreatectomy; Narrow margin, no tumour cells at margin; N/A, not available; PD, pancreaticoduodenectomy; TP, total pancreatectomy; Wide margin, no tumour cells >1 mm from margin.

impact of R0 direct and that of R1 direct resection on OS (Table 3). With regard to DFS, the data for the narrow margin definition were not sufficient for sensitivity analysis of partial pancreatoduodenectomies only. Regarding the wide margin definition, there is a statistically significant association between R0 greater than 1 mm and both prolonged OS and prolonged DFS when analysing partial pancreatoduodenectomies only (Table 3). Separate sensitivity analyses could not be performed for distal or total pancreatectomies due to the lack of eligible studies. Additionally, sensitivity analysis including the study by Sekigami *et al*.[33] was performed for the provided HR and p values from multivariable data for OS and DFS (Figure S4, Supplemental Digital Content 7, http://links.lww.com/JS9/B94). Meta-regression analysis to examine the effect modification based on variable length of follow-up was feasible for OS from univariable data in the R0 greater than 1 mm versus the R1 less than or equal to 1 mm group. No significant associations among margin status, length of follow-up and effect size were detected ($P = 0.95$).

Table 2

Patient characteristics.

Variable	*N* (%)
Total no. patients	4929 (100)
Age, range	59–67
Neoadjuvant treatment regimen	
FOLFIRINOX	1916 (38.9)
Gemcitabine-based	1712 (34.7)
Other/not specified	1301 (26.4)
Chemoradiotherapy	
Yes	3387 (68.7)
No/not specified	1542 (31.3)
Resectability	
Resectable	542 (11.0)
Borderline resectable	1590 (32.3)
Locally advanced	1123 (22.8)
Not specified	1674 (34.0)
Type of resection	
Pancreaticoduodenectomy	3550 (72.0)
Distal pancreatectomy	740 (15.0)
Total pancreatectomy	326 (6.6)
Not specified	313 (6.3)
Adjuvant therapy	
Yes	2083 (42.3)
No	1690 (34.3)
Not specified	1156 (23.5)

Quality assessment of included studies and publication bias

Owing to the non-randomised study designs of all studies except that by Hartlapp *et al*.[34], the overall risk of bias according to ROBINS-I was universally serious or critical, with the exception of the Hartlapp study, where the overall low risk of bias was low (Figure S5, Supplemental Digital Content 8, http://links.lww.com/JS9/B95). Six studies reported missing values and stated how the missing data were handled[14,17,34,41,42]. Funnel plotting did not demonstrate relevant asymmetry for the association between a wide margin and OS when univariable data were pooled, indicating absence of publication bias[32] (Figure S6, Supplemental Digital Content 9, http://links.lww.com/JS9/B96). This was confirmed by Egger's test, which did not detect a significant association between effect size and the predictor SE ($z = 0.37$, $P = 0.71$, 95% CI 0.74–2.59).

Discussion

The prognostic impact of the R status in resected PDAC after neoadjuvant treatment is controversial. This systematic review

Table 3

Summary statistics of meta-analyses on the prognostic impact of R status on overall and disease-free survival.

	All patients		Partial pancreatoduodenectomies only	
Variables	**No. studies**	**HR [95% CI]; *p* value; I^2 (%)**	**No. studies**	**HR [95% CI]; p value; I^2 (%)**
R0 direct versus R1 direct				
Overall survival				
Univariable data	7	**1.67 [1.24, 2.23]; 0.0007; 31**	2	1.34 [0.68, 2.64]; 0.40; 48
Univariable data only	2	1.77 [0.41, 7.66]; 0.45; 81	—	—
Multivariable data	8	**1.47 [1.04, 2.09]; 0.03; 63**	2	2.67 [0.94, 7.56]; 0.07; 82
Multivariable data only	2	1.31 [0.87, 1.98]; 0.19: 39	—	—
Disease-free survival				
Univariable data	2	**1.56 [1.15, 2.11]; 0.004; 0**	—	—
R0 >1 mm versus R1 ≤1 mm				
Overall survival				
Univariable data	13	**1.76 [1.57, 1.97]; <0.00001; 0**	3	**1.93 [1.53, 2.43]; <0.00001; 0**
Univariable data only	5	**01.64 [1.22, 2.21]; 0.001; 24**	—	—
Multivariable data	9	**1.65 [1.39, 1.97]; <0.00001; 27**	2	**1.66 [1.29, 2.13]; <0.00001; 66**
Disease-free survival				
Univariable data	9	**1.66 [1.39, 1.97]; <0.00001; 31**	2	**1.79 [1.40, 2.28]; <0.00001; 0**
Multivariable data	5	**1.76 [1.30, 2.39]; 0.0003: 58**	2	2.09 [0.86, 5.05]; 0.10; 78

HR, hazard ratio.
bold values indicate statistical significance.

and meta-analysis summarises critically appraised data from 22 recently published studies including 4929 patients. The majority of studies, and in particular all of the most recent studies, used a wide margin definition. Results from quantitative synthesis show that R0 greater than 1 mm resections are significantly associated with prolonged OS and DFS in meta-analysis of data from both

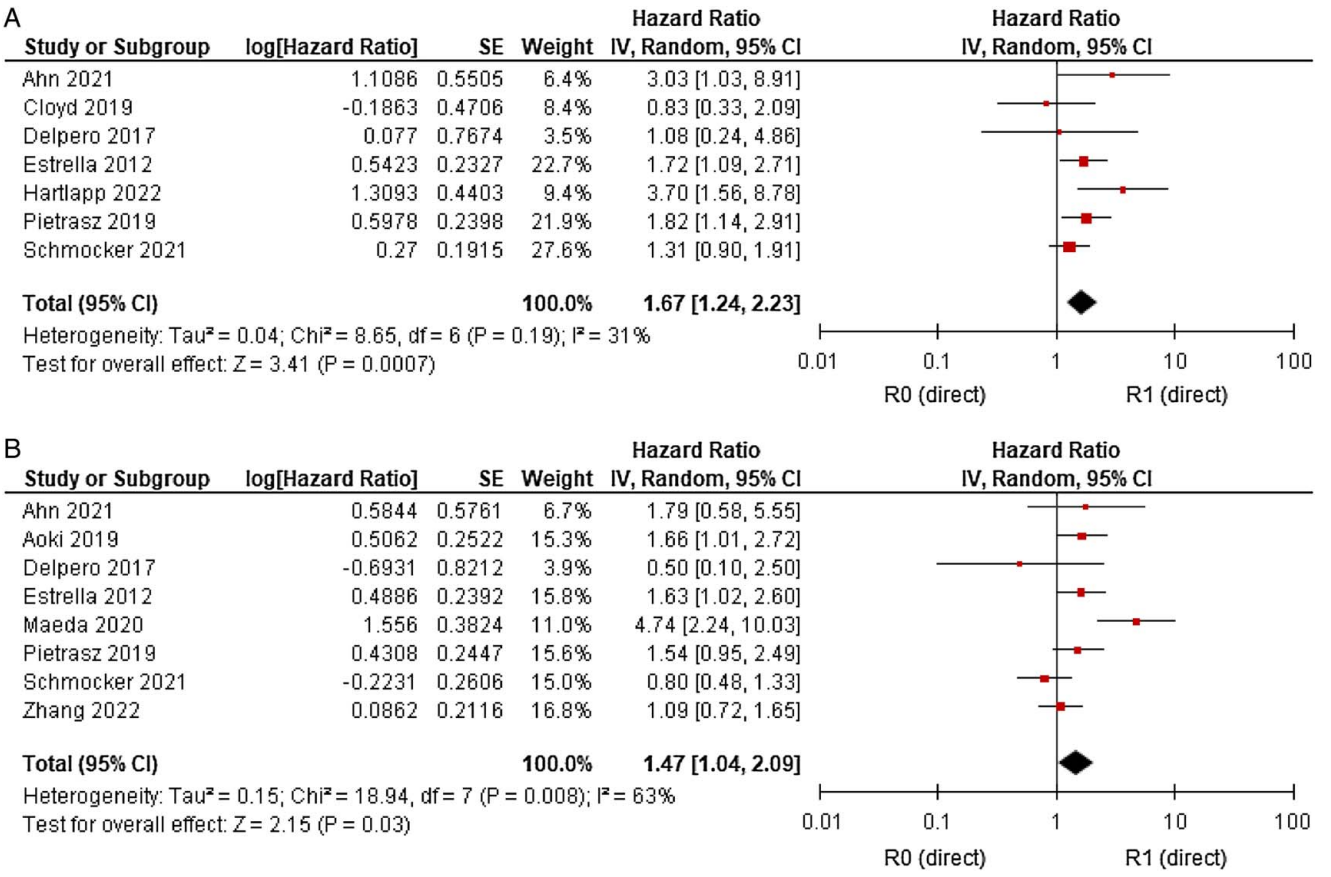

Figure 2. Forest plot on the prognostic impact of R0 direct versus R1 direct resection on overall survival. (A) Meta-analysis of univariable data. (B) Meta-analysis of multivariable data.

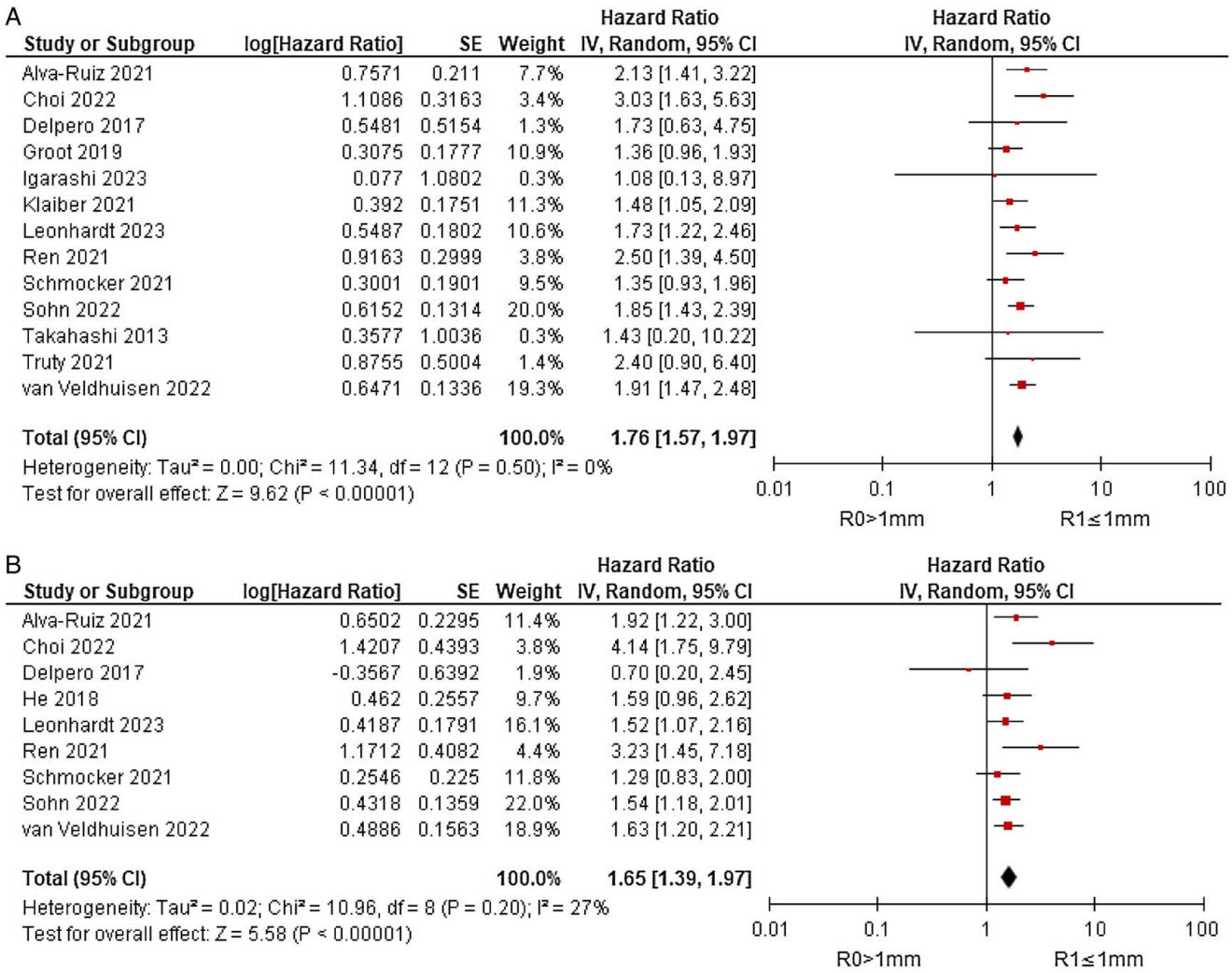

Figure 3. Forest plot on the prognostic impact of R0 > 1 mm versus R1 ≤ 1 mm resection on overall survival. (A) Meta-analysis of univariable data. (B) Meta-analysis of multivariable data.

univariable and multivariable analyses. This is the first meta-analysis on the prognostic impact of the R status in PDAC patients after neoadjuvant treatment. The findings confirm that similar to upfront resections, a surgical margin clearance greater than 1 mm is of significant prognostic relevance for PDAC patients who have received neoadjuvant treatment. Of note, R0 direct resections were also significantly associated with prolonged OS and DFS, but the significance diminished in the sensitivity analysis including only partial pancreatoduodenectomies. However, only few studies were eligible for sensitivity analysis so conclusions have to be drawn with caution.

Neoadjuvant chemotherapy with or without radiotherapy is increasingly offered to patients with (borderline) resectable and locally advanced pancreatic cancer, both in the context of clinical trials and in other settings[47]. While neoadjuvant therapy is the current standard treatment for locally advanced, primarily unresectable PDAC, it can also be considered as an individual approach for oligometastatic disease in selected patients with exceptional response to neoadjuvant treatment[48]. Additionally, there is growing evidence of the benefit of neoadjuvant treatment concepts in borderline and primary resectable PDAC, and the trend towards neoadjuvant treatment is likely to continue[4,5]. For example, the rate of neoadjuvant treatment in PDAC patients in the United States rose from 3.5% in 2004 to 26.4% in 2016[49].

Previous studies have reported inconsistent results regarding the prognostic relevance of an R0 resection and, especially, the impact of a wide margin after neoadjuvant treatment. A recent large two-centre cohort study including 357 patients with primary and borderline resectable as well as locally advanced PDAC who underwent neoadjuvant treatment identified R0 greater than 1 mm versus R1 less than or equal to 1 mm as an independent prognostic factor for median OS as well as DFS[14]. In contrast, a cohort study from a high-volume centre including 280 patients with locally advanced PDAC identified R0 greater than 1 mm resection as significant prognostic factor in univariable but not in multivariable analysis for DFS and OS[6]. The discrepancies among study results may be partially explained, among other factors, by differences in pre-treatment resectability status and varying neoadjuvant treatment protocols.

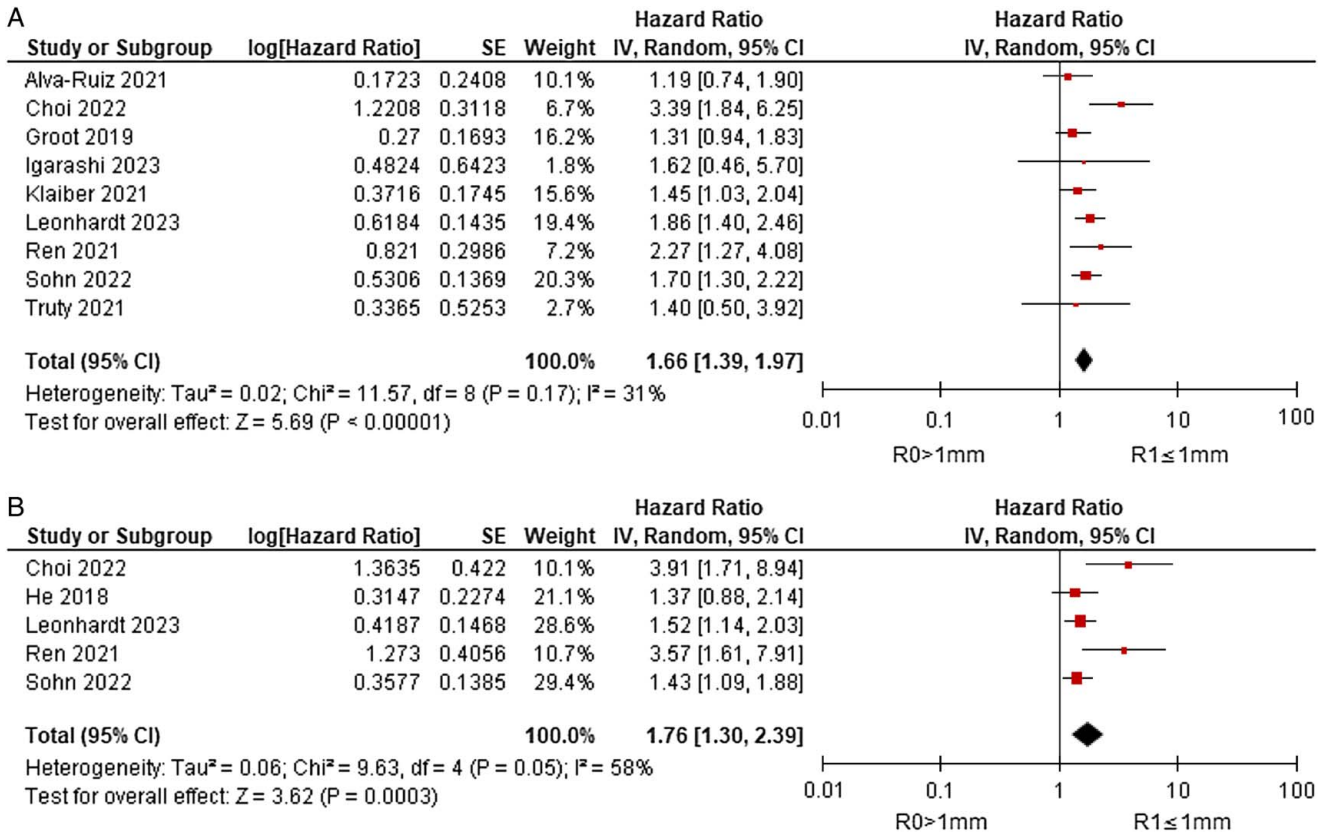

Figure 4. Forest plot on the prognostic impact of R0 > 1 mm versus R1 ≤ 1 mm resection on disease-free survival. (A) Meta-analysis of univariable data. (B) Meta-analysis of multivariable data.

Unfortunately, this meta-analysis does not provide direct comparisons between a narrow and a wide margin definition due to the lack of appropriate data from the available studies. Importantly, the pathology assessment of a PDAC specimen after neoadjuvant treatment is particularly challenging due to the dispersed growth pattern of PDAC and the difficulties during specimen grossing of identifying the outlines of a tumour after neoadjuvant treatment[50,51]. However, the pooled HR for R0 greater than 1 mm versus R1 less than or equal to 1 mm were slightly higher with considerably lower *p* values and lower statistical heterogeneity compared to R0 direct versus R1 direct, indicating the prognostic benefit of R0 greater than 1 mm resection. In addition, sensitivity analyses of partial pancreatoduodenectomies confirmed the prognostic impact of R0 greater than 1 mm versus R1 less than or equal to 1 mm.

The effect of R0 resections on recurrence patterns after neoadjuvant treatment and resection requires further investigation. In the present study, R less than or equal to 1 mm resections were significantly associated with reduced DFS in both univariable and multivariable analysis, but no information was available on local versus distant recurrence. A recently published cohort study from our group indicated that R1 resections are significantly associated with local but not distant recurrence after neoadjuvant treatment[14]. Additionally, neoadjuvant chemoradiotherapy was shown to be associated with a reduction in the incidence of local recurrence[52]. Furthermore, peri-arterial divestment of visceral arteries after neoadjuvant treatment has been proposed to improve local tumour control while avoiding arterial resection with its associated morbidity and mortality[53]. Notably, divestment has been associated with increased rates of R1 resection versus arterial resection and with currently inconclusive oncological outcomes[54]. In context with the available evidence and the results from the present meta-analysis including vascular resections also, the oncological benefit of peri-arterial and sub-adventitial divestment needs be evaluated in future studies.

In the present study pooled R1 less than or equal to 1 mm rates of 22% were fairly low compared with upfront-resected PDAC, for which a pooled R1 less than or equal to 1 mm rate of 58% was reported, despite the inclusion of more patients with borderline and locally advanced PDAC than with upfront resectable PDAC[8]. This may be partially attributable to the specific effects of neoadjuvant treatment, resulting in scattered foci of cancer cells separated by areas of extensive fibrosis[51]. Hence, margin assessment becomes more complex as residual cancer cells may be located beyond the resection margins. Consequently, the variable effect of neoadjuvant treatment within the individual tumour is intimately connected with pathology-based margin assessment and patient outcomes. Notably, assessment of tumour regression itself is highly observer-dependent[55].

Potentially, even wider margins might be more appropriate in PDAC after neoadjuvant treatment, similarly to upfront-resected PDAC[41,56]. The tumour bed post-surgical resection cannot be reliably examined for microscopic residual disease; hence, margin

status can merely be used as a predictor of cancer cells left in situ[57]. In that regard, current pathology practice considers R status a categorical variable, while in reality microscopic residual tumour burden is potentially more likely to behave as a continuous variable associated with differences in prognostic impact.

This systematic review and meta-analysis has several limitations. Above all, the studies reviewed featured considerable clinical variability, especially regarding the neoadjuvant treatment protocols, resectability status, surgical procedures and pathology workup. To account for differences in the type of resection specimens, appropriate sensitivity analyses were performed. In addition, a random-effects rather than a fixed-effects meta-analysis was used to account for potential inter-study heterogeneity, especially in terms of pathology protocols[29,30]. While most European centres use axial slicing, centres in the USA frequently tend to use a bivalving protocol[58]. Axial slicing may allow easier evaluation of circumferential resection margins[59]. Bivalving is technically more demanding and hence may introduce more variability of the specimens for examination. However, a recent randomised controlled trial did not detect a significant difference in R1 resection rate between axial slicing and bivalving protocols[60]. Yet, it is important to note that the primary outcome of the trial was the level of certainty regarding the tumour origin based on these protocols, and only 24% of the trial patients received neoadjuvant treatment. Analysis of an association of positive margin status and survival based on the location of the affected margin was impossible, as very few studies provide data on the affected margin[41]. Furthermore, there is inter-study heterogeneity with regard to the adjusting factors included in the multifactorial analyses of the different individual studies. However, well known and important prognostic factors such as lymph node status, tumour size and R status were used consistently[6,14]. Another shortcoming of this meta-analysis results from the limitations in the methodological quality of the studies included. Only one randomised controlled trial providing HR on the prognostic impact of margin status after neoadjuvant treatment, that by Hartlapp and colleagues, was identified[34]. According to the "garbage in, garbage out" principle, the inclusion of non-randomised studies in meta-analysis bears a relevant risk of bias regarding the pooled data. Thus, results from this meta-analysis need to be interpreted with caution. Nevertheless, this first meta-analysis to summarise effect sizes from the best available individual studies provides conclusive evidence that R status is of prognostic relevance after neoadjuvant treatment in PDAC.

In conclusion, similar to upfront resection, microscopic tumour clearance is an independent prognostic factor of OS and DFS in patients undergoing resection after neoadjuvant treatment for pancreatic cancer. In particular, R0 resection especially when a wide margin (>1 mm) definition is used, is associated with prolonged survival: this emphasises the importance of radical surgical resection, potentially guided by intraoperative evaluation of frozen sections. In this context, reliable radiological and blood-based markers of neoadjuvant response evaluation are urgently needed to permit better selection of candidates for surgical treatment and to determine the optimal time for surgery.

Ethical approval

This is a systematic review and meta-analysis of individual studies.

Patient consent

Not applicable.

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Author contribution

U.K., C.S.L. and O.S. have made substantial contributions to the conception and design of the study, acquisition of data, analysis and interpretation of data. C.G., D.P., T.H., K.S. and M.S. have made substantial contributions to the conception and design of the study, analysis and interpretation of data. C.S.V. has made substantial contributions to the conception and design of the study and interpretation of data. All authors have participated in drafting the article or revising it critically for important intellectual content and all authors have given final approval of this version to be published.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

This systematic review and meta-analysis was registered with the international prospective register of systematic reviews (PROSPERO) on 5 April 2023 (registration number CRD42023411235).

Guarantor

Not applicable.

Provenance and peer review

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Data availability

Data are available upon request (including template data collection forms, data extracted from included studies, data used for all analyses, analytic code, any other materials used in the review). Any datasets generated during and analysed during the current study are available upon reasonable request.

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