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The Prognostic Value of a Pathologic Complete Response After Neoadjuvant Therapy for Digestive Cancer: Systematic Review and Meta-Analysis of 21 Studies

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ABSTRACT

Background. Neoadjuvant therapy (NAT) before radical excision has become the preferred initial option for locally advanced digestive cancers such as esophageal cancer (EC), esophagogastric junction adenocarcinoma (EGJAC), gastric adenocarcinoma (GAC), rectal cancer (RC), and pancreatic cancer (PC). Although some patients reportedly achieve a pathologic complete response (pCR) after neoadjuvant therapy, the published data are inconsistent regarding whether pCR yields a survival benefit. The current meta-analysis was performed to assess the potential prognostic value of pCR after preoperative therapy for patients with digestive cancers.

Methods. An extensive electronic search in PubMed, Web of Science, and the Cochrane Library was performed for relevant articles, from which data relative to independent correlations of pCR with overall survival (OS) and disease-free survival (DFS) were extracted for analysis. A random-effects model was used to calculate the pooled hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs).

Results. The study identified 6780 patients who met the inclusion and exclusion criteria. The results showed that pCR was significantly correlated with better OS (HR, 0.50; 95% CI, 0.43–0.58; $P < 0.001$) and DFS (HR, 0.49; 95% CI, 0.40–0.60; $P < 0.001$) for the digestive cancer patients who achieved pCR than for those who did not achieve pCR. Subgroup analysis showed that the correlation of pCR with OS was significant in EC (HR, 0.57; 95% CI, 0.47–0.69; $P < 0.001$), EGJAC/GAC (HR, 0.38; 95% CI, 0.17–0.86; $P = 0.02$), RC (HR, 0.48; 95% CI, 0.28–0.81; $P = 0.006$), and PC (HR, 0.41; 95% CI, 0.17–0.97; $P = 0.04$). In addition, the survival benefit for pCR patients was of similar magnitude, irrespective of the type of study, type of NAT, or ethnicity.

Conclusions. A pCR is correlated with favorable survival outcomes compared with a non-pCR for digestive cancer patients after NAT.

Digestive cancer can develop from any anatomic sites of the digestive system, ranking as one of the most frequently diagnosed and deadly human cancers worldwide.[1,2] Neoadjuvant therapy (NAT), including neoadjuvant chemoradiotherapy (NCRT) and neoadjuvant chemotherapy (NCT) before radical excision, has become a standard therapy for locally advanced digestive cancers during the past decade. Several randomized trials have demonstrated that NAT can improve the local control and long-term survival of digestive cancer patients, and the impact of this outcome is generally considered to result from tumor downstaging.[3–5]

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However, classical prognostic factors such as tumor size and number of invaded lymph nodes at the primary cancer site are no longer applicable to patients who have achieved clinical downstaging after NAT. Therefore, several studies have correlated the grade of pathologic response to NAT with the survival of digestive cancer patients. Based on data from the published literature, some cancer patients have achieved pCR after NAT,[6,7] as represented by ypT0N0M0, which indicates the absence of residual tumor cells in the surgical resection specimen.

To date, the prognostic impact of pCR on survival in digestive cancers has not been completely established. For example, one retrospective cohort study[8] showed that pCR was associated with improved overall survival (OS), whereas another study[9] argued that OS between pCR and non-pCR patients did not differ significantly.

Evidence-based medicine has played an increasingly pivotal role in decision-making for the treatment of cancer patients since the early 1990s. Due to the relatively low pCR rate of digestive cancers after NAT, it is difficult to obtain sufficient data about the outcome for patients with pCR in a single center. In addition, most current studies have focused on comparing major pathologic response with no response or minor pathologic response in digestive cancers,[10–12] and few studies have addressed the independent relationship between pCR and survival. Therefore, we performed a systematic literature review and meta-analysis to clarify the prognostic role of pCR for patients with digestive cancers after NAT.

MATERIALS AND METHODS

Study Search Strategy

This study was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria.[13] A systematic literature search of the PubMed, Web of Science, and Cochrane Library databases was performed by two investigators independently (updated to 10 April 2018). The retrieved articles were restricted to those published in English by using the following search terms: ("pathological complete response" or "pathologic regression" or "pathological complete remission" or "pCR") and ("cancer" or "tumor" or "neoplasm" or "carcinoma" or "adenocarcinoma") and ("neoadjuvant therapy" or "preoperative therapy" or "chemoradiotherapy" or "chemotherapy") and ("survival" or "prognosis" or "prognostic").

We also manually cross-searched the citation lists of all included studies to screen additional eligible articles. When multiple studies involved the same patient population, only the published study with the largest cases and complete information was finally included in the meta-analysis.

Criteria for Inclusion and Exclusion

Studies eligible for selection were required to meet the following criteria: (1) studies using a prospective or retrospective study design, (2) studies involving only patients with cancers of the human digestive system including the gastrointestinal tract and the accessory organs (tongue, salivary gland, pancreas, liver, and gallbladder) who underwent NAT before surgery, (3) studies with pCR confirmed in surgical specimens according to the American Joint Committee on Cancer (AJCC) staging system, (4) studies that evaluated the association between pCR and OS or disease-free survival (DFS), and (5) studies that presented hazard ratios (HRs) and 95% confidence intervals (CIs) for survival results or provided data sufficient for calculating HRs and 95% CIs.

The exclusion criteria ruled out (1) conference abstracts, reviews, case reports, letters, and laboratory studies, (2) studies with a sample smaller than 50 patients, and (3) insufficient original data for further analysis.

Data Extraction and Quality Assessment

Two reviewers (T.W. and X.Z.) independently assessed all eligible studies, and any disagreement between the reviewers was resolved by debate or by consulting the senior author (YM.Z.). The data extracted from each article included the first author, year of publication, country of origin, cancer type, preoperative tumor- node-metastasis (TNM) stage, case, number and percentages of patients achieving pCR, type of NAT, percentages of surgical patients, survival statistics, and median follow-up months. If the HR for OS or DFS was not directly provided in the study, we extracted data from Kaplan–Meier curves using the Engauge Digitizer V4.1 (Markmitch, Goteborg, Sweden) in combination with the Tierney's method to estimate HR and 95% CI.[14]

The Newcastle–Ottawa Quality Assessment Scale (NOS) was applied to evaluate the overall quality of all the eligible studies. The maximum score of the assessment scale was 9 points, and studies with a score of 7 or higher were considered to be high-quality studies.

Statistical Analysis

RevMan software 5.3 (The Cochrane Collaboration, Oxford, UK) and Stata 12.0 (Stata Corporation, College Station, TX, USA) were used for all the statistical analyses. The primary objective of our meta-analysis was to assess the association between pCR and OS or DFS of digestive cancer patients. When the pooled HR and its 95% CI did

not overlap with 1, pCR had a statistically significant effect on survival.

Heterogeneity across studies was measured using Cochran's Q test and Higgins I^2 statistic, and the criterion for significant heterogeneity was defined as a P value lower than 0.1 and an I^2 greater than 50%.[15] Taking into account the possibility of relatively significant heterogeneity between different digestive cancers, the random-effects model according to Der Simonian-Laird's method was always applied to provide better estimates for HRs with 95% CIs.[16]

The potential publication bias was statistically assessed through Begg's funnel plots and Egger linear regression, and a P value lower than 0.05 for the Egger's test indicated the presence of significant statistical publication bias.[17] We also conducted the sensitivity analysis by sequentially omitting each single study to evaluate the stability of the synthetic results. Two-tailed P values lower than 0.05 were considered to denote statistical significance.

RESULTS

Study Selection and Patient Characteristics

Initially, the search strategy identified 1062 potentially relevant articles. After further screening according to the inclusion and exclusion criteria, 21 studies were finally included for evidence synthesis.[18–38] The details of the eligible literature selection process are presented in Fig. S1.

In these 21 studies, five types of common digestive cancer were compared including esophageal cancer (EC), esophagogastric junction adenocarcinoma (EGJAC), gastric adenocarcinoma (GAC), rectal cancer (RC), and pancreatic cancer (PC). Of the 21 studies, 16 provided data about the prognostic role of pCR in OS, and 11 focused on DFS. In 20 studies, HRs with 95% CIs were directly extracted through multivariate analyses and calculated from Kaplan–Meier survival curves, and Tierney's method was used in only 1 study.[20] The NOS scale was applied to evaluate these studies, and the quality scores ranged from 5 to 8 (median, 6.8), indicating that the quality of the entire cohort was relatively high.

Of the 21 included studies, 5 were prospective studies,[21,22,30,31,34] and the remaining 16 studies[18–20,23–29,32,33,35–38] were retrospective studies, with sample sizes ranging from 100 to 1384, totaling 6780 patients who received NAT, including NCRT in 18 studies and NCT in the remaining 3 studies. The findings showed that 1494 patients achieved pCR after NAT, and the mean pCR rate for the entire population was 22% (range, 10.2–52.1%). The median follow-up period ranged from 24.6 to 72 months. The main characteristics of all the eligible studies are summarized in Table 1.

Overall Survival

As shown in Fig. 1, 16 studies reported OS for 5267 patients. The pooled results suggested that digestive cancer patients with pCR had significantly better OS (HR, 0.50; 95% CI, 0.43–0.58; $P < 0.001$). A random-effects model was applied because of the obvious heterogeneity in the synthesis analysis ($I^2 = 53\%$; $P = 0.006$).

Considering that different cancer types may affect the synthetic result of pCR, further analysis was performed to explore the correlation between pCR and OS in various digestive cancers. The pooled HRs showed an association between pCR and favorable prognosis for patients with EC (HR, 0.57; 95% CI, 0.47–0.69; $P < 0.001$), GAC/EGJAC (HR, 0.38; 95% CI, 0.17–0.86; $P = 0.02$), RC (HR, 0.48; 95% CI, 0.28–0.81; $P = 0.006$), and PC (HR, 0.41; 95% CI, 0.17–0.97; $P = 0.04$). Also, the results from three subgroup analyses were in line with those from the overall analyses (Table 2).

Disease-Free Survival

In 11 studies that included 3603 patients, DFS was compared between pCR and non-pCR. Notably, one study reported the survival data from patients with esophageal squamous cell carcinoma and esophageal adenocarcinoma, and both sets of data were included in the synthetic analysis. The final result showed that pCR was significantly associated with a DFS benefit (HR, 0.49; 95% CI, 0.40–0.60; $P < 0.001$; Fig. 2). A random-effects model was used because of the moderate heterogeneity ($I^2 = 45\%$; $P = 0.05$).

Sensitivity Analysis and Publication Bias

We sequentially removed each individual study to evaluate whether any single study had a remarkable impact on the pooled HR for OS, and the result of the sensitivity analysis demonstrated that the synthetic evidence was robust (Fig. 3a). Besides, we also performed Begg's funnel plot and Egger's test to assess the potential publication bias in the pooled analysis of the correlation between pCR and OS. As illustrated in Fig. 3b, the funnel plot showed the absence of remarkable asymmetry, and the P value of Egger's test was 0.142, with the results of both tests showing no obvious publication bias.

TABLE 1 Main characteristics of the eligible studies

Authors	Year	Country	Cancer type	Preoperative stage	Case	pCR *n* (%)	Neoadjuvant therapy	Operation (%)	Outcome	MFu time (months)	Nos. score
Brucher et al.[18]	2006	Germany	ESCC	2–3	311	162 (52.1)	NCRT	100	OS	55.2	8
Miyata et al.[19]	2010	Japan	ESCC	2–4A	195	32 (16.4)	NCRT	53.8	OS	60	5
Tong et al.[20]	2010	China	ESCC	1–4	175	55 (31.4)	NCRT	100	OS	20	6
Orditura et al.[21]	2012	Italy	EC	NR	113	27 (23.9)	NCRT	76.1	OS	36	5
Donohoe et al.[22]	2013	Ireland	EC/EGJAC	1–4	393	92 (23.4)	NCRT	99.0	OS	48	8
Wang et al.[23]	2015	China	ESCC	3	125	40 (32.0)	NCRT	100	OS	24.6	6
Alnaji et al.[24]	2016	USA	EAC/EGJAC	1–4	205	38 (18.5)	NCRT	100	OS/DFS	50	8
Blum Murphy et al.[25]	2017	USA	EC	1–4	911	218 (23.9)	NCRT	100	OS/DFS	60	8
Hamai et al.[26]	2018	Japan	ESCC	1B–4	130	29 (22.3)	NCRT	77.7	OS/DFS	60	7
Xi et al.[27]	2018	China	ESCC	1–3	207	93 (44.9)	NCRT	84.5	DFS	34.1	6
			EAC		688	178 (25.9)					
Ott et al.[28]	2011	Germany	GAC/EAC	2–4	238	77 (32.4)	NCT	100	OS	49.3	8
Koh et al.[29]	2013	Korea	GAC/EGJAC	NR	143	16 (11.2)	NCT	100	OS	35	6
Lorenzen et al.[30]	2013	Germany	GAC/EGJAC	2–4	120	18 (15.0)	NCT	100	OS/DFS	72	8
Chan et al.[31]	2005	Canada	RC	2–4	128	32 (25.0)	NCRT	100	DFS	60	7
Topova et al.[32]	2011	Germany	RC	1–3	174	35 (20.1)	NCRT	100	DFS	45	6
Mace et al.[33]	2015	USA	RC	1–4	538	105 (19.5)	NCRT	100	OS/DFS	57.6	8
De Felice et al.[34]	2016	Italy	RC	2–3	100	24 (24.0)	NCRT	97.0	OS	60	6
Wasmuth et al.[35]	2016	Norway	RC	2–3	1384	147 (10.6)	NCRT	100	OS	60	8
Wilkins et al.[36]	2016	Australia	RC	2–3	118	26 (22.0)	NCRT	100	DFS	36.9	6
Suzuki et al.[37]	2017	Japan	RC	2–3	198	31 (15.7)	NCRT	100	DFS	52	7
He et al.[38]	2018	USA	PC	NR	186	19 (10.2)	NCRT	100	OS/DFS	27	6

pCR pathologic complete response, *MFu* median follow-up period, *NOS* Newcastle–Ottawa Scale, *ESCC* esophageal squamous cell carcinoma, *NCRT* neoadjuvant chemoradiotherapy, *OS* overall survival, *EC* esophageal cancer, *NR* not reported, *EGJAC* esophagogastric junction adenocarcinoma, *DFS* disease-free survival, *EAC* esophageal adenocarcinoma, *NCT* neoadjuvant chemotherapy, *GAC* gastric adenocarcinoma, *RC* rectal cancer, *PC* pancreatic cancer

DISCUSSION

With the increasing incidence of digestive cancers worldwide, there is no doubt that the management of digestive cancers currently has become a major workload in the field of medicine. It is generally accepted that surgery alone has reached the technical limit in prolonging the survival of patients.[1,39,40] Accordingly, NAT is recommended by the National Comprehensive Cancer Network (NCCN) clinical practice guidelines as a priority treatment strategy for locally advanced (e.g., T3, T4, or lymph-node positive) digestive cancers.

Based on the concept of therapy practice, a number of clinical studies have proved that multimodal treatment can improve the survival outcome for cancer patients in varying degrees.[41–45]

Although NAT approaches vary with the location and stage of cancer, as well as with individual patients, it is generally accepted that NCRT or NCT is undoubtedly associated with potential survival advantages. The main underlying mechanisms include downsizing of the tumor, increasing the possibility of radical resection, and eliminating micrometastasis of cancer cells.[46,47] On the other hand, we also found that the traditional pathologic features such as primary tumor size, margin status, and number of lymph nodes involved are no longer perfectly applicable to

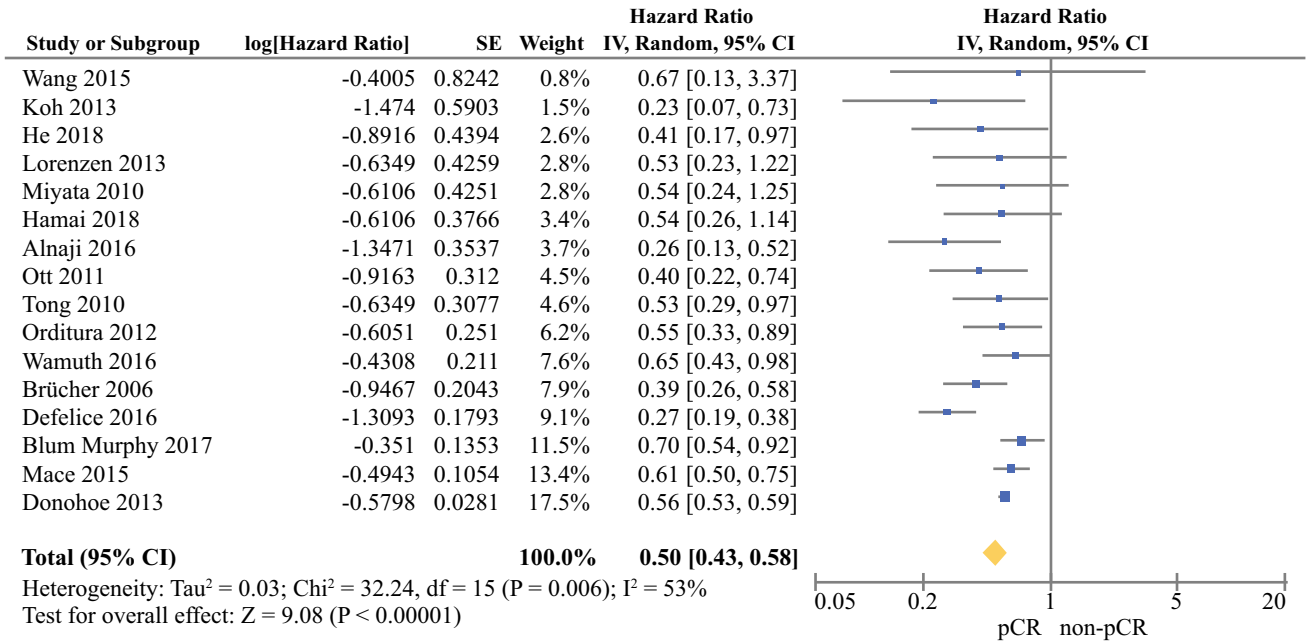


FIG. 1 Forest plot presenting the pooled hazard ratio (HR) for overall survival of digestive cancer patients with pathologic complete response (pCR) versus those without pCR

TABLE 2 Subgroup analysis results of pathologic complete response (pCR) and overall survival for digestive cancer patients

Subgroup analysis	No. of studies	No. of patients	HR (95% CI)	*P* value	Heterogeneity	
					I^2 (%)	P_h
Overall survival	16	5267	0.50 (0.43–0.58)	< 0.001	53	0.006
Type of cancer						
EC	7	1960	0.57 (0.47–0.69)	< 0.001	2	0.41
GAC/EGJAC	2	263	0.38 (0.17–0.86)	0.02	12	0.34
RC	3	2022	0.48 (0.28–0.81)	0.006	88	< 0.001
PC	1	186	0.41 (0.17–0.97)	0.04	–	–
Type of study						
Prospective	4	726	0.45 (0.30–0.68)	< 0.001	81	0.001
Retrospective	12	4541	0.52 (0.44–0.63)	< 0.001	31	0.14
Type of neoadjuvant therapy						
NCRT	13	4766	0.51 (0.43–0.60)	< 0.001	59	0.004
NCT	3	501	0.40 (0.25–0.63)	< 0.001	0	0.51
Ethnicity						
Asiatic	5	768	0.50 (0.34–0.72)	< 0.001	0	0.74
Non-asiatic	11	4499	0.49 (0.42–0.59)	< 0.001	67	< 0.001

HR hazard ratio, *CI* confidence interval, *EC* esophageal cancer, *GAC* gastric adenocarcinoma, *EGJAC* esophagogastric junction adenocarcinoma, *RC* rectal cancer, *PC* pancreatic cancer, *NCRT* neoadjuvant chemoradiotherapy, *NCT* neoadjuvant chemotherapy

patients who have achieved clinical downstaging after NAT. Therefore, realizing that accurate prognostic information is crucial for guiding additional adjuvant treatment needs, a new set of more reliable and feasible prognostic predictors need to be identified further for patients receiving NAT.

Recently, several studies have explored the prognostic value of pathologic response grades after NAT in digestive cancers. However, the conclusions drawn from these studies are inconsistent. For example, a retrospective study of 106 patients failed to find a significant correlation between pCR and the survival benefit, and the study data

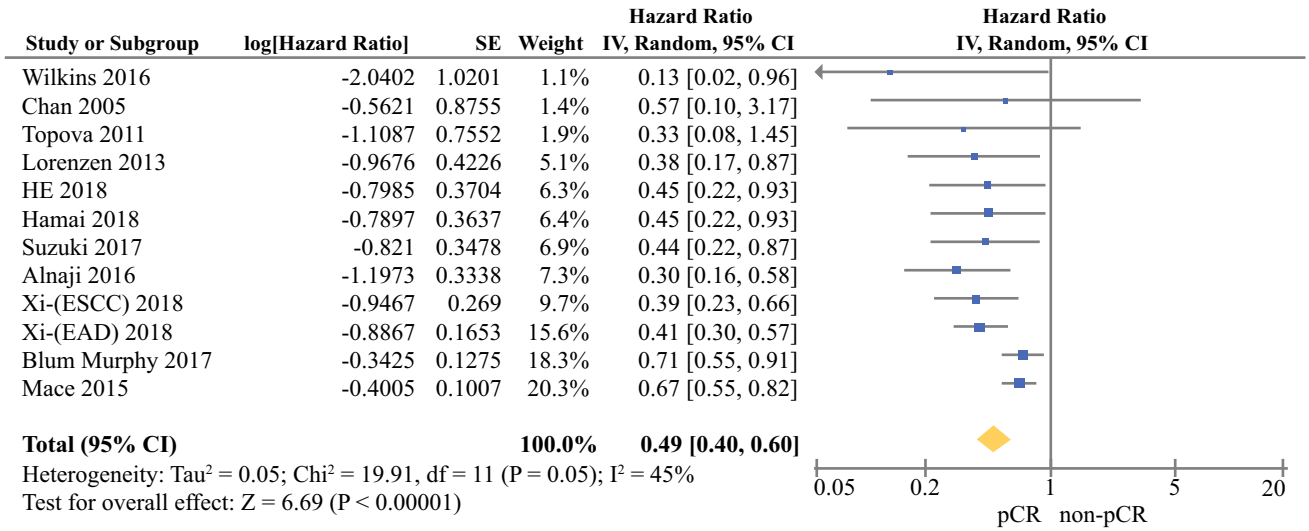


FIG. 2 Forest plot showing the pooled hazard ratio (HR) for disease-free survival of digestive cancer patients with pathologic complete response (pCR) versus those without pCR

suggested that neoadjuvant chemoradiotherapy regimens and pretreatment T stage were the most accurate predictors for the outcome.[48] Given the limited sample size and the short follow-up period of these studies, the findings show no level 1 evidence that pCR is an independent predictor for long-term outcomes of digestive cancer patients.

The primary aim of the current meta-analysis was to investigate the prognostic impact of pCR after NAT on OS and DFS for patients with digestive cancers, and to elucidate further the degree of the impact. Based on the survival data from the 21 eligible studies involving 6780 patients, the pooled results suggested that digestive cancer patients with pCR are clearly associated with a 50% lower risk of death than patients without pCR, similar to the results from the pooled analysis of bladder cancer and breast cancer.[49–52] Furthermore, the results of our further subgroup analysis also showed that the survival benefit did not disappear, irrespective of the type of cancer, type of study, type of NAT, or ethnicity.

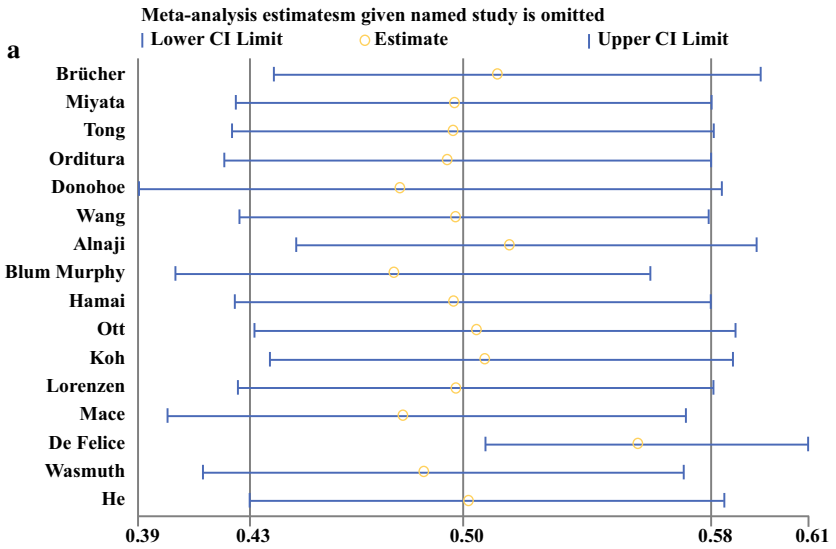
Our meta-analysis validated that pCR has important clinical implications for the following reasons. First, this study demonstrated that digestive cancer patients who achieved pCR after receiving NAT were more likely to have significantly better OS or DFS. Second, molecular biology research on the group of patients with pCR should facilitate finding sensitive therapeutic targets so tailored NAT can be delivered to individual patients. Finally, pCR can be considered a valuable prognostic factor for better guidance in clinical decision-making for postoperative adjuvant treatment and follow-up observation.

Notaably, the pCR rate varied from 10.2 to 52.1% in the 21 studies our study analyzed. The main reason for this discrepancy may have been the different treatment regimens used in these studies. In fact, many clinical trials have begun exploring the possibility of improving the pCR rate by means of adding targeted agents in NAT [53,54] and using concomitant boost radiotherapy [55] as well as an appropriate delay between NAT and surgery.[56] Considering the great clinical implications of pCR, further analysis of the aforementioned parameters would be a worthwhile endeavor in the future.

Although our meta-analysis had considerable merits, it also had several limitations involving the following points. First, we found that only nine included studies reported the use of postoperative adjuvant therapy. However, the detailed descriptive data on adjuvant therapy were incomplete. It would be of interest to know what proportion of patients with pCR and without pCR received postoperative adjuvant therapy, but these data were not provided. Therefore, the findings did not show whether postoperative adjuvant treatment had different effects on the survival outcomes between the pCR patients and the non-pCR patients.

Second, most of the included studies were retrospective in design. In addition, we extracted the HR and 95% CI from one of the included studies by using the Tierney's method, which may have introduced bias.

Third, given the limited number of studies included in the NCT trial and certain types of cancer (PC and GAC/EGJAC), the pooled conclusions of the subgroup analysis should be considered with caution.



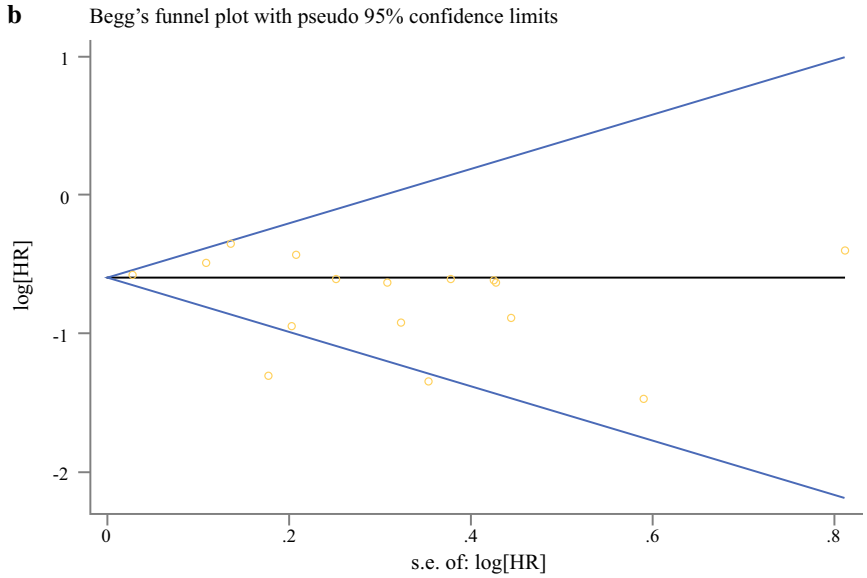


FIG. 3 **a** The random-effects sensitivity analysis of overall survival. **b** Begg's funnel plot and Egger's test evaluating the publication bias regarding overall survival in the meta-analysis

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>| t |	[95% Conf.	Interval]
slope	-.5554268	.0430522	-12.90	0.000	-.6477645	-.463089
bias	-.6750422	.4340048	-1.56	0.142	-1.60589	.2558056

Finally, the analysis had a relatively high level of heterogeneity, which we presume may be attributed to the blending of both potentially resectable and locally advanced digestive cancers, as well as different cancer types, pathologic types, and therapy regimens in the included studies. However, the major strengths of our work were the confirmation of pCR as favorable prognostic information for digestive cancer patients treated with NAT and the impressively reduced risk of death recorded in the multivariate analysis among 21 studies with more than 6000 patients included.

CONCLUSION

The findings of our meta-analysis substantiate the favorable prognostic value of pCR for long-term outcomes of digestive cancer patients receiving NAT. It is anticipated that the clinical outcomes for digestive cancer patients will be further improved with continuous research progress in increasing the pCR rate.

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CONFLICT OF INTEREST There are no conflicts of interest.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68:7–30.
2. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin.* 2017;67:177–93.
3. Hsu PK, Chen HS, Liu CC, et al. Pre-versus postoperative chemoradiotherapy for locally advanced esophageal squamous cell carcinoma. *J Thorac Cardiovasc Surg.* 2017;154:732–40;e732.
4. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol.* 2012;30:1926–33.
5. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol.* 2011;12:681–92.
6. Cho H, Nakamura J, Asaumi Y, et al. Long-term survival outcomes of advanced gastric cancer patients who achieved a pathological complete response with neoadjuvant chemotherapy: a systematic review of the literature. *Ann Surg Oncol.* 2015;22:787–92.
7. de Campos-Lobato LF, Stocchi L, da Luz Moreira A, et al. Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence. *Ann Surg Oncol.* 2011;18:1590–8.
8. Dossa F, Acuna SA, Rickles AS, et al. (2018) Association between adjuvant chemotherapy and overall survival in patients with rectal cancer and pathological complete response after neoadjuvant chemotherapy and resection. *JAMA.* 4:930–7.
9. Mansour JC, Tang L, Shah M, et al. Does graded histologic response after neoadjuvant chemotherapy predict survival for completely resected gastric cancer? *Ann Surg Oncol.* 2007;14:3412–8.
10. Hatogai K, Fujii S, Kojima T, et al. Prognostic significance of tumor regression grade for patients with esophageal squamous cell carcinoma after neoadjuvant chemotherapy followed by surgery. *J Surg Oncol.* 2016;113:390–6.
11. Smyth EC, Fassan M, Cunningham D, et al. Effect of pathologic tumor response and nodal status on survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial. *J Clin Oncol.* 2016;34:2721–7.
12. McCoy MJ, Hemmings C, Hillery S, et al. Neoadjuvant chemoradiotherapy for rectal cancer: how important is tumour regression? *ANZ J Surg.* 2017;87:E233–9.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8:336–41.
14. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials.* 2007;8:16.
15. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Brit Med J.* 2003;327:557–60.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials.* 2015;45(Pt A):139–45.
17. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Brit Med J.* 1997;315:629–34.
18. Brucher BL, Becker K, Lordick F, et al. The clinical impact of histopathologic response assessment by residual tumor cell quantification in esophageal squamous cell carcinomas. *Cancer.* 2006;106:2119–27.
19. Miyata H, Yamasaki M, Takiguchi S, et al. Pre- and post-therapy nodal status equally affects survival of patients with oesophageal squamous cell carcinoma receiving preoperative chemoradiation. *Oncol Rep.* 2010;23:1331–7.
20. Tong DK, Law S, Kwong DL, Chan KW, Lam AK, Wong KH. Histological regression of squamous esophageal carcinoma assessed by percentage of residual viable cells after neoadjuvant chemoradiation is an important prognostic factor. *Ann Surg Oncol.* 2010;17:2184–92.
21. Orditura M, Galizia G, Morgillo F, et al. Complete response to preoperative chemoradiation and survival in esophageal cancer: a pooled analysis of three single-institution phase II trials. *Dis Esophagus.* 2012;25:130–6.
22. Donohoe CL, O'Farrell NJ, Grant T, et al. Classification of pathologic response to neoadjuvant therapy in esophageal and junctional cancer: assessment of existing measures and proposal of a novel 3-point standard. *Ann Surg.* 2013;258:784–92; **discussion 792**.
23. Wang CC, Cheng JC, Tsai CL, et al. Pathological stage after neoadjuvant chemoradiation and esophagectomy superiorly predicts survival in patients with esophageal squamous cell carcinoma. *Radiother Oncol.* 2015;115:9–15.
24. Alnaji RM, Du W, Gabriel E, et al. Pathologic complete response is an independent predictor of improved survival following neoadjuvant chemoradiation for esophageal adenocarcinoma. *J Gastrointest Surg.* 2016;20:1541–46.
25. Blum Murphy M, Xiao L, Patel VR, et al. Pathological complete response in patients with esophageal cancer after the trimodality approach: the association with baseline variables and survival: the University of Texas MD Anderson Cancer Center experience. *Cancer.* 2017;123:4106–13.
26. Hamai Y, Hihara J, Emi M, et al. Preoperative prediction of a pathologic complete response of esophageal squamous cell carcinoma to neoadjuvant chemoradiotherapy. *Surgery.* 2018;164:40–48.
27. Xi M, Yang Y, Zhang L, et al. Multi-institutional analysis of recurrence and survival after neoadjuvant chemoradiotherapy of esophageal cancer: impact of histology on recurrence patterns and outcomes. *Ann Surg.* 2018. https://doi.org/10.1097/SLA.0000000000002670.
28. Ott K, Rachakonda PS, Panzram B, et al. DNA repair gene and MTHFR gene polymorphisms as prognostic markers in locally advanced adenocarcinoma of the esophagus or stomach treated with cisplatin and 5-fluorouracil-based neoadjuvant chemotherapy. *Ann Surg Oncol.* 2011;18:2688–98.
29. Koh YW, Park YS, Ryu MH, et al. Postoperative nodal status and diffuse-type histology are independent prognostic factors in resectable advanced gastric carcinomas after preoperative chemotherapy. *Am J Surg Pathol.* 2013;37:1022–9.
30. Lorenzen S, Thuss-Patience P, Al-Batran SE, et al. Impact of pathologic complete response on disease-free survival in patients with esophagogastric adenocarcinoma receiving preoperative docetaxel-based chemotherapy. *Ann Oncol.* 2013;24:2068–73.
31. Chan AK, Wong A, Jenken D, Heine J, Buie D, Johnson D. Posttreatment TNM staging is a prognostic indicator of survival and recurrence in tethered or fixed rectal carcinoma after preoperative chemotherapy and radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005;61:665–77.

32. Topova L, Hellmich G, Puffer E, et al. Prognostic value of tumor response to neoadjuvant therapy in rectal carcinoma. *Dis Colon Rectum.* 2011;54:401–11.
33. Mace AG, Pai RK, Stocchi L, Kalady MF. American Joint Committee on Cancer and College of American Pathologists regression grade: a new prognostic factor in rectal cancer. *Dis Colon Rectum.* 2015;58:32–44.
34. De Felice F, Musio D, Magnante AL, et al. disease control, survival, and toxicity outcome after intensified neoadjuvant chemoradiotherapy for locally advanced rectal cancer: a single-institution experience. *Clin Colorect Cancer.* 2016;15:e17–22.
35. Wasmuth HH, Rekstad LC, Trano G. The outcome and the frequency of pathological complete response after neoadjuvant radiotherapy in curative resections for advanced rectal cancer: a population-based study. *Colorect Dis.* 2016;18:67–72.
36. Wilkins S, Haydon A, Porter I, et al. Complete pathological response after neoadjuvant long-course chemoradiotherapy for rectal cancer and its relationship to the degree of t3 mesorectal invasion. *Dis Colon Rectum.* 2016;59:361–8.
37. Suzuki T, Sadahiro S, Tanaka A, et al. A modified classification of prognostic factors based on pathological stage and tumor regression grade in patients with rectal cancer who receive preoperative chemoradiotherapy. *Oncology.* 2017;93:287–94.
38. He J, Blair AB, Groot VP, et al. (2018) Is a pathological complete response following neoadjuvant chemoradiation associated with prolonged survival in patients with pancreatic cancer? *Ann Surg.* 268:1–8.
39. Sung JJ, Ng EK, Lin JT, et al. Digestive cancer management in Asia: position statements: a report on GI Oncology Summit in 2011. *J Gastroenterol Hepatol.* 2012;27:1417–22.
40. Sherman KL, Merkow RP, Shah AM, Wang CE, Bilimoria KY, Bentrem DJ. Assessment of advanced gastric cancer management in the United States. *Ann Surg Oncol.* 2013;20:2124–31.
41. Pasini F, de Manzoni G, Zanoni A, et al. Neoadjuvant therapy with weekly docetaxel and cisplatin, 5-fluorouracil continuous infusion, and concurrent radiotherapy in patients with locally advanced esophageal cancer produced a high percentage of long-lasting pathological complete response: a phase 2 study. *Cancer.* 2013;119:939–45.
42. Al-Batran SE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: the AIO-FLOT3 Trial. *JAMA Oncol.* 2017;3:1237–44.
43. Jang JY, Han Y, Lee H, et al. (2018) Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. *Ann Surg.* 268:215–22.
44. Onaitis MW, Noone RB, Hartwig M, et al. Neoadjuvant chemoradiation for rectal cancer: analysis of clinical outcomes from a 13-year institutional experience. *Ann Surg.* 2001;233:778–85.
45. Foxtrot Collaborative G. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. *Lancet Oncol.* 2012;13:1152–60.
46. Garces CA, McAuliffe PF, Hochwald SN, Cance WG. Neoadjuvant therapy in the treatment of solid tumors. *Curr Probl Surg.* 2006;43:457–551.
47. Trimble EL, Ungerleider RS, Abrams JA, et al. Neoadjuvant therapy in cancer treatment. *Cancer.* 1993;72(11 Suppl):3515–24.
48. Pucciarelli S, Toppan P, Friso ML, et al. Complete pathologic response following preoperative chemoradiation therapy for middle to lower rectal cancer is not a prognostic factor for a better outcome. *Dis Colon Rectum.* 2004;47:1798–807.
49. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384:164–72.
50. Houssami N, Macaskill P, von Minckwitz G, Marinovich ML, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. *Eur J Cancer.* 2012;48:3342–54.
51. Kong X, Moran MS, Zhang N, Haffty B, Yang Q. Meta-analysis confirms achieving pathological complete response after neoadjuvant chemotherapy predicts favourable prognosis for breast cancer patients. *Eur J Cancer.* 2011;47:2084–90.
52. Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Vavassori I, Barni S. Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. *Eur Urol.* 2014;65:350–7.
53. Garcia M, Martinez-Villacampa M, Santos C, et al. Phase II study of preoperative bevacizumab, capecitabine and radiotherapy for resectable locally advanced rectal cancer. *BMC Cancer.* 2015;15:59.
54. Xiao J, Chen Z, Li W, et al. Sandwich-like neoadjuvant therapy with bevacizumab for locally advanced rectal cancer: a phase II trial. *Cancer Chemother Pharmacol.* 2015;76:21–7.
55. Badakhshi H, Ismail M, Boskos C, Zhao K, Kaul D. The role of concomitant radiation boost in neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Anticancer Res.* 2017;37:3201–5.
56. Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M. An interval > 7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. *Ann Surg Oncol.* 2008;15:2661–7.