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The Effect of Neoadjuvant Chemoradiotherapy in Converting Unresectable and Locally Advanced Pancreatic Adenocarcinoma to Resectable Status: A Systematic Review and Meta-analysis

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Abstract

Background: Neoadjuvant chemoradiotherapy (NCRT) is increasingly used in locally advanced unresectable pancreatic adenocarcinoma. In the present study, we systematically evaluated the effects of NCRT on downstaging, resectability, and survival.

Method: A systematic review and meta-analysis of 70 full-text studies published before December 2023 (PubMed, Scopus, and Web of Science) was conducted. Data were extracted independently. Random-effects models were applied with substantial heterogeneity (Cochran's Q, I^2). Subgroup analyses and publication-bias assessments (Egger's test, funnel plots, trim-and-fill) were conducted ($P < 0.05$).

Results: The pooled conversion rate from unresectable to resectable disease was 30.6% (95% confidence interval (CI): 28.2–32.2%). Conversion was higher with

chemoradiotherapy than with chemotherapy alone (32.5% vs. 22.9%). Tumors in the pancreatic body showed a higher conversion rate than tumors in mixed locations (37.0% vs 29.7%). Overall tumor size reduction was 23% (95% CI: 15–30%), greater with chemoradiotherapy than chemotherapy (25% vs 16.7%). Mean overall survival after neoadjuvant therapy was 17.96 months (95% CI: 16.40–19.52), with no clear difference between regimens. Disease-free survival was 12.97 months (95% CI: 11.22–14.72). The pooled R0 resection rate was 41.7% (95% CI: 33.2–50.2%).
Conclusion: The results of the study indicate that NCRT improves conversion to resection and tumor shrinkage versus chemotherapy alone, particularly for pancreatic body tumors, but does not demonstrate a consistent survival advantage.

Keywords: Pancreatic neoplasms, Neoadjuvant therapy, Treatment outcome, Tumor size reduction

Introduction

Pancreatic ductal adenocarcinoma represents over 90% of all pancreatic malignancies, making it the most prevalent neoplastic disease of the pancreas. The late detection of this highly aggressive and fatal form of cancer is correlated with a dismal prognosis.[1] Pancreatic cancer ranks seventh in terms of cancer-related fatalities among both men and women worldwide. It has become a significant public health concern in the United States, Europe, and France, where the incidence has increased over the past few decades. Inactivity, age, smoking, obesity, genetics, diabetes, and diet are all recognized as the main risk factors of pancreatic cancer.[1, 2] Tumors classified as locally progressed unresectable pancreatic adenocarcinomas are those that have metastasized to nearby organs or major arteries, making tumor excision challenging. About one-third of pancreatic cancer patients have metastatic disease, and less than 10% of these patients may be surgically resectable.[3] Due to local invasion of nearby structures, the remaining patients, more than half of all pancreatic cancer patients, have a condition known as locally advanced and incurable pancreatic cancer.[3, 4] These individuals present with complications from local tumor invasion before metastasis, making therapy difficult for them.[4] While there may be some disagreements on the precise definition, it is widely acknowledged that the degree and existence of local vascular involvement indicate unresectability, with surgical intervention serving as the final means of treatment.[3] Neoadjuvant chemoradiotherapy (NCRT) is a potential treatment strategy aimed at reducing tumor size and increasing the chance of complete surgical resection.[5] It seems reasonable to treat patients with locally advanced tumors to achieve secondary resectability (downstaging) because surgery is the only definitive treatment option for these patients.

Accordingly, the majority of neoadjuvant treatment trials include patients with locally progressed and incurable pancreatic cancer.[5,6] Several studies showed the conversion from unresectable to resectable disease after neoadjuvant therapy (NAT).

The efficacy of NCRT in transforming locally advanced unresectable pancreatic adenocarcinoma (LAUPA) into resectable adenocarcinoma has received attention in recent years. Several studies investigated its effect on tumor response, overall survival, and the ability to achieve R0 resection (complete removal of the tumor).[6]

Nevertheless, divergent findings across various research investigations

necessitate a thorough systematic review and meta-analysis to furnish a more substantiated evaluation of the existing body of evidence.[4,6] The present study aimed to conduct a comprehensive analysis of recent research to ascertain the overall efficacy of NCRT in terms of tumor size reduction, R0 resection, and survival improvement. Our study provides clinicians, researchers, and policymakers engaged in managing locally advanced pancreatic adenocarcinoma with a valuable resource.

Methods

Protocol and registration

The present systematic review and meta-analysis was reported using the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) 2020 guidelines. The registration number assigned to the study's protocol in the International Prospective Register of Systematic Reviews (PROSPERO)database was CRD42024498663. Detailed protocol information is accessible at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=498663

Ethical principles were rigorously followed throughout the study process. The protocol for this review was approved by the Ethics Committee of the Iran University of Medical Sciences, with the approval code IR.IUMS.FMD.REC.1404.475.

Since this study involved secondary data analysis, no additional participant consent was required.

Search strategy

From the commencement of inquiry until December 2023, the researchers performed an unrestricted search of international databases, including PubMed, Web of Science, and Scopus, for relevant articles. The search methodology employed a blend of pertinent keywords and constrained vocabulary unique to each database (Table 1).

The search strategy encompassed publications in the English vernacular. The Boolean operators "AND" and "OR" were applied to combine the search terms efficiently. Furthermore, a manual search was conducted in the reference lists of the identified articles to guarantee a thorough examination of the pertinent literature.

Three databases, PubMed (n = 1,249), Scopus (n = 1,771), and Web of Science (n = 72), provided a total of 3,092 records. After eliminating 916 duplicate records, 2,176 titles were screened, excluding 926 records. Case reports, conference abstracts, letters, editorials, notes, reviews, meta-analyses, and animal studies were excluded at this stage. Then, 848 abstracts were screened, and 294 records were excluded due to irrelevance, language other than English, reviews, or animal studies. Full-text articles of 529 were assessed for eligibility, and 459 were excluded based on predefined criteria. At last, 70 studies met the inclusion criteria and were included in the systematic review and meta-analysis. The step-by-step screening and selection are given in the PRISMA flow diagram (Figure 1).

Eligibility criteria

Eligible papers consisted of original research on patients diagnosed with pancreatic adenocarcinoma who had received neoadjuvant chemotherapy, chemoradiotherapy, or radiotherapy. Prospective and retrospective cohort studies and phase I and II clinical trials were considered, provided they reported on relevant clinical outcomes such as resectability, R0 resection rate, and survival. Case reports, editorials, letters, review articles, and those studies with poor or non-extractable data were excluded. Articles with inappropriate statistical analysis or non-human and irrelevant pancreatic

disorders were excluded as well. All studies were selected based on pre-defined inclusion and exclusion criteria while doing full-text screening.

Study risk of bias assessment

The included publications were evaluated critically by two evaluators employing the JBI quality assessment methodology for studies.[7] The instrument comprises various features that evaluate a broad spectrum of aspects. These include concealing the allocation of participants to treatment groups, maintaining groups similar at the outset, employing outcomes assessors who are blind to treatment assignment, measuring follow-up complete outcomes for treatment groups similarly, and using appropriate statistical analysis. A response of "Yes" was assigned a score of 1, while responses of "No" or "Unclear" were assigned a score of 0. The methodology above was implemented on every parameter. The average rating for every article was calculated. The reviewers were given full access to the journal's identity and the authors' identities so they could evaluate the research on their own. The interrater agreement was measured using Cohen's Kappa test, and the reliability value was 0.838 ($P < 0.001$), indicating very good agreement between the two reviewers. Each paper had a maximum score of between 0 and 9. The studies were categorized into three groups based on their total scores: low risk of bias (8, 9), moderate risk of bias (4–7), and high risk of bias (0–3). Consensus talks were used to settle disputes amongst reviewers. When the differences emerged in the evaluation of specific research, two reviewers talked about how they interpreted and justified the scores they gave each criterion. If an agreement could not be reached, the disagreement was decided by consulting a third independent reviewer.

Selection process

To obtain accurate data, a multi-step methodology was employed. Any duplicate entries were eliminated after importing the chosen articles into EndNote X8. Then, to eliminate irrelevant research, the two team members examined the titles and abstracts of the remaining papers individually. The reports that met the requirements of the research query and adhered to analytical study methodologies formed the basis of the selection criteria.

Data extraction

We used a standardized data-gathering form to extract relevant information from the included studies. The extracted data included the names of the author(s), year of publication, country, sample size, study type, location of the pancreatic adenocarcinoma, type of neoadjuvant treatment, percentage of locally advanced and unresectable pancreatic adenocarcinoma cases that transformed into resectable cases, percentage of tumor size reduction, OS, disease-free survival (DFS), and percentage of surgeries with R0 margins.

Synthesis methods

A statistical analysis was conducted for this meta-analysis using STATA version 14. The researchers used the inverse variance and Cochran Q statistics to measure the level of heterogeneity present in the studies. The I2 test findings characterized heterogeneity as low, moderate, or high. We categorized heterogeneity as low, moderate, and high when the I2 value was below 50%, between 50% and 80%, and over 80%, respectively. Due to heterogeneity, it is necessary to use the Dersimonian and Liard random-effects models. In order to ascertain the sources of heterogeneity, subgroup analyses, and univariate meta-regression techniques will be employed.

Sensitivity analysis was done through one-out-remove, where each study was removed one at a time to ascertain its impact on overall findings. This helped in determining whether any single study greatly influences the findings of meta-analysis.

Egger's regression and funnel plot techniques were used to quantify publication bias. Furthermore, the trim-and-fill approach was used to adjust the total estimate, accounting for any potential omission of studies due to censoring.

Certainty assessment

As per PRISMA 2020 guidelines, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was applied to the certainty of evidence in the present meta-analysis. This method was based on critical domains like risk of bias, inconsistency, indirectness, imprecision, and publication bias. According to those domains, evidence was rated as very low, low, moderate, or high, indicating an increasing amount of confidence that how much the estimated effect is close to the actual effect.

Results

Features of the Eligible Studies

Pooled percentage of transformation from unresectable and locally advanced pancreatic adenocarcinoma to resectable

A comprehensive analysis of 70 studies encompassing 4976 patients was conducted to determine the aggregate percentage of transformation from unresectable and locally advanced pancreatic adenocarcinoma to resectable status. By incorporating heterogeneity (specifically, I-V heterogeneity) into a random-effects model, the aggregate transformation percentage was computed to be 30.61% (95% confidence interval (CI): 28.2–32.2%). Nevertheless, considerable variation was noted among the studies (I2 = 97.9%, Q statistic = 3259.87, $P < 0.0001$). Further examination revealed distinct transformation rates among the patients receiving different treatment modalities. Specifically, the transformation percentage among the patients undergoing chemotherapy treatment was 29.9% (95%CI: 23.2-36.7%), while for those receiving chemoradiotherapy treatment, the rate was 32.5% (95%CI: 28.3-32.9%) (Figure 2).

Sensitivity analysis was performed using the leave-one-out approach to determine the stability of the total resectability conversion estimate for patients with unresectable or locally advanced pancreatic adenocarcinoma. The analysis revealed that the omission of any individual study did not create a significant change in the total effect size, indicating no single study had an overbearing influence on the overall estimate.

The meta-regression analysis was employed to examine potential sources of heterogeneity in the transformation rate of unresectable to resectable pancreatic cancer across studies. Seven covariates were incorporated as moderators into the model. Our results indicated that the use of chemoradiotherapy (versus chemotherapy alone) was statistically associated with higher transformation rates ($\beta = 0.084$, $P = 0.002$). Additionally, the location of the tumor in the body of the pancreas ($\beta = 0.093$, $P = 0.030$), having a larger number of patients ($\beta = 0.005$ per 50 patients, $P = 0.010$), and high study quality ($\beta = 0.072$, $P = 0.017$) were associated with resectability. Furthermore, newer studies were associated with higher transformation rates ($\beta = 0.010$ for each 5-year increment, $P = 0.012$), possibly

reflecting the advance of treatment regimens. There was no significant contrast between study types (RCT vs. cohort). There was no considerable contrast between countries (β = -0.047, P = 0.061) (Table 2).

When considering the type of pancreatic adenocarcinoma, the overall transformation from unresectable to resectable was stratified. For tumors located in the body of the pancreas, the transformation rate was estimated at 37.0% (95% CI: 18.8–55.2%). However, this estimate is based on a single study and should, therefore, be interpreted with caution. In contrast, for tumors located in the head, body, or tail of the pancreas, the transformation rate was slightly lower at 29.7% (95% CI: 24.7–34.6%) based on a larger pooled sample (Table 3).

Pooled percentage of reduction of tumor size

The study findings showed a pooled percentage reduction of tumor size at 23% (95%CI: 15-30), with a significant degree of heterogeneity (I2 = 85.8%, Q statistic = 84.30, P < 0.0001). Within the neoadjuvant, the reduction observed in chemoradiotherapy was 25% (95%CI: 16-34), showing substantial heterogeneity (I2 = 88.6%, Q statistic = 78.70, P < 0.0001). Conversely, for chemotherapy alone, the reduction was 16.7% (95%CI: 10.8-31.7), with relatively lower heterogeneity (I2 = 62.4%, Q statistic = 5.32, P = 0.070) (Figure 3).

Sensitivity analysis was performed using the leave-one-out approach to determine the stability of the pooled percentage of reduction of tumor size. The analysis revealed that the omission of any individual study did not create a significant change in the total effect size, indicating no single study had an overbearing influence on the overall estimate.

Pooled survival

To ascertain patients' overall mean survival time following NAT, a comprehensive analysis was performed on 69 studies involving 5007 patients. By incorporating heterogeneity (I-V heterogeneity) into a random-effects model, the aggregated survival was determined to be 17.96 months (95%CI: 16.40–19.52 months) (I2 = 97%, Q statistic = 2132.15, P < 0.0001). Moreover, this survival time was not significantly different among the patients receiving chemotherapy alone and those receiving chemoradiotherapy (17.96 months: 95%CI: 15.23-20.63 vs. 17.96 months: 95%CI: 16.02-19.91, P > 0.05) (Figure 4).

Sensitivity analysis was performed using the leave-one-out approach to determine the stability of pooled survival. The analysis revealed that the omission of any individual study did not create a significant change in the total effect size, indicating no single study had an overbearing influence on the overall estimate.

The pooled mean DFS at 12.97 months (95%CI: 11.22-14.72), (I2 = 96.7%, Q statistic= 1285.75, P < 0.0001). Within the types of NAT, the survival free from the disease in chemoradiotherapy was 13.47 months (95%CI: 11.02-15.92), (I2 = 97.3%, Q statistic = 1010.98, P < 0.0001). For chemotherapy alone, survival-free time was 12.09 months (95%CI: 9.89-14.29), (I2 = 94.2%, Q statistic = 258.07, P < 0.0001) (Figure 5). Sensitivity analysis was performed using the leave-one-out approach to determine the stability of pooled mean DFS. The analysis revealed that the omission of any individual study did not create a significant change in the total effect size, indicating no single study had an overbearing influence on the overall estimate.

Pooled percentage of surgery with R0

To ascertain the aggregate pooled percentage of surgery with R0, a

comprehensive analysis of 61 studies involving 4818 patients was performed. By considering I-V heterogeneity through the use of a random-effects model, the pooled Percentage of Surgery with R0 was computed to be 41.7% (95%CI: 33.2-50.2) (I2 = 98.2%, Q statistic = 3296.19, $P < 0.0001$). This surgery with R0, among patients undergoing chemotherapy treatment, was 46.1% (95%CI: 29.5-62.56%), while for those receiving chemoradiotherapy treatment, the percentage was 40.2% (95%CI: 32.2-48.1%) (Figure 6). Sensitivity analysis was performed using the leave-one-out approach to determine the stability of the pooled Percentage of Surgery with R0. The analysis revealed that the omission of any individual study did not create a significant change in the total effect size, indicating no single study had an overbearing influence on the overall estimate.

Based on tumor location, the R0 resection rate for pancreatic adenocarcinomas located in the body of the pancreas was reported as 49.8% (95% CI: 6.05–93.1%). However, this estimate is derived from a single study and thus lacks sufficient statistical power to allow for definitive conclusions. In comparison, the pooled R0 resection rate for tumors located in the head, body, or tail was 43.9% (95% CI: 36.1–51.7%), based on a substantially larger number of studies (n = 38) and patient population (n = 3,553). Given the limited evidence for tumors located exclusively in the body, comparisons with more comprehensive subgroups should be interpreted with caution due to potential heterogeneity and the risk of overgeneralization (Table 4).

Reporting publication bias

The meta-analysis incorporated studies that examined the transformation of locally advanced pancreatic adenocarcinoma from undesirable to resectable. The publication bias was identified through the irregularity in the funnel plot and Egger's regression test (bias = 2.20, 95% CI: 0.62 to 3.78, $P = 0.007$) (Figure 7). A Trim-and-fill model that is not parametric was implemented to account for this bias. The estimation of 21 prospective studies that were excluded from the meta-analysis examining the percentage change in resectable versus unresectable and locally advanced pancreatic cancer was provided by this model. The estimated adjusted aggregated percentage of transformation for the random-effects model was 20.5% (95% CI: 18.31-22.8) using this method.

GRADE assessment

The GRADE evaluation is suggestive of variation in the quality of evidence regarding key clinical outcomes. Respectability conversion and OS were rated as Good (4/5), whereas R0 resection rate and reduction of tumor size was labeled as Low (2/5).

Discussion

This systematic review and meta-analysis of 70 studies involving 4976 patients demonstrated that approximately 30.6% of patients with unresectable or locally advanced pancreatic adenocarcinoma could be converted to resectable status following NAT. Chemoradiotherapy showed a higher transformation rate (32.5%) compared with chemotherapy alone (22.9%). The pooled mean OS following neoadjuvant treatment was 17.96 months, while the pooled DFS was 12.97 months. Furthermore, the overall R0 resection rate was 41.7%, with chemotherapy alone yielding a slightly higher rate than chemoradiotherapy. A moderate reduction in tumor size was also observed (23%), with a greater reduction achieved using chemoradiotherapy. Despite high

heterogeneity, these findings suggest that neoadjuvant therapies, particularly chemoradiotherapy, play a significant role in improving resectability and survival outcomes in patients with advanced pancreatic cancer.

The results presented here align with those of Roselló et al. (2020), who documented a comparable transformation rate in a retrospective series of neoadjuvant-treated patients with LAUPA. According to Roselló et al. (2020), neoadjuvant chemotherapy followed by curative intent surgery produced a resection rate of 44.9% and a median OS of 24.9 months. These findings showed that NAT can effectively convert unresectable tumors into resectable tumors and thus provide an opportunity for curative surgical resection in initially unresectable patients.[80]

Also, the study showed a pooled percentage reduction of tumor size by 23%. However, significant heterogeneity was observed, indicating potential variation in treatment response. Subgroup analysis showed that chemoradiotherapy led to a greater reduction in tumor size by 25% compared with chemotherapy alone by 16.7%, further highlighting the potential benefits of combining radiotherapy with chemotherapy in the neoadjuvant setting.[81] It is important to note that, in another section of our analysis, the frequency of R0 resection was slightly higher in patients receiving chemotherapy alone compared with those receiving chemoradiotherapy (49.7% vs. 39.8%). This apparent discrepancy may be attributed to several factors, including differences in study populations, surgical eligibility criteria, tumor biology, timing of surgery after treatment, and radiation-induced fibrosis, which may obscure resection margins or complicate the surgical procedure. Therefore, although chemoradiotherapy may lead to greater radiologic tumor shrinkage, it does not necessarily translate into higher rates of margin-negative (R0) resection. These findings underscore the complexity of therapeutic response in locally advanced pancreatic cancer (LAPC) and the multifactorial nature of achieving optimal surgical outcomes.

Further analysis by tumor location showed a higher conversion rate for tumors located in the body of the pancreas at 37.0 % compared with tumors located in the head, body, or tail at 29.7%. This suggests that tumor location may play a role in the success of NAT in achieving resectability. These findings are consistent with the study conducted by Ninomiya et al. (2023), which aimed to evaluate the effectiveness of conversion surgery (CS) after modified FOLFIRINOX (mFFX) treatment in patients with locally advanced locally advanced and incurable pancreatic cancer and identify predictors of CS.[82]

A total number of 43 patients received mFFX, of whom 20 underwent CS.[4] Factors associated with CS included ≥90% dose intensity, ≥35% tumor reduction, and ≥70% reduction in the normalization of CA19-9 levels.[4] CS increases long-term survival after FFX.[82] These similar findings in multiple studies suggest that NAT is essential in reducing tumor size, potentially facilitating surgical resection, and improving patient outcomes.[80]

The meta-analysis of patient survival outcomes projected an average survival time of 17.96 months following neoadjuvant treatment. Surprisingly, there was no discernible disparity in median survival rates between patients who received chemotherapy exclusively and those who received chemotherapy in conjunction with radiotherapy. This finding implies that including radiotherapy could potentially confer a substantial survival

advantage regarding median time. The pooled mean DFS, which indicates the period when the patients were free from the disease, was estimated at 12.97 months. The treatment of chemotherapy and radiotherapy has slightly better results than chemotherapy alone.

This finding is inconsistent with the study of Gemenetzis et al. (2020), who examined the survival outcomes of patients with LAPC surgically resected after NAT.[82] This study included 415 LAPC patients, in which surgical resection after NAT was possible in 20% of the patients and with a significantly longer OS compared with patients not resected (35.3 vs. 16.3 months).[82] The difference in the results of studies may be related to the individual characteristics of the patients and the type of chemotherapy regimen or radiotherapy treatment, which has different effects in improving the survival of patients. Therefore, surgical resection after NAT can improve outcomes for a specific group of LAPC patients. These results of different survival outcomes suggest that NAT may provide different survival improvements among various patient populations.[83]

However, it is essential to observe that in the present study, the inclusion of radiotherapy to neoadjuvant chemotherapy did not substantially enhance patient survival outcomes. According to this finding, radiotherapy may not provide a substantial survival advantage as a neoadjuvant. Additional research is required to elucidate the effect of radiotherapy on survival outcomes and identify subgroups of patients who may benefit from this treatment modality.

Subsequently, examining surgical resection success with negative margins (R0 resection) yielded a cumulative percentage of 42.4%. In contrast, patients undergoing chemoradiotherapy had a lower R0 resection rate of 39.8%, while those undergoing chemotherapy alone had a rate of 49.7%. Furthermore, R0 resection success varied by tumor location, with a higher rate observed for tumors located in the body of the pancreas at 49.8% compared with tumors located in the head, body, or tail at 43.9%.

The present investigation found that incorporating radiotherapy alongside neoadjuvant chemotherapy did not yield a statistically significant improvement in the success rate of surgical resection with negative margins (R0 resection) or patient survival. This discovery aligns with the results reported by Fietkau et al. (2021), who examined the impact of resecting tumors with negative margins (R0 resection) on patient survival.[84] The researchers concluded that patients with resected R0 tumors had significantly improved DFS and OS compared with other patients (median DFS and OS: 16.6 and 26.5 months, respectively), and two-year survival was 72.0% in the R0 resection.

The success rate of surgical resection with negative margins (R0 resection) is comparatively lower in this regard when compared with the finding of Zakem et al. (2021), who examined the efficacy of stereotactic body radiation therapy (SBRT) in individuals diagnosed with LAPC.[85] In a retrospective analysis, researchers studied eight patients who underwent SBRT after chemotherapy. According to the results, 71 percent of the 103 identified patients underwent definitive surgery after NAT. Among those whose definitive tumors were resected, 97% achieved R0 resection, and 7% had a complete pathologic response. The patients with a full or marked response had better OS than those with a moderate response or could not undergo surgery (41 vs. 24 months). These findings suggest that NAT, regardless of treatment type, can facilitate

successful surgical resection with negative margins and potentially improve long-term outcomes.

Nevertheless, it is critical to acknowledge that the efficacy of R0 resection differs based on the site of the tumor, as demonstrated in this analysis. The success rate of R0 resection is greater for tumors in the body of the pancreas than those in the head, body, or tail. This discovery aligns with the research conducted by Versteijne et al. (2018), which similarly documented variations in R0 resection rates according to the tumor's location.[86] The consistent results underscore tumor location's criticality in formulating neoadjuvant treatment strategies.

The main limitation of the present study was the lack of standard definitions for staging in the available studies, which could introduce the heterogeneity of outcomes. Institutional variation in treatment and surgeon skills can introduce selection bias. Future studies should try to use standardized definitions for disease staging and provide center-specific data in an effort to allow for more standardized comparisons.

Conclusion

The present systematic review and meta-analysis is a comprehensive investigation that indicates the effect of NCRT on unresectable LAPC patients. Our study shows that NCRT has improved tumor resectability and greater tumor downsizing compared with chemotherapy alone, particularly in tumors located within the pancreatic body. These improvements in the surgical indicators do not, however, appear to confer an OS benefit. These results highlight the importance of individualized treatment planning and document the need for further high-quality research to optimize therapeutic strategy and long-term outcomes in LAPC patients.

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Authors' Contributions

B.Sh.A: Data gathering, study design, drafting, and reviewing the manuscript;
S.M: Data gathering, study design, analysis, drafting the manuscript;
N.F: Data gathering, drafting the manuscript;
V.R: Study design, analysis, project administration, supervision, drafting, and reviewing the manuscript;
M.Kh.M: Data gathering, drafting the manuscript;
S.S: Study search, selection process, data gathering, study design, drafting the manuscript;
All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest

The authors state that they have no financial, professional, or personal relations that could be viewed as a potential conflict of interest for this study. There are no funding or professional ties that would have impacted the findings of this research.

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Table 1. Summary of Included Studies Evaluating the Effect of Neoadjuvant Chemotherapy or Chemoradiotherapy in Patients with Unresectable or Locally Advanced Pancreatic Adenocarcinoma (LAPC) Regarding Surgical Conversion, Tumor Response, and Survival Outcomes

First Author	year	location	Sample size	Study Design	Neoadjuvant Modality	Tumor Location/Stage	Resectability Conversion (%)	Tumor Size Reduction (%)	Overall Survival (months)	Disease-Free Survival (months)	R0 Resection Rate (%)	Quality Assessment
Eran.et al.[8]	2018	Netherland	54	cohort	chemotherapy	LAPC	20.31%	NA	0	NA	55%	Moderate
Wada K.et al.[9]	2015	Japan	52	cohort	chemotherapy	Head, Body, Tail	11.52%	NA	18.20	10.41	NA	Moderate
White R.et al.[10]	1999	US	25	cohort	chemoradiotherapy	Head, Body, Tail	20.01%	0.64	10	NA	20%	Moderate
Ralf wilkowski.et al.[11]	2004	Germany	47	clinical trial	chemoradiotherapy	Head, Body, Tail	57.02%	NA	10.70	7.80	48%	High
Ralf Wilkowski.et al.[12]	2006	Germany	32	clinical trial	chemoradiotherapy	Head, Body, Tail	37.54%	NA	13.61	8.91	13%	High
Sang Myung Woo.et al.[13]	2017	Korea	44	clinical trial	chemoradiotherapy	Head, Body, Tail	30.04%		16.88	10.10	100%	High
Suguru Yamada.et al.[13]	2018	Japan	12	clinical trial	chemotherapy	Head, Body, Tail	50.05%	0.187	13	3.70	100%	High
Michele Reni.et al.[13]	2009	Italy	91	cohort	chemoradiotherapy	stage III non-resectable pancreatic adenocarcinoma	14.03%	NA	16.22	9.95	69%	High
O.Turrini.et al.[16]	2009	France	64	clinical trial	chemoradiotherapy	LAPC	14.05%	NA	14	NA	11%	High
R. Gillmore. et al.[17]	2010	UK	48	cohort	chemoradiotherapy	Head, Body, Tail	14.07%	NA	17	NA	42%	Moderate
Gian C.et al.[17]	2010	Italy	40	clinical trial	chemoradiotherapy	Head, Body, Tail	10.09%	NA	15.50	MFS: 10	50%	High
Francesco.et al[19]	2010	US	23	cohort	chemoradiotherapy	Head, Body, Tail	8.01%	0.3	10.61	NA	66%	Moderate
Cardenes.et al.[20]	2011	US	28	clinical trial	chemoradiotherapy	Head, Body, Tail	14.01%	NA	10.32	6.10	50%	High
Klaus Sahora.et al.[21]	2011	Austria	33	clinical trial	chemotherapy	Head, Body, Tail	39.05%	0.07	12	10	69%	High
Naumann.et al.[22]	2020	Germany	49	cohort	chemoradiotherapy	Head, Body, Tail	16.06%	0.19	15	NA	50%	Moderate
Prof Philip.et al.[23]	2020	5 countries (USA, France, Spain, Canada, Italy)	107	clinical trial	chemotherapy	LAPC	16.04%	NA	18.80	10.09	41%	High
Maximilian Weniger.et al.[24]	2020	Germany	165	cohort	chemotherapy	LAPC	77.30%	NA	NA	NA	NA	Moderate
Maximilian Weniger.et al.[25]	2020	Europe	239	cohort	chemotherapy	LAPC	NA	NA	35.65	24.50	92	High
Changhoon Yoo. et al.[26]	2020	Korea	199	cohort	chemotherapy	Head, Body, Tail	31.70%	NA	18.12	10.65	49	Moderate
William T.et al.[27]	2021	US	50	cohort	chemoradiotherapy	Head, Body, Tail	25.04%	NA	17	NA	7, 78%	Moderate
Edouard Auclin.et al.[28]	2021	UK	330	cohort	chemoradiotherapy	Head, Body, Tail	42.15%	NA	21.45	12.44	74.70%	High
R. Fietkau.et al.[29]	2021	Germany	126	clinical trial	chemoradiotherapy	nonmetastatic unresectable pancreatic cancer	28.56%	NM	15	11.22	69%	High
Masaru Fukahori.et al.[30]	2021	Japan	24	clinical trial	chemotherapy	Head, Body, Tail	16.78%	0.3	21.20	11	75%	High
Kotone Hayuka.et al.[31]	2021	Germany	25	clinical trial	chemotherapy	Head, Body, Tail	15.01%	NA	15.60	5.35	0	Moderate

Prof Volker.et al.[32]	2020	Germany	130	clinical trial	chemotherapy	Head, Body, Tail	35.05%	NA	18.54	7.70	NA	Moderate
Ryoji Takada.et al.[33]	2021	Netherlands	63	cohort	chemoradiotherapy	Head, Body, Tail	15.60%	NA	29.24	15.25	85.70%	High
Marieke S.et al.[34]	2021	Netherlands	422	cohort	chemotherapy	Head, Body, Tail	13.05%	NA	10	8	50%	High
Gregory P.et al.[35]	2023	US	52	cohort	chemotherapy	Head, Body, Tail	29.02%	NA	26.25	16.40	21%	Moderate
Hosein, P.J.et al.36	2012	US	18	cohort	chemotherapy	Head, Body, Tail	55.05%	NA	12	12	80%	Moderate
Jessup, J.M.et al.[36]	1993	US	16	clinical trial	chemoradiotherapy	Head, Body, Tail	12.51%	0.2	8	25	NA	High
Kamachi, H.et al.[38]	2018	Japan	34	clinical trial	chemoradiotherapy	Head, Body, Tail	58.06%	NA	39	14.94	80%	High
Karachaliou, G.-S.et al.[39]	2020	Cyprus	30	pilot study	chemotherapy	LAPC	43.31%	NA	30	NA	76.90%	Moderate
Ke, Q. H.et al.[40]	2014	China	32	clinical trial	chemoradiotherapy	LAPC	NA	NA	15.28	9.30	NA	High
Khushman. M.et al.[41]	2015	US	51	cohort	chemoradiotherapy	Head, Body, Tail	25.05%	NA	35.40	13.64	20%	High
Edward J. Kim. et al.[42]	2013	America	68	clinical trial	chemoradiotherapy	Head, Body, Tail	55.0%	0.033	18.21	31%	60%	Moderate
Hong Jin Kim.et al.[43]	2002	America	87	cohort	chemotherapy	head and neck	1.11%	NA	11	NA	1.14%	Moderate
Naru Kondo.et al.[44]	2017	Japan	16	clinical trial	chemotherapy	Head, Body, Tail	81.05%	NA	8.51	NA	75%	High
Jongchan Lee.et al.[45]	2018	Korea	64	cohort	chemotherapy	Head, Body, Tail	23.40%	NA	17	20.30	73.30%	Moderate
Jae-Lyun Lee.et al.[46]	2012	Korea	43	clinical trial	chemotherapy	Head, Body, Tail	4.84%	NA	NA	16.64	32.50%	Moderate
Francesco Leone.et al.[47]	2013	America	39	clinical trial	chemoradiotherapy	Head, Body, Tail	38.41%	NA	16.70	10.24	23%	Moderate
Janet E. Murphy. et al.[48]	2019	America	49	clinical trial	chemoradiotherapy	Head, Body, Tail	69.08%	NA	31.40	17.50	61%	High
Mattia F Osti.et al.[49]	2001	Italy	31	cohort	chemoradiotherapy	Head, Body, Tail	26.01%	0.45	15.20	10	13%	Moderate
Alessandro Passardi.et al.[50]	2019	Italy	42	clinical trial	chemoradiotherapy	Head, Body, Tail	25.05%	NA	15.81	9.30	12.50%	Moderate
SHAWN L.et al[51]	2018	America	32	clinical trial	chemotherapy	NA	28.06%	NA	13.10	8.80	19%	Moderate
J. MARC PIPAS.et al.[52]	2001	Lebanon	21	clinical trial	chemoradiotherapy	NA	28.01%	0.09	20	NA	23%	Moderate
J. M. Pipas.et al.[53]	2012	Lebanon	37	clinical trial	chemoradiotherapy	NA	76.04%	0.3	17.35	NA	62%	High
Claudia Pouypoudat.et al.[54]	2019	france	79	cohort	chemoradiotherapy	NA	47.04%	NA	21.56	25.54	43%	Moderate
Howard Safran.et al.[55]	1998	America	25	clinical trial	chemoradiotherapy	NA	40.05%	NA	NA	NA	12%	Moderate
Muhammad.et al.[56]	2007	canada	20	clinical trial	chemoradiotherapy	NA	10.06%	0.39	12	NA	5%	Moderate
Jacob E.et al.[57]	2018	Germany	13	clinical trial	chemoradiotherapy	NA	44.40%	NA	NA	NA	44.40%	Moderate
William H.et al.[58]	2015	America	45	clinical trial	chemoradiotherapy	NA	88.00%	NA	32.54	30	62%	High
William Small Jr.et al.[59]	2008	America	39	clinical trial	chemoradiotherapy	NA	44.01%	NA	12	NA	41%	Moderate
Mustafa Suker.et al.[60]	2019	Netherland	50	cohort	chemoradiotherapy	Head, Body, Tail	12.01%	NA	23	17	12%	Moderate
Hans G. Smeenk.et al.[61]	2005	Netherlands	38	cohort	chemoradiotherapy	Head, Body, Tail	16.02%	NA	9.23	NA	5%	Moderate
AkikoTsujimoto.et al.[62]	2019	Japan	30	cohort	chemotherapy	Head, Body, Tail	26.06%	NA	29.90	14.84	20%	Moderate
Michele Fiore.et al.[63]	2017	Italy	34	clinical trial	chemoradiotherapy	Head, Body, Tail	55.50%	NA	20	19.20	55.50%	High
Michele Fiore.et al.[64]	2015	Italy	21	cohort	chemoradiotherapy	head	33.31%	NA	15.31	10.80	33.30%	Moderate
Georgios Gemenetzis.et al.[65]	2019	America	415	cohort	chemoradiotherapy	Head, Body, Tail	20.02%	0.16	35.31	11.34	18%	High

Daniel Habermehl.et al.[66]	2012	Germany	215	cohort	chemoradiotherapy	Head, Body, Tail	26.04%	NA	12.35	8.10	39.20%	High
Peter J. Hosein.et al.[67]	2012	America	18	cohort	chemotherapy	Head, Body, Tail	55.04%	NA	12	12	44.40%	Moderate
Thilo Hackert.et al.[68]	2016	Germany	575	cohort	chemoradiotherapy	Head, Body, Tail	50.80%	NA	15.35	NA	43%	High
Aristu. J.et al.[69]	2003	Spain	47	cohort	chemoradiotherapy	NA	25.56%	NA	36	NA	16.60%	Moderate
Badiyan. S.et al.[70]	2016	USA	32	cohort	chemoradiotherapy	Head, Body, Tail	31.07%	NA	13.90	NA	28.10%	Moderate
Bjerregaard. J.et al.[71]	2009	Denmark	63	cohort	chemoradiotherapy	NA	17.07%	0.25	8.80	NM	11	Moderate
Brunner. T.et al.[72]	2000	Germany	27	clinical trial	chemoradiotherapy	body	37.06%	NA	9	NA	37%	Moderate
Brunner. T.et al.[73]	2003	USA	22	clinical trial	chemoradiotherapy	NA	45.00%	NA	18	NA	40%	Moderate
Cetin.V.et al.[74]	2013	USA	11	clinical trial	chemoradiotherapy	Head, Body, Tail	36.09%	NA	NA	9	100%	High
Chadha. A.et al.[75]	2016	USA	17	clinical trial	chemoradiotherapy	NA	29.44%	NA	17.44	8.10	29%	Moderate
Chao, Y. J.et al.[76]	2014	Taiwan	41	cohort	chemoradiotherapy	Head, Body, Tail	41.55%	NA	12.50	9	34.10%	Moderate
Chen-Zhao. X.et al.[77]	2020	Spain	45	clinical trial	chemoradiotherapy	NA	71.11%	NA	21.85	NA	93.80%	High
Epelbaum. R..et al.[78]	2002	Israel	20	clinical trial	chemoradiotherapy	Head, Body, Tail	15.03%	NA	NA	NA	10%	Moderate
Faris. J. E.et al.[79]	2013	USA	22	clinical trial	chemoradiotherapy	Head, Body, Tail	22.74%	NA	NA	NA	100%	Moderate

NA: Not applicable

Table 2. Univariate meta-regression results to find possible causes of heterogeneity among studies included in the meta-analysis of transformation from unresectable to resectable pancreatic cancer

Variable	Coefficient (β)	Standard error	95% Confidence interval	*P*-value
Type of neoadjuvant	0.084	0.027	0.031 to 0.137	0.002
Study design	0.051	0.035	-0.017 to 0.120	0.140
Tumor location	0.093	0.043	0.008 to 0.178	0.030
Sample size	0.005	0.002	0.001 to 0.009	0.010
Study quality	0.072	0.030	0.013 to 0.131	0.017
Year of publication	0.010	0.004	0.002 to 0.018	0.012
Country	-0.047	0.025	-0.096 to 0.002	0.061

Table 3. Subgroup meta-analysis of conversion rate from unresectable or LAPC to resectable status, stratified by type of neoadjuvant therapy and tumor location

Variable	Grouping	No. studies	No. examined	%Overall transformation (95%CI	Heterogeneity		
					χ^2	*P*-value	I^2 (%)
Neoadjuvant	Chemotherapy	21	1618	22.90% (23.20-36.71)	730.27	< 0.001	97.30%
	Chemoradiotherapy	49	3418	32.54% (28.30-32.95).	638.19	< 0.001	92.51%
Location of pancreatic adenocarcinoma	Head, Body, Tail	46	3563	29.76% (24.71-34.64)	536.84	< 0.001	91.65%
	Head and neck	1	48	99.09% (1.01-99.94)	NA	NA	NA
	NA	19	1154	40.24% (28.30-52.14)	681.17	< 0.001	97.41%
	head	1	21	33.34% (13.12-53.12)	NA	< 0.001	NA
	body	1	27	37.01% (18.80-55.21)	NA	NA	NA

NA: Not applicable; LAPC: Locally advanced pancreatic adenocarcinoma; No.: Number; CI: Confidence interval

Table 4. Subgroup meta-analysis of R0 resection rate in patients with unresectable or LAPC, Stratified by type of neoadjuvant therapy and tumor location

Variable	Grouping	No. studies	No. examined	%Overall percentage surgery with R0 (95%CI	Heterogeneity	
					χ^2	*P*-value
Neoadjuvant	Chemotherapy	16	1416	49.7% (28.8-70.5)	1860.85	< 0.001
	Chemoradiotherapy	45	3402	39.8% (31.7-47.9)	1371.97	< 0.001
Location of pancreatic adenocarcinoma	Head, body, tail	38	3553	43.9% (36.1-51.7)	956.03	< 0.001
	Head and neck	1	48	99.01% (0.01-99.9)	NA	NA
	NA	18	934	39.0% (21.0-57.0)	966.35	< 0.001
	Head	1	21	33.3% (13.1-53.1)	NA	NA
	Body	1	27	37.0% (18.8-55.2)	NA	NA

NA: Not applicable; LAPC: Locally advanced pancreatic adenocarcinoma

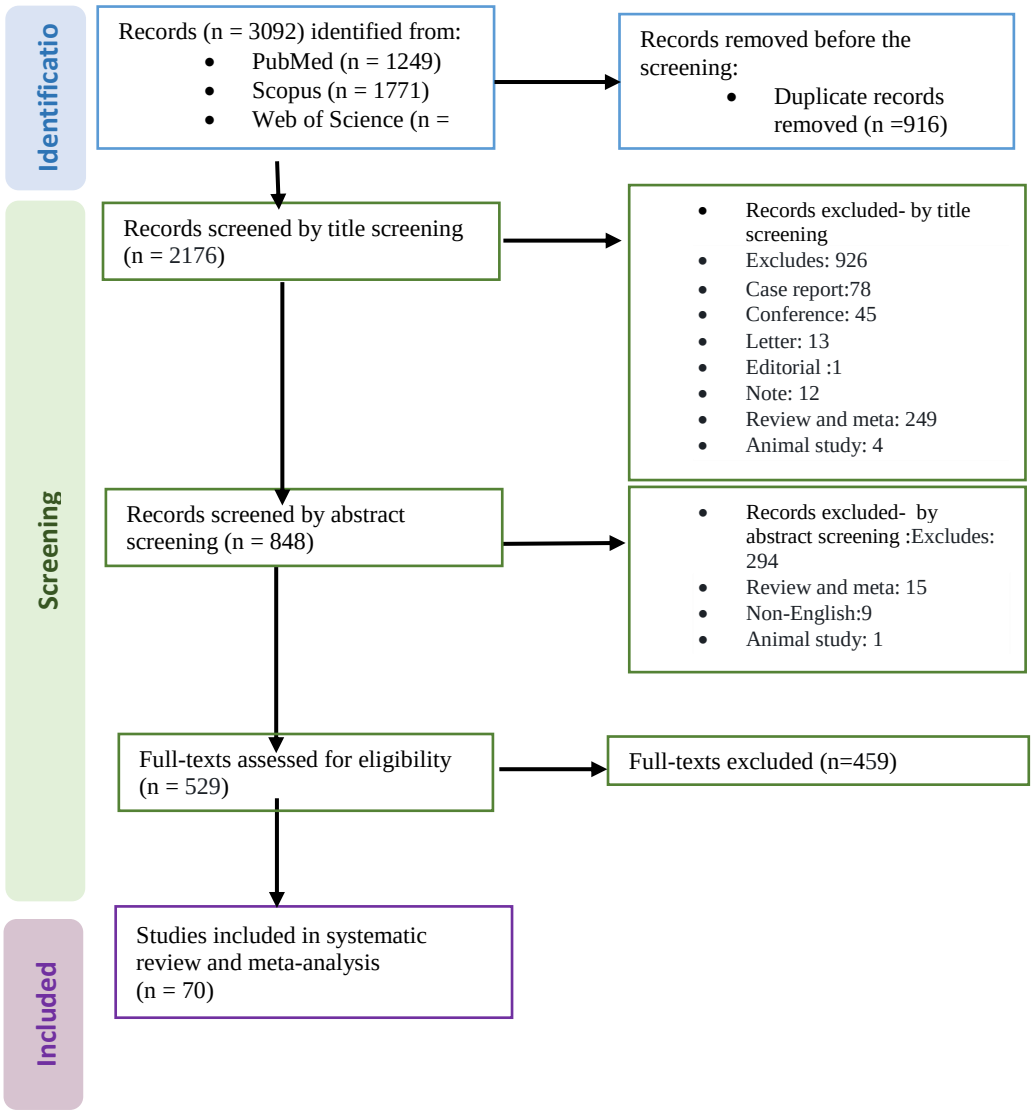

Figure 1. This PRISMA flow diagram illustrates the study selection process for the present systematic review and meta-analysis.

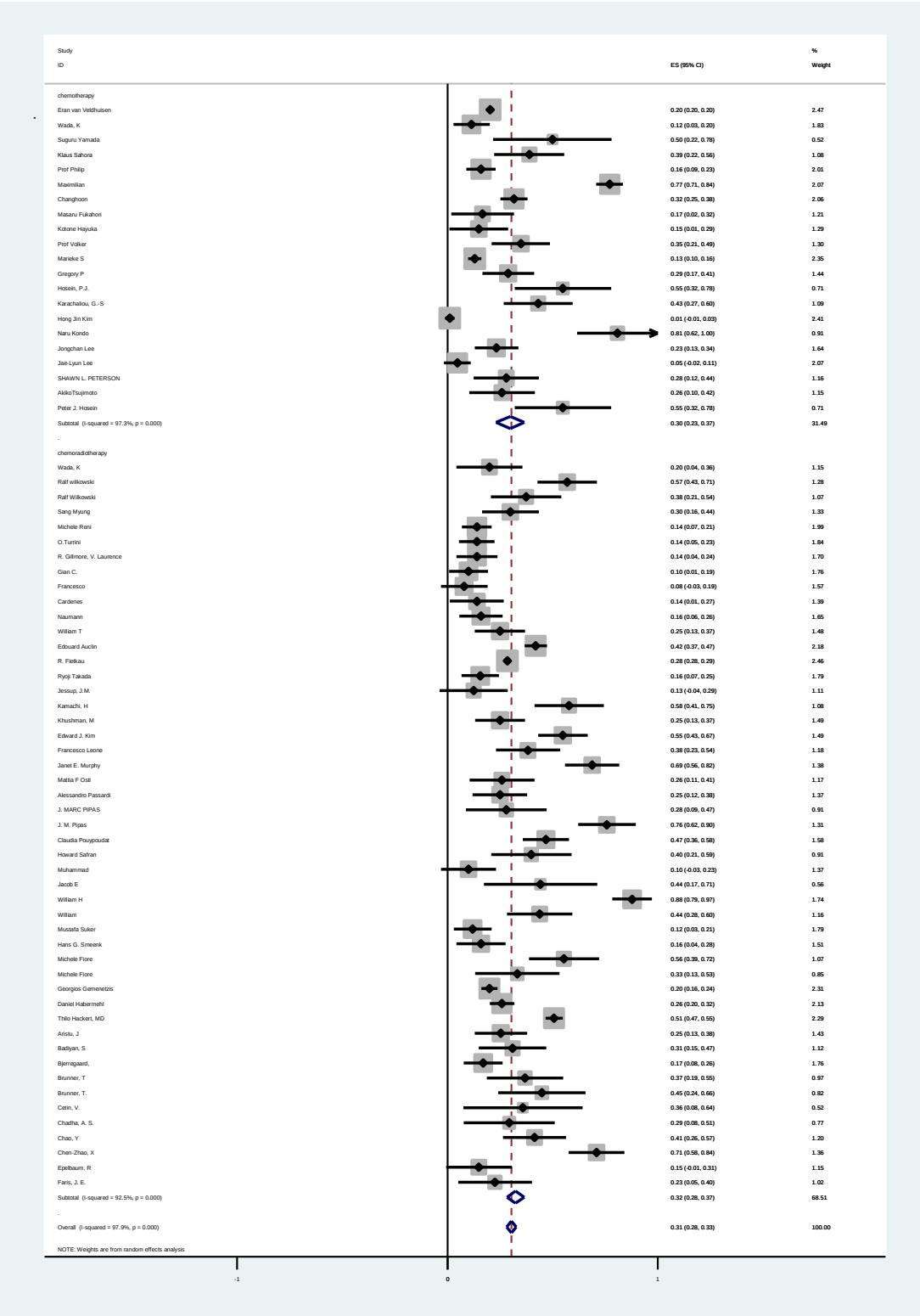

Figure 2. This figure shows the transformation rates from unresectable to resectable pancreatic adenocarcinoma by chemotherapy modality.

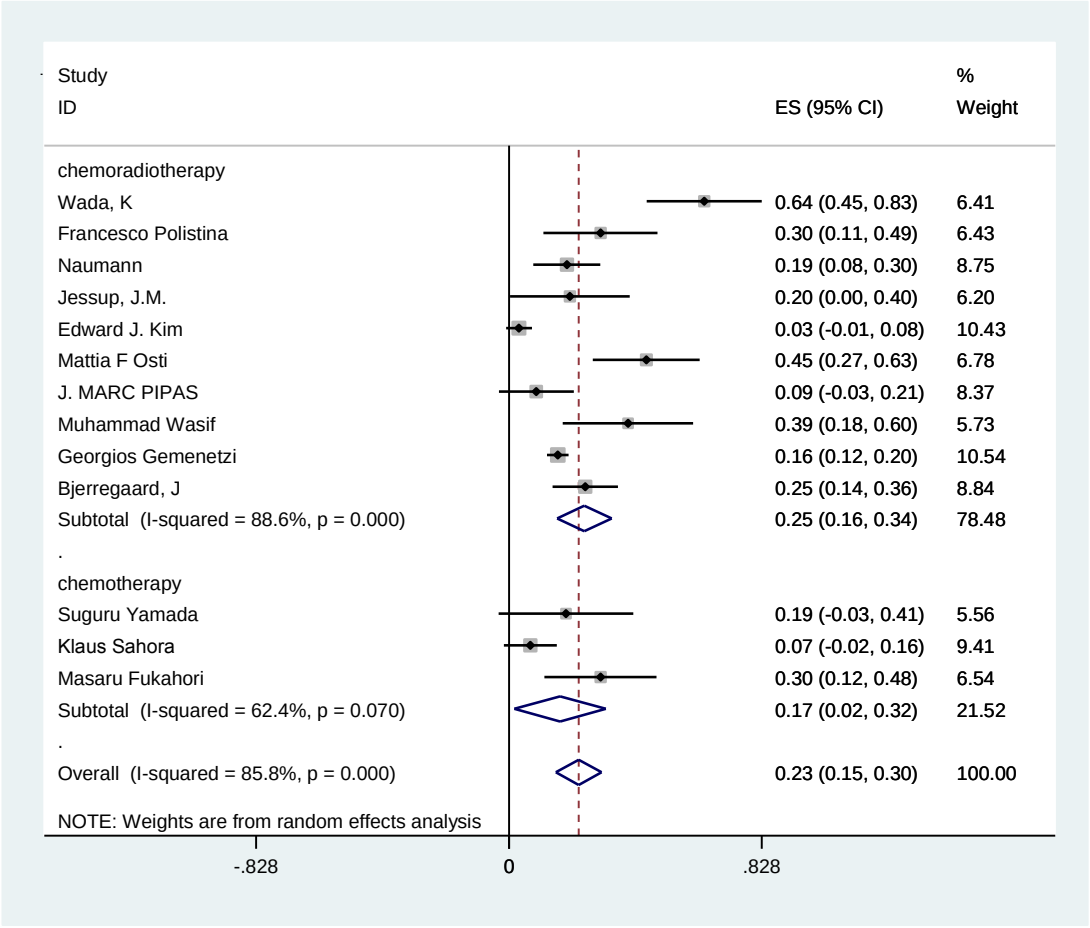

Figure 3. This figure shows the Forest plot demonstrating the distribution of included studies reporting percentage reduction in tumor size, stratified by type of neoadjuvant therapy (chemotherapy vs. chemoradiotherapy).

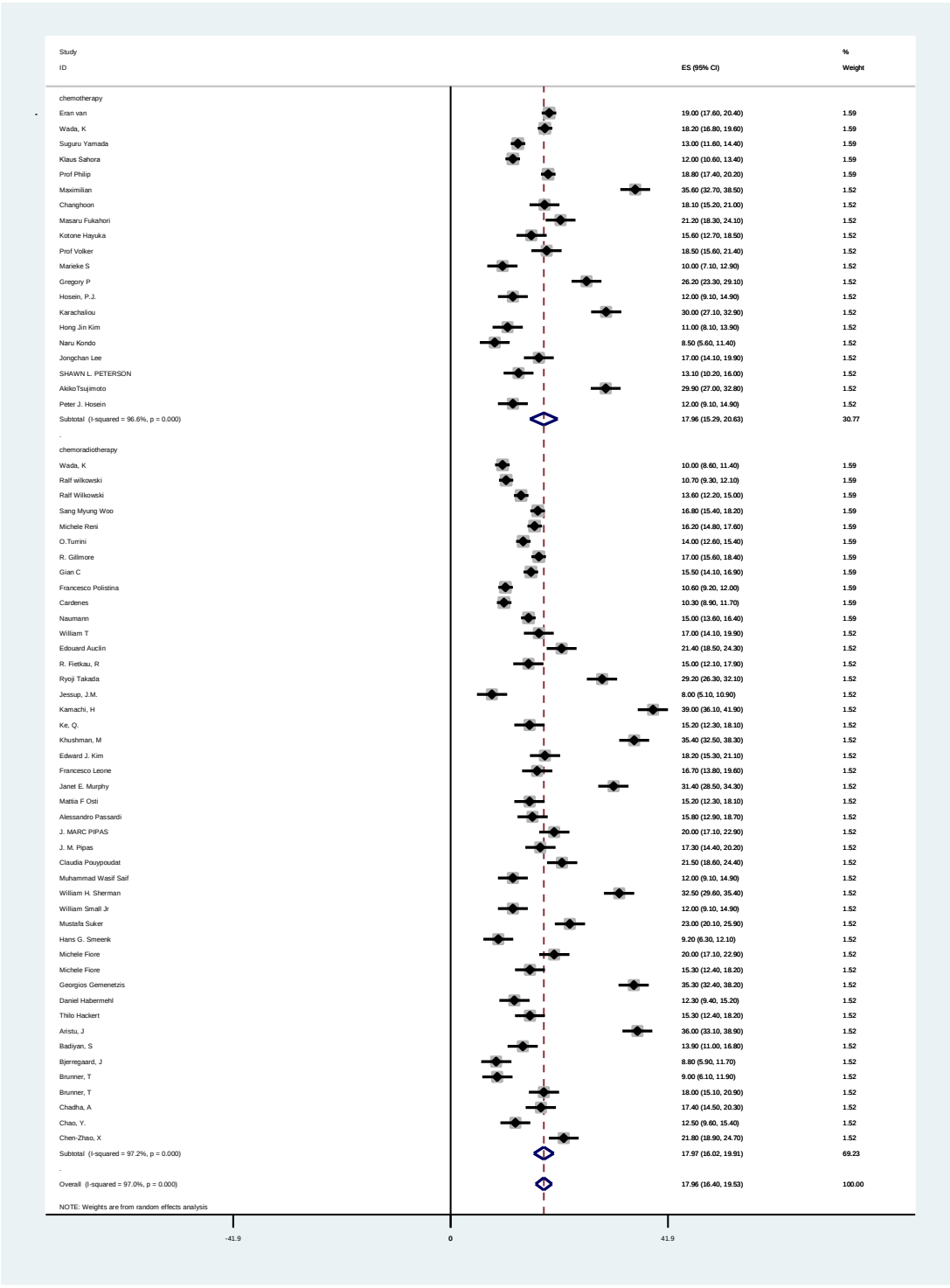

Figure 4. This figure shows the Forest plot of overall mean survival time after neoadjuvant chemotherapy and chemoradiotherapy in pancreatic cancer patient.

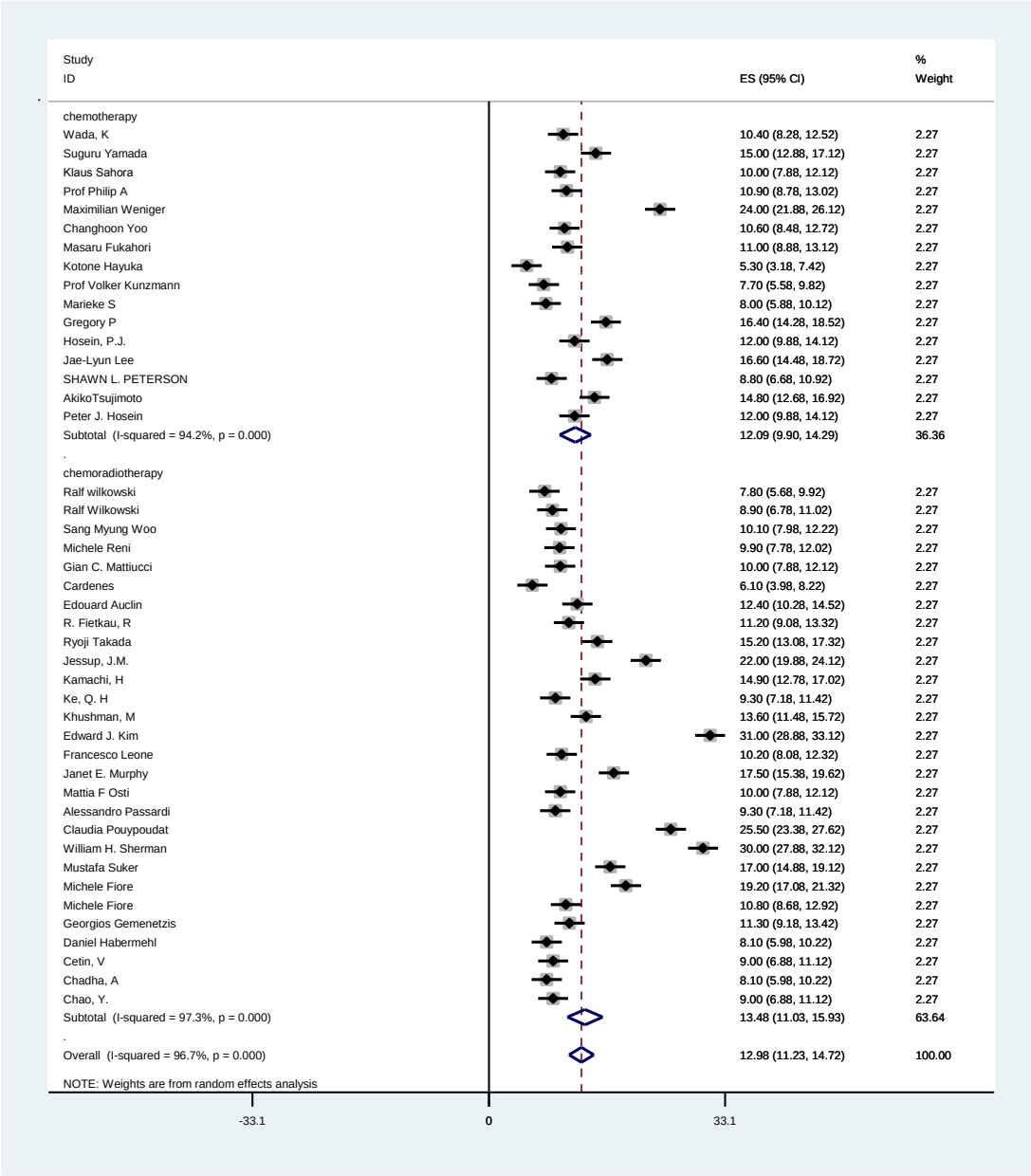

Figure 5. This figure depicts the Forest plot illustrating the distribution of included studies reporting mean DFS in months, based on the type of neoadjuvant therapy.
DFS: Disease-free survival

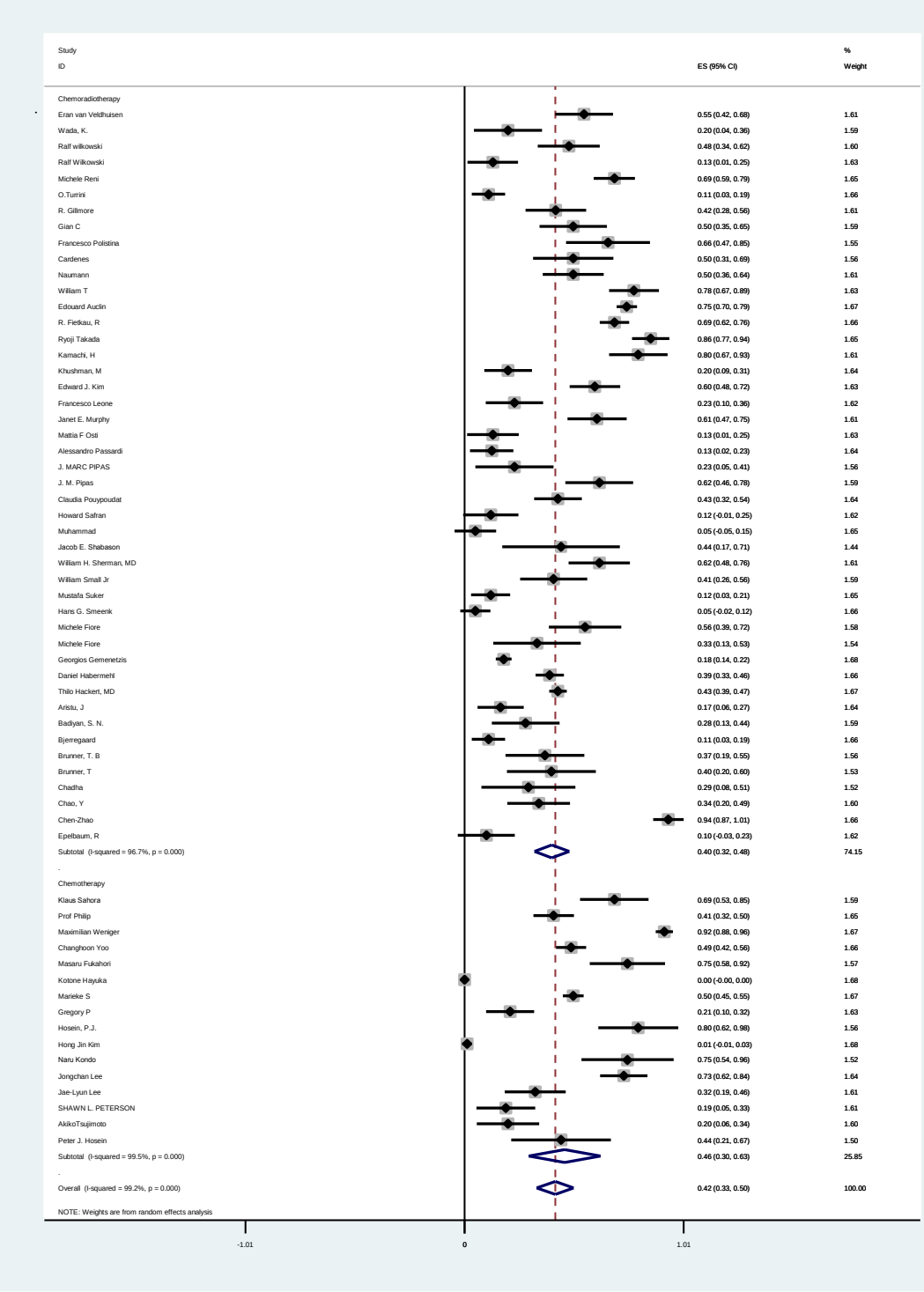

Figure 6. This figure shows the Forest plot of the pooled percentage of R0 resection following neoadjuvant therapy, stratified by chemotherapy and chemoradiotherapy treatment modalities.

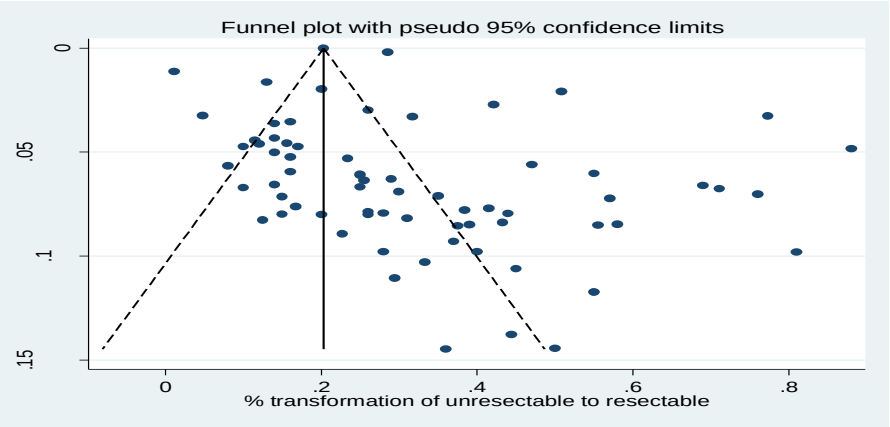

Figure 7. This figure shows the Funnel plot with pseudo 95% confidence limits used to detect potential publication bias across studies included in the meta-analysis