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Chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: Pooled analysis of the CAO/ARO/AIO-12 and the OPRA randomized phase 2 trials

Emmanouil Fokas[a,b,c,d,e,*,1], Hannah Williams[f,1], Markus Diefenhardt[a,b,c,d], Sabrina Lin[g], Li-Xuan Qin[g], Pompiliu Piso[h], Hendrik Dapper[e], Christoph-Thomas Germer[i], Robert Grützmann[j], J. Tim Friede[k], J. Joshua Smith[f], Leonard B. Saltz[l], Abraham J. Wu[m], Martin R. Weiser[f], Dana Omer[n], Michael Ghadimi[o], Ralf-Dieter Hofheinz[p], Julio Garcia-Aguilar[f,2], Claus Rödel[a,b,c,d,2], on behalf of the German Rectal Cancer Study Group and the OPRA Consortium

[a] Department of Radiotherapy and Oncology, University of Frankfurt, Germany
[b] German Cancer Consortium (DKTK), Partner Site: Frankfurt, Germany
[c] German Cancer Research Center (DKFZ), Partner Site: Frankfurt, Heidelberg, Germany
[d] Frankfurt Cancer Institute, Frankfurt, Germany
[e] Department of Radiation Oncology, Cyberknife and Radiotherapy, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD), Faculty of Medicine Cologne, University Hospital Cologne, Cologne, Germany
[f] Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[g] Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[h] Department of General and Visceral Surgery, Barmherzige Brüder Hospital, 93049 Regensburg, Germany
[i] Department of General and Visceral Surgery, University of Würzburg, Germany
[j] Department of General and Visceral Surgery, University of Erlangen-Nürnberg, Germany
[k] Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany
[l] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[m] Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[n] Surgery Residency Program, Hackensack Meridian School of Medicine, Hackensack, NJ, USA
[o] Department of General and Visceral Surgery, University Medical Center Göttingen, Germany
[p] Department of Medical Oncology, University Hospital Mannheim, Germany

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SUMMARY

Background: Total neoadjuvant therapy (TNT) has been used for patients with locally advanced rectal cancer. The optimal sequence of chemoradiotherapy (CRT) and chemotherapy (CT) is a matter of debate.

Methods: We performed a pooled analysis of the CAO/ARO/AIO-12 and OPRA multicenter, randomized phase 2 trials to identify patient subsets that could benefit from one TNT sequence over the other regarding disease-free survival (DFS). Patients with stage II/III rectal cancer were randomized to CRT (50.4–54 Gy) with either induction (INCT-CRT) or consolidation CT (CRT-CNCT) with fluorouracil, leucovorin, oxaliplatin (CAO/ARO/AIO-12 and OPRA) or capecitabine and oxaliplatin (OPRA) followed by mandatory total mesorectal excision (TME) (CAO/ARO/AIO-12) or selective watch-and-wait surveillance (OPRA). 311 and 324 patients were recruited from June 15, 2015 to January 31, 2018; and from April 12, 2014 to March 30, 2020 in the two trials, respectively. Pretreatment clinical and tumor characteristics included were age, sex, ECOG, cT-category, cN-category, clinical UICC stage, location from anal verge, and tumor grade.

Findings: In total, 628 eligible patients were included in the pooled analysis (CAO/ARO/AIO-12, n = 304; OPRA, n = 324). Of those, 313 were randomly assigned to the INCT-CRT group, and 315 to the CRT-CNCT group.

* Correspondence to: Department of Radiation Oncology, Cyberknife and Radiotherapy, University of Cologne, Kerpener Straße 62, Building 3, 50937 Cologne, Germany.

E-mail address: emmanouil.fokas@uk-koeln.de (E. Fokas).

[1] joint first authors
[2] joint last authors

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Median follow-up was 43 months (IQR, 35–49) months in the CAO/ARO/AIO-12 trial and 61,2 months (IQR, 42–68,4) in the OPRA trial. Pooled analysis of baseline clinical and tumor characteristics did not identify any subgroups of patients that would benefit by the one TNT sequence over the other with regard to DFS.
Interpretation: To our knowledge, this is the first pooled analysis of two randomized trials after direct head-to-head comparison of both TNT sequences. Both trials reported higher rates of complete response with CRT-CNCT, and this should be considered the preferred TNT sequence if organ preservation is a priority.

1. Introduction

Total neoadjuvant therapy (TNT) delivers chemoradiotherapy (CRT) or short-course radiotherapy (SCRT) and chemotherapy (CT) before surgery (or non-operative management, NOM), and has been increasingly adopted for rectal cancer treatment [1–4]. Two TNT sequences have emerged, that is induction CT (INCT) followed by CRT/SCRT, and CRT/SCRT followed by consolidation CT (CNCT)[5]$^{-85-85-85-85-82}$, [6–9]. A head-to-head comparison of both TNT sequences has only been investigated in the CAO/ARO/AIO-12 [10,11] and the OPRA [12,13] randomized phase 2 trials. In these studies, CRT-CNCT resulted in higher pathologic complete response (pCR)/clinical complete response (cCR) rates, and organ preservation (TME-free survival) compared to INCT-CRT. On the other hand, INCT introduces early systemic treatment of micrometastases and may facilitate selective CRT omission based on treatment response, as recently demonstrated in the PROSPECT trial [14,15].

As such, the optimal sequence of CRT and CT remains a matter of debate in the scientific community. The present study pools the data from the CAO/ARO/AIO-12 and OPRA trials to identify patient subgroups that could potentially benefit from the one TNT sequence over the other with respect to disease-free survival (DFS).

2. Patients and methods

2.1. Patient selection, treatment and objectives

The CAO/ARO/AIO-12 and the OPRA trials were multicenter, randomized, phase 2 trials (ClinicalTrials.gov, NCT02363374 and NCT02008656, respectively) [10–13]. The inclusion criteria and the TNT schedules (INCT-CRT and CRT-CNCT) for each trial have been previously reported and are provided in the **Supplementary Methods.** The ethics committees of the University of Frankfurt and MSKCC approved the studies. All patients signed a consent.

The primary endpoints, pCR and DFS of the CAO/ARO/AIO-12 and OPRA trials, respectively, have been previously reported [10–13]. DFS was defined as the time from randomization to the occurrence of one of the following events: no resection of primary tumor owing to local disease progression or the patient being unfit for surgery; nonradical (R2) resection of the primary tumor; locoregional recurrence after R0/1 resection of the primary tumor; non-salvageable local regrowth (no operation or only R2 salvage resection possible) in patients undergoing nonoperative management; development of distant metastatic disease at any time; a second primary other cancer; death from any cause.

2.2. Statistical analysis

Wilcoxon rank sum test and Fisher's exact test were used to compare the baseline characteristics between the two TNT groups (**shown in** Table 1). Exploratory subgroup analysis looking at the association between treatment arm and DFS in the present pooled study of the CAO/ARO/AIO-12 and OPRA trials is shown in a forest plot. The analysis utilized Cox regression models with the study included as a stratification variable to account for any potential differences between the two trials.

Prior to the subgroup analysis assessing the association between treatment arm and DFS (**shown in** Figure 1), univariable and multivariable Cox regression models for DFS were performed. In particular, to take into account any potential differences between the two trials, the study is included as a stratification variable in the Cox regression models; covariates that are clinically relevant or were statistically significant in the univariable setting were selected for the multivariable Cox models (**shown in** Table 2). For exploratory purposes, a multivariable model that includes both the main effects and an interaction term for treatment arm and cT stage were built. The interaction term represents the change in the hazard ratio for treatment arm on DFS between the two non-reference categories of cT stage (**shown in** Table 3**)**.

All analyses were conducted using R version 4.3.2 with the tidyverse (v2.0.0), gtsummary (v1.7.2), survival (v3.5.7) and ggsurvfit (v1.0.0) packages (R Core Team 2021). A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Accrual and patient characteristics

The CAO/ARO/AIO-12 trial recruited 311 patients from June 15, 2015, to January 31, 2018, and the OPRA trial recruited 324 patients from April 12, 2014 to March 30, 2020 (CONSORT diagrams shown in **Supplementary Figures 1–2**). A total of 628 patients (n = 304 [CAO/ARO/AIO-12], n = 324 [OPRA]) were eligible for inclusion in the present pooled analysis. Of those, 313 received INCT-CRT, and 315 CRT-

Table 1
Baseline clinical and tumor characteristics in the pooled analysis of the CAO/ARO/AIO-12 and OPRA trials.

Characteristics	N	Induction,N = 313[1]	Consolidation,N = 315[1]	p-value[2]
Age	628	60 (53, 68)	59 (51, 68)	0.7
Gender	628			0.5
Male		208 (66 %)	201 (64 %)	
Female		105 (34 %)	114 (36 %)	
ECOG Performance Status	621			0.11
0		232 (75 %)	217 (69 %)	
1 and 2		76 (25 %)	96 (31 %)	
Unknown		5	2	
cT category	628			0.3
cT1 −2		16 (5.1 %)	25 (7.9 %)	
cT3		256 (82 %)	244 (77 %)	
cT4		41 (13 %)	46 (15 %)	
cN category	621			0.8
N0		62 (20 %)	61 (19 %)	
N +		245 (80 %)	253 (81 %)	
Unknown		6	1	
TNM stage	621			0.8
Stage II		62 (20 %)	61 (19 %)	
Stage III		245 (80 %)	253 (81 %)	
Unknown		6	1	
Tumor Distance from AV (cm)	618	5.00 (3.50, 8.00)	5.00 (3.50, 8.00)	0.6
Unknown		8	2	
Grade of tumor differentiation	628			0.8
Low Grade (G1 −2)		265 (85 %)	263 (83 %)	
High Grade (G3)		17 (5.4 %)	16 (5.1 %)	
Not Reported or Missing Data		31 (9.9 %)	36 (11 %)	

[1] Median (IQR); n (%)
[2] Wilcoxon rank sum test; Fisher's exact test

CNCT. Table 1 shows the baseline demographic and tumor characteristics of the pooled cohort. There were no significant differences in the baseline characteristics between the two treatment groups. The median follow-up in the two trials was 43 months (IQR, 35–49) and 61,2 months (IQR, 42–68,4), respectively.

3.2. Treatment effect analysis

Subgroup analyses of DFS in the intention-to-treat population according to baseline characteristics did not identify subsets of patients that significantly benefited from one TNT sequence over the other (Figure 1).

To further explore whether there was a relationship between TNT arm and cT-category, multivariable models with interaction terms between TNT arm and the cT-category were built for DFS. Of note, covariates in the model were either covariates of clinical interest or were statistically significant in the univariable setting (Table 2**).** Although patients with cT4 tumors had significantly worse DFS in the univariable setting (p = 0.047; Table 2), we failed to identify any significant interaction of the TNT arm with any of the baseline characteristics for DFS (Table 3).

4. Discussion

The CAO/ARO/AIO-12 demonstrated that CRT-CNCT followed by TME exhibited a higher pCR rate when compared to INCT-CRT without any significant differences in oncological endpoints [10,11]. The OPRA used similar TNT regimens with more CT cycles and offered NOM to patients with a clinical complete or near complete response to treatment [12,13]. With a median follow-up of 5.1 years, TME-free survival was 39% and 54% in the INCT-CRT and the CRT-CNCT groups, respectively (P = 0.012), with a similar 5-year DFS (71% and 69%; P = 0.68). Hence, TNT with upfront CRT resulted in better pCR (CAO/ARO/AIO-12) or sustained cCR/organ preservation (OPRA).

As the sequence of (C)RT with CT as part of TNT remains a matter of controversy, we conducted a pooled analysis of the CAO/ARO/AIO-12 and OPRA trials to determine whether specific subgroups of patients may benefit from one TNT sequence over the other with respect to the clinically important endpoint DFS. Given the better compliance and earlier onset of effective systemic treatment with INCT-CRT, we hypothesized that this sequence may be superior for patients with lymph node positive disease. In contrast, the early onset and improved compliance of effective local treatment with CRT-CNCT may be beneficial for locally advanced (cT4) tumors. However, we failed to identify any patient subsets that derived a DFS benefit from one TNT sequence over the other.

Thus, the choice of TNT sequence should be guided by the ultimate treatment goal. In the PRODIGE23 phase 3 trial, TNT with INCT-CRT using FOLFIRINOX followed by mandatory TME and adjuvant CT resulted in significant improvement of 3-year DFS compared to the standard of care (CRT followed by TME and adjuvant CT) (76% vs 69%; P = .034) [16]. The 7-year follow-up reported superior DFS (67.6% vs. 62.5%; P = 0.048) and OS (81.9 vs 76.1 months, P = 0.033) based on the restricted median survival time (RMST) method [17]. Furthermore, INCT may facilitate selective CRT omission based on treatment response, in patients with intermediate risk rectal cancer as shown in the PROSPECT trial [14,15]. Conversely, for patients prioritizing organ preservation, CRT-CNCT may be the preferred TNT approach.

Our pooled analysis has limitations. First, despite the large patient number included, our pooled analysis was exploratory. Second, although both trials directly compared the two TNT sequences, in the CAO/ARO/AIO-12 only 41% of tumors were 0–5 cm, and 10% 10–15 cm from the anal verge. The OPRA trial included more CT cycles and longer waiting interval before tumor response reassessment compared to the CAO/ARO/AIO-12 trial (34 vs 18 weeks). Third, some pretreatment MRI-based risk-factors such as cT3-subcategory, mesorectal facia involvement or extramural venous invasion were not available from all patients for this pooled analysis.

In summary, the present pooled analysis of the CAO/ARO/AIO-12 and the OPRA trials failed to identify any patient subgroups benefiting significantly from one TNT sequence over the other and showed similar DFS. Upfront CRT followed by consolidation CT should be the preferred TNT sequence if organ preservation is a priority. We propose that treatment goals (e.g., adoption of selective CRT schedules, mandatory TME surgery, intended organ preservation), along with patient-centered decision-making, rather than pretreatment characteristics should guide

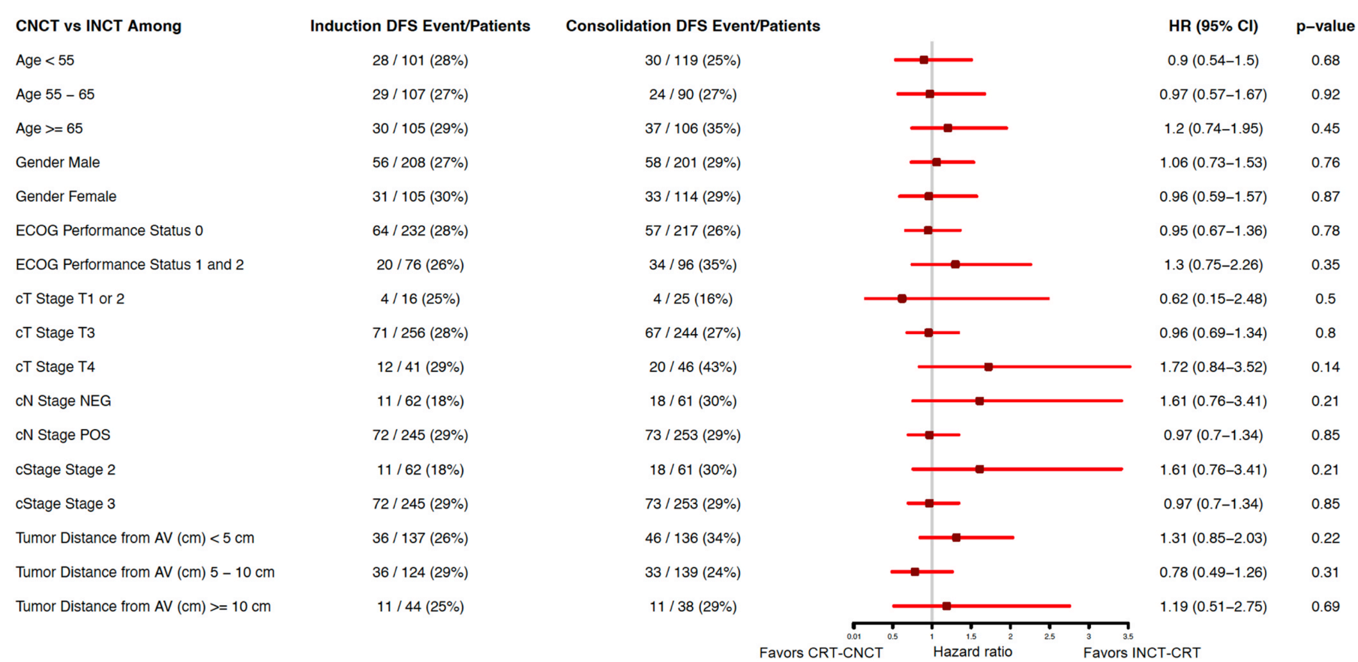

Fig. 1. Forest plot of the effect of treatment on disease-free survival (DFS) according to pretreatment characteristics in the pooled analysis of the CAO/ARO/AIO-12 and OPRA trials. Abbreviations: DFS, disease free survival; HR, Hazard Ratio; CI, Confidence Interval; INTCT, induction chemotherapy; CRT, chemoradiotherapy; CNCT, consolidation chemotherapy.

the preferred TNT sequence.

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CRediT authorship contribution statement

Robert Grützmann: Writing – review & editing, Investigation. **Christoph Thomas Germer:** Writing – review & editing, Investigation. **Claus Rödel:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Joshua Smith:** Writing – review & editing, Investigation, Conceptualization. **Tim Friede:** Writing – review & editing, Methodology. **Michael Ghadimi:** Writing – review & editing, Investigation. **Hendrik Dapper:** Writing – review & editing, Investigation. **Julio Garcia Aguilar:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Pompiliu Piso:** Writing – review & editing, Investigation. **Ralf Dieter Hofheinz:** Writing – review & editing, Resources, Methodology, Investigation. **Li-Xuan Qin:** Project administration, Methodology, Formal analysis, Data curation. **Hannah Williams:** Writing – review & editing, Validation, Software, Resources, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Abraham Wu:** Writing – review & editing, Resources, Investigation. **Emmanouil Fokas:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Leonard Saltz:** Writing – review & editing, Resources, Project administration, Investigation. **Sabrina Lin:** Methodology, Formal analysis. **Dana Omer:** Writing – review & editing, Investigation. **Markus Diefenhardt:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Martin Weiser:** Writing – review & editing, Resources, Investigation.

Declaration of Competing Interest

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Table 3
Multivariable model of treatment type and clinical covariates for DFS.

Characteristic	N	Event N	HR	95 % CI	p-value
TNT Treatment Arm	621				
INTCT-CRT		83	—	—	
CRT-CNCT		91	0.61	0.15, 2.45	0.5
cT category	621				
cT1 −2		8	—	—	
cT3		135	1.27	0.46, 3.51	0.6
cT4		31	1.27	0.40, 4.01	0.7
cN category	621				
cN0		29	—	—	
cN+		145	1.37	0.90, 2.07	0.14
TNT Treatment Arm * cT category	621	174			
CRT-CNCT * cT3		67	1.61	0.39, 6.71	0.5
CRT-CNCT * cT4		20	3.07	0.64, 14.8	0.2

Abbreviations: DFS, Disease Free Survival; HR, Hazard Ratio; CI, Confidence Interval; INTCT, induction chemotherapy; CRT, chemoradiotherapy; CNCT, consolidation chemotherapy
*The interaction term represents the change in the hazard ratio for treatment type on DFS between the two non-reference categories of cT.

Table 2
Univariable and multivariable Cox regression models analyses for DFS.

Characteristic	Univariable					Multivariable				
	N	Event N	HR[1]	95 % CI[1]	p-value	N	Event N	HR[1]	95 % CI[1]	p-value
Age	628	178	1.00	0.99, 1.01	> 0.9					
Gender	628	178								
Male			—	—						
Female			1.09	0.80, 1.48	0.6					
TNT Treatment Arm	628	178				611	169			
INTCT-CRT			—	—				—	—	
CRT-CNCT			1.03	0.77, 1.39	0.8			1.11	0.82, 1.51	0.5
ECOG Performance Status	621	175								
0			—	—						
1 and 2			1.21	0.88, 1.67	0.2					
cT category	628	178				611	169			
cT1 −2			—	—				—	—	
cT3			1.54	0.75, 3.15	0.2			1.66	0.80, 3.44	0.2
cT4			2.21	1.01, 4.81	**0.047**			2.13	0.96, 4.75	0.063
cN category	621	174				611	169			
cN0			—	—				—	—	
cN+			1.29	0.85, 1.95	0.2			1.47	0.95, 2.26	0.081
TNM stage	621	174								
Stage II			—	—						
Stage III			1.29	0.85, 1.95	0.2					
Tumor Distance from AV (cm)	618	173	0.97	0.92, 1.03	0.3	611	169	0.97	0.92, 1.03	0.3

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EF, HW, MD, SL, LXQ, JGA and CR conceived the idea, conducted the analysis, had full access to all the data in the study and take responsibility for the integrity and the accuracy of the present pooled analysis. All authors contributed to writing or review of the manuscript, and approved the final manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114291.

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