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ORIGINAL ARTICLE

Upfront resection versus no resection of the primary tumor in patients with synchronous metastatic colorectal cancer: the randomized phase III CAIRO4 study conducted by the Dutch Colorectal Cancer Group and the Danish Colorectal Cancer Group

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Background: Upfront primary tumor resection (PTR) has been associated with longer overall survival (OS) in patients with synchronous unresectable metastatic colorectal cancer (mCRC) in retrospective analyses. The aim of the CAIRO4 study was to investigate whether the addition of upfront PTR to systemic therapy resulted in a survival benefit in patients with synchronous mCRC without severe symptoms of their primary tumor.

Patients and methods: This randomized phase III trial was conducted in 45 hospitals in The Netherlands and Denmark. Eligibility criteria included previously untreated mCRC, unresectable metastases, and no severe symptoms of the primary tumor. Patients were randomized (1 : 1) to upfront PTR followed by systemic therapy or systemic therapy without upfront PTR. Systemic therapy consisted of first-line fluoropyrimidine-based chemotherapy with bevacizumab in both arms. Primary endpoint was OS in the intention-to-treat population. The study was registered at ClinicalTrials.gov, NCT01606098.

Results: Between August 2012 and February 2021, 206 patients were randomized. In the intention-to-treat analysis, 204 patients were included ($n = 103$ without upfront PTR, $n = 101$ with upfront PTR) of whom 116 were men (57%) with median age of 65 years (interquartile range 59-71 years). Median follow-up was 69.4 months. Median OS in the arm without upfront PTR was 18.3 months (95% confidence interval 16.0-22.2 months) compared with 20.1 months (95% confidence interval 17.0-25.1 months) in the upfront PTR arm ($P = 0.32$). The number of grade 3-4 events was 71 (72%) in the arm without upfront PTR and 61 (65%) in the upfront PTR arm ($P = 0.33$). Three deaths (3%) possibly related to treatment were reported in the arm without upfront PTR and four (4%) in the upfront PTR arm.

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Conclusions: Addition of upfront PTR to palliative systemic therapy in patients with synchronous mCRC without severe symptoms of the primary tumor does not result in a survival benefit. This practice should no longer be considered standard of care.

Key words: metastatic colorectal cancer, primary tumor resection, systemic therapy

INTRODUCTION

Approximately 15%-30% of colorectal cancer (CRC) patients present with distant metastases at time of diagnosis.[1,2] Between 55% and 71% of patients with synchronous metastatic CRC (mCRC) have been reported to experience minimal or no symptoms of the primary tumor.[3-5] The question whether an upfront primary tumor resection (PTR) should be carried out in these patients has been extensively debated.[6,7] Multiple retrospective cohort studies and subgroup analyses of prospective randomized studies have indicated that PTR was associated with improved median overall survival (OS) compared with no PTR.[8-11] In contrast, the results of some retrospective analyses did not demonstrate an association between upfront PTR and improved survival,[12,13] and some authors even concluded that PTR is used too frequently in clinical practice.[14]

Since PTR may be associated with morbidity and even mortality,[15] and retrospective data may be hampered by significant selection bias, several randomized studies were initiated, including the CAIRO4 in Denmark and the Netherlands. In this article, we present the results of the primary endpoint of the CAIRO4 study in which patients with synchronous unresectable mCRC without severe symptoms of the primary tumor were randomized to upfront PTR followed by fluoropyrimidine-based chemotherapy plus bevacizumab or fluoropyrimidine-based chemotherapy plus bevacizumab without upfront PTR. An important argument for the use of bevacizumab in this study was the observed interaction between bevacizumab and the primary tumor, with data showing that the presence of the primary tumor provides an angiogenic environment for metastases,[16] as well as a decreased efficacy of bevacizumab.[17,18] The primary aim of the study was to investigate the potential OS benefit of the upfront PTR approach.

METHODS

Study design

The randomized phase III CAIRO4 study initiated (ClinicalTrials.gov identifier NCT01606098) by the Dutch Colorectal Cancer Group and the Danish Colorectal Cancer Group was carried out in 45 hospitals in the Netherlands and Denmark. The study design has previously been published.[19] Main eligibility criteria included an age of $\geq$18 years, histologically confirmed mCRC, unresectable metastases (based on the decision of the local multidisciplinary tumor board), no severe symptoms of the primary tumor, a resectable primary tumor, and an Eastern Cooperative Oncology Group/World Health Organization performance status (PS) 0-2. Patients were excluded if they required neoadjuvant (chemo) radiation for rectal cancer, had a comorbidity affecting the safety or feasibility of the intervention, or had another primary malignancy within 5 years before the randomization. The protocol was amended in 2013 to allow the inclusion of rectal cancer patients who had no indication for neoadjuvant treatment.

The study was conducted in accordance with the Declaration of Helsinki and was approved by both the Medical Research Ethics Committee (Arnhem-Nijmegen, 16 May 2012, registration number: 2011/391, 38155.091.11) and local institutional review boards. Written informed consent was requested from all patients before study entry. Data monitoring and data registration were conducted by the Netherlands Comprehensive Cancer Organisation.

Randomization and masking

Patients were centrally randomized (1 : 1) to first-line fluoropyrimidine-based chemotherapy plus bevacizumab with or without upfront PTR, including the addition of irinotecan or oxaliplatin at the discretion of the local investigator. Randomization was carried out using a minimization technique with stratification according to serum lactate dehydrogenase [LDH: normal versus $>$ upper limit of normal (ULN)], metastatic sites (one versus more), PS (0-1 versus 2), and institution. The protocol was amended in 2017 to include primary tumor sidedness (right-sided versus left-sided) as a stratification factor. Investigators, patients, physicians, and data managers were aware of the assigned treatment.

Procedures

In the systemic therapy arm without upfront PTR (henceforth referred to as arm without upfront PTR), patients were allocated to receive first-line fluoropyrimidine-based chemotherapy with bevacizumab within 4 weeks after randomization. These patients only received PTR when necessitated by symptoms of the primary tumor that occurred during follow-up. In the upfront PTR arm followed by systemic therapy (henceforth referred to as upfront PTR) patients were scheduled to undergo PTR within 4 weeks after randomization. Not earlier than 4 weeks after PTR, patients were scheduled to receive first-line fluoropyrimidine-based chemotherapy with bevacizumab. Systemic therapy was continued until disease progression or unacceptable toxicity. Subsequent salvage treatment was left to the discretion of the treating physician. Patients were evaluated by computed tomography scan every 8-9 weeks for clinical response on treatment according to RECIST version 1.1 criteria, or at any other time point when progression was suspected. Grade 3-4 adverse events (AEs)

occurring up to 30 days following the last administration of any of the study interventions were registered. Serious AEs in the upfront PTR arm were reviewed centrally by the study coordinators (MK, JdW).

Outcomes

Primary endpoint was OS, defined as time between randomization and death from any cause. The analysis of the primary endpoint is a confirmatory analysis. The previously published 60-day mortality analysis should be considered as exploratory.[20] Secondary endpoints included progression-free survival (PFS, defined as time between randomization and progression on systemic treatment or death from any cause), time to initiation of systemic treatment, grade 3-4 AEs (classified according to the Common Terminology Criteria for Adverse Events version 4.0[21]), and any subsequent treatment.

Sample size

We estimated that a total of 360 patients would be required to detect a difference in median OS of 13 versus 19 months in the treatment arm without versus with upfront PTR, respectively, with 80% power based on an accrual period of 30 months.[19] Since accrual was slower than expected, the protocol was amended in 2018 to reduce the sample size to 206 patients. This new sample size calculation was based on 189 required events and a power of 74% (two-sided significance level of 5%). In August 2022 the total number of observed events was 181, corresponding to a power of 71% for detection of the increase in OS from 13 to 19 months, which was considered acceptable as it was only slightly lower than the 74% mentioned in the most recent sample size calculation. Weighing the options of waiting longer or stopping the trial, we decided to stop the trial as waiting for the other eight events (in the remaining 25 survivors) would likely have resulted in trial outcomes losing their relevance.

Statistical analysis

All analyses were prespecified in the statistical analysis plan, unless indicated otherwise. We analyzed the primary endpoint OS and the secondary endpoint PFS in the intention-to-treat population. Subsequently, the same endpoints were investigated in the per protocol population as a sensitivity analysis, which was defined as the group of patients in whom the randomized treatment was actually initiated. Since a violation of the proportional hazards assumption was expected due to perioperative complications and a potential beneficial effect of PTR on OS in the long term, the Max-Combo test was used as the primary analysis method for comparing survival outcomes between treatment arms.[22] Survival over time was visualized using Kaplan—Meier curves. As prespecified, the aforementioned analyses for OS were also carried out separately for the following prespecified subgroups defined by: number of affected organs by metastatic disease (1 versus >1), location of the site of metastatic disease [liver-only versus extrahepatic, PS (0.1 versus 2), serum LDH (normal versus ULN)], sex, age (<70 versus ≥70 years), location of the primary tumor (right-sided versus left-sided primary tumor; demarcation at splenic flexure). Cox regression was carried out to estimate the hazard ratio (HR) for treatment arm in both the intention-to-treat population and the per protocol population, adjusting for number of organs affected by metastases, serum LDH, location of the primary tumor, sex, and age. The planned adjustment for PS could not be carried out, due to the very low number of participants with PS of 2. In case of non-proportional hazards, the estimated HR for treatment arm was presented visually over follow-up time. AEs were analyzed in the per protocol population. The median number of systemic therapy cycles was compared using the Mann—Whitney *U* test, which was not prespecified. The Medical Research Ethics Committee approved not carrying out an interim analysis after observing one-third of required events as planned in the initial protocol, as it was no longer considered to be of added value for a safety evaluation because correct interpretation of the results would be impeded by large differences in follow-up period.[23] For all analyses, a two-sided *P* value <0.05 was considered significant. Statistical analyses were carried out in R version 1.4.

RESULTS

Between August 2012 and February 2021, 206 patients were randomized; 103 patients to each arm (31 patients were randomized in Danish and 175 in Dutch hospitals). In the upfront PTR arm, two patients were excluded from the analysis (Figure 1). One patient was excluded due to the absence of measurable metastatic lesions according to RECIST criteria. Another participant was erroneously randomized despite the absence of informed consent. The treatment of five participants deviated from protocol in the arm without upfront PTR and were excluded from the per protocol analysis: one patient insisted to undergo PTR and four patients needed emergency surgery (three PTR and one intestinal bypass) before systemic therapy could be initiated. In the upfront PTR arm, five patients did not receive upfront PTR: one patient suffered from a cerebrovascular event, one patient requested euthanasia, two patients refused PTR, and in one patient the primary tumor was considered irresectable before surgery.

Baseline characteristics were well balanced between the treatment arms in the intention-to-treat population, except for sex (Table 1), with more men being randomized to the upfront PTR arm (64%) compared with the arm without upfront PTR (50%). The majority of the patients in both treatment arms had a PS of 0-1, and had multiple organs affected by metastases. A total of eight patients had rectal cancer.

In the intention-to-treat population of 204 patients, 1 patient (1%) in the arm without upfront PTR did not receive systemic therapy compared with 13 patients (13%) randomized to the upfront PTR arm ($P = 0.0020$, Supplementary Table S1 and Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.06.001).

The patient in the arm without upfront PTR did not receive systemic therapy due to emergency surgery and subsequent poor general condition. In the upfront PTR arm, reasons for not administering systemic therapy were diverse: 10 patients died before systemic therapy could be initiated, 1 patient preferred a watch and wait approach, and 2 experienced rapid progression. The median time until start of systemic therapy in the intention-to-treat population was 7 days [95% confidence interval (CI) 7-9 days] in the arm without upfront PTR and 48 days (95% CI 44-53 days) in the upfront PTR arm ($P < 0.01$). The median number of systemic therapy cycles in the intention-to-treat population was 11 cycles [interquartile range (IQR) 6-16 cycles] in the arm without upfront PTR versus 10 cycles (IQR 4-14 cycles) in the upfront PTR arm ($P = 0.20$). The median time on first-line systemic therapy was 6.7 months (IQR 4.2-11.3 months) in the arm without upfront PTR and 6.9 months (IQR 2.8-10.6 months) in the upfront PTR arm ($P = 0.37$). Systemic therapy regimens containing bevacizumab were more frequently administered to patients in the arm without upfront PTR during the first systemic therapy cycle compared with patients in the upfront PTR arm (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.06.001). The total exposure to bevacizumab was not significantly different between the two treatment arms: 89 patients (87%) randomized to the arm without upfront PTR were treated with bevacizumab during one or more systemic therapy cycles compared with 80 patients (79%) in the upfront PTR arm ($P = 0.239$). In the upfront PTR arm, a laparoscopic surgical approach was carried out in 72 patients (71%, Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.06.001).

At database lock on 1 September 2023, median follow-up was 69.4 months and the number of events (deaths) was 187. The median OS was 18.3 months (95% CI 16.0-22.2 months) for the patients randomized to the arm without upfront PTR and 20.1 months (95% CI 17.0-25.1 months) for patients randomized to upfront PTR ($P = 0.32$, Max-Combo test, Figure 2A). No subgroups were identified in which PTR resulted in a survival benefit (Figure 3). In the per protocol analysis, data on median OS did not change significantly, with 19.7 months (95% CI 16.8-22.8 months) in the arm without upfront PTR and 21.3 months (95% CI:17.5-25.4 months) in the upfront PTR arm ($P = 0.36$, Supplementary Figure S2 available at https://doi.org/10.1016/j.annonc.2024.06.001). Time-varying HRs indicated that considerable mortality occurred in the first 3 months after PTR compared with the arm without upfront PTR (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2024.06.001). Adjustment for PS as

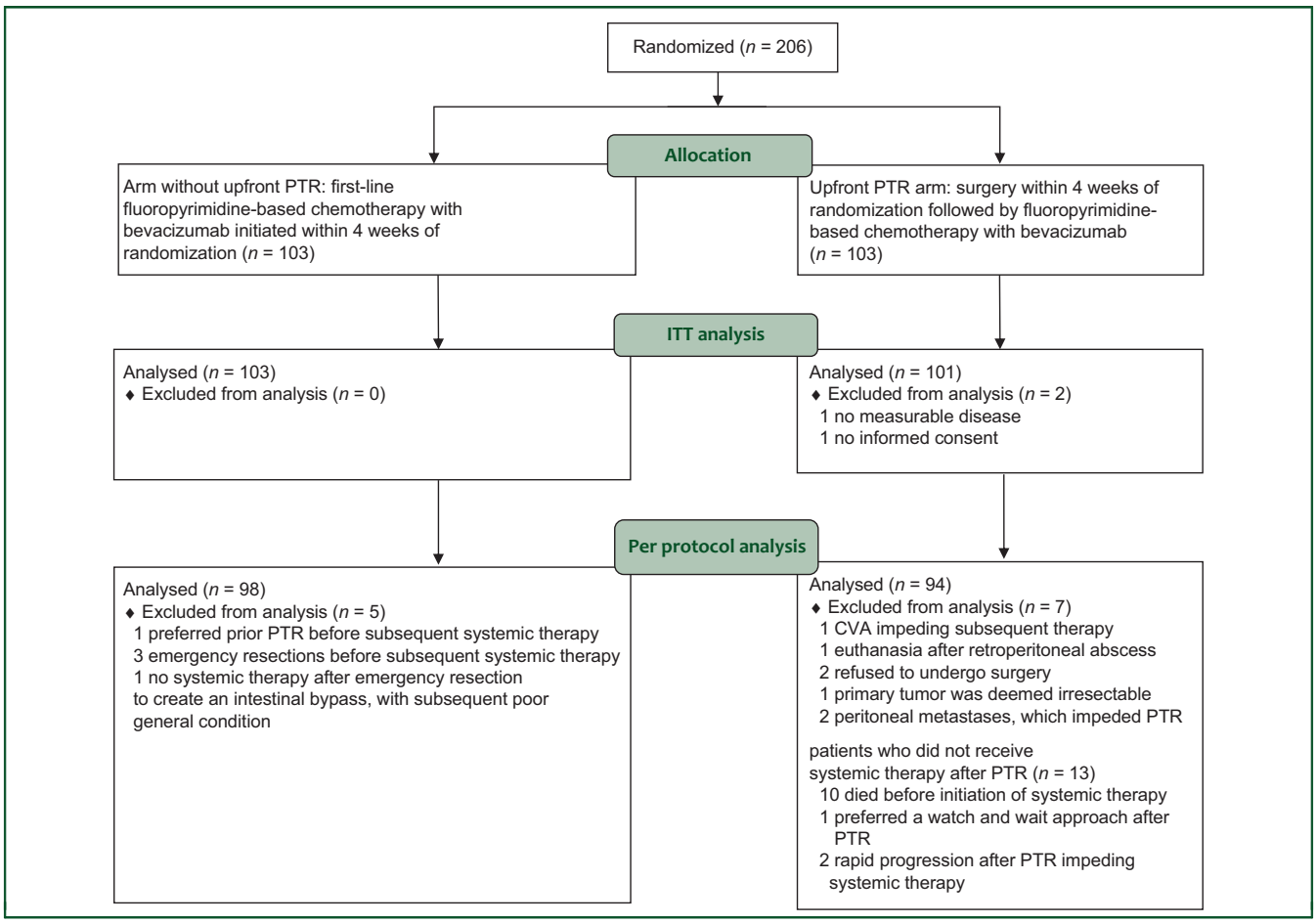

Figure 1. Study flowchart.
CVA, cerebrovascular accident; ITT, intention-to-treat; PTR, primary tumor resection.

Table 1. Baseline characteristics according to intention-to-treat analysis

	Systemic therapy without upfront PTR $N = 103$, n (%)	Upfront PTR followed by systemic therapy $N = 101$, n (%)
Sex		
Male	51 (50)	65 (64)
Female	52 (50)	36 (36)
Age, median, years [IQR]	65 [58-71]	64 [59-71]
WHO performance status		
0-1	101 (98)	99 (98)
2	2 (2)	2 (2)
Location of primary tumor		
Right	49 (48)	53 (52)
Left[a]	54 (52)	48 (48)
>1 Organ affected by metastases	65 (63)	63 (62)
Liver involvement	89 (86)	91 (90)
Liver only disease	27 (26)	31 (31)
Elevated serum LDH[b]	59 (57)	59 (58)
Hemoglobin		
Anemia (<8.6 mmol/l)	79 (77)	77 (76)
Leukocytes		
Elevated (>10 × 10^9/l)	37 (36)	40 (40)
Neutrophils		
Elevated (>8.3 × 10^9/l)	16 (17)	15 (18)
Missing	11	19
Serum albumin		
Hypoalbuminemia (<35 g/l)	10 (12)	20 (23)
Missing	17	14
Serum aspartate transaminase and alanine aminotransferase[c]		
Elevated[d]	41 (40)	45 (45)
Missing	0	1
CEA		
Elevated (>3 µg/l)	88 (93)	81 (91)
Missing	8	12

CEA, carcinoembryonic antigen; IQR, interquartile range; LDH, lactate dehydrogenase; PTR, primary tumor resection; WHO, World Health Organization.
[a]Including eight patients with rectal cancer.
[b]Elevated as defined by the local hospital.
[c]Elevated if aminotransferase was >45 U/l or if aspartate transaminase was >35 U/l.
[d]Maximum of five times the upper limit of normal if liver metastases are present; if no liver metastases were present: a maximum of three times the upper limit of normal was allowed.

prespecified was not carried out because of low numbers with PS 2. Median PFS was 9.7 months (95% CI 8.5-10.8 months) in the arm without upfront PTR compared with 9.9 months (95% CI 8.7-11.7 months) in the upfront PTR arm ($P = 0.67$, Figure 2B). Despite some differences in the use of systemic regimens (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.06.001), no difference in overall response rate was observed between the two treatment arms (Table 2).

In the arm without upfront PTR, four grade 5 events occurred. Two events were likely related to the allocated treatment (perforation of the colon and severe diarrhea), one event was possibly treatment-related (septic shock due to necrotizing fasciitis or abscess after systemic therapy), and one event was not considered related to the allocated systemic therapy (rupture of ascending aortic aneurysm). In the upfront PTR population, five grade 5 events were reported. Four events were likely treatment related (multiorgan failure after PTR, hepatic failure after PTR, cardiac arrest after systemic therapy treatment, and colitis during systemic therapy administration) and one event was not related to the treatment received (non-neutropenic sepsis and pulmonary embolism after systemic therapy).

In the arm without upfront PTR, 71 patients (72%; 95% CI 63% to 80%) experienced at least one grade 3-4 AE related to surgery and/or systemic therapy, compared with 61 patients (65%; 95% CI 55% to 74%) in the upfront PTR arm ($P = 0.33$, Table 3). The grade 3-4 AEs occurring in ≥10% of patients in the arm without upfront PTR were diarrhea (20%), fatigue (15%), hematological toxicity (15%), abdominal pain (13%), hand-foot syndrome (13%), nausea (12%), anorexia (11%), hypertension (11%), and in the upfront PTR arm fatigue (12%), infections (12%), hypertension (11%), neuropathy (10%), and diarrhea (10%).

During follow-up, 13 out of 103 patients (13%, 95% CI 8% to 20%) in the arm without upfront PTR required surgery for symptom palliation: 11 patients (11%; 95% CI 6% to 18%) underwent PTR, of whom 1 patient required PTR due to a perforation at the location of a stent that became broken. In one (1%) patient a loop ileostomy was constructed and one patient required an intestinal bypass (1%). Four patients in the arm without upfront PTR (4%; 95% CI 2% to 10%) required stenting of the colon due to obstruction and three patients (3%; 95% CI 1% to 8%) underwent radiotherapy on the primary tumor for symptom control.

In the arm without upfront PTR, four patients (4%, 95% CI 2% to 10%) underwent subsequent metastasectomy compared with seven patients (7%, 95% CI 3% to 14%) in the upfront PTR arm ($P = 0.51$). All aforementioned patients underwent metastasectomy with curative intent, except for one patient in the PTR arm who underwent debulking with palliative intent. During subsequent treatment lines, 69% of patients randomized to systemic therapy without upfront PTR received a doublet chemotherapy regimen with or without bevacizumab compared with 46% of patients randomized to upfront PTR (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.06.001).

The exposure to specific agents in the subsequent treatment lines that were considered standard of care at the time were comparable in both treatment arms.

DISCUSSION

The results of the CAIRO4 study show that the addition of upfront PTR to first-line fluoropyrimidine-based chemotherapy with bevacizumab has no survival benefit in patients with synchronous mCRC without severe symptoms of their primary tumor. We previously reported, based on an exploratory analysis, that 60-day mortality was considerable in the upfront PTR arm (11% versus 3% in the arm without upfront PTR).[20] This, and the fact that we demonstrated that patients who underwent PTR started on average 41 days later with palliative systemic therapy than patients who received systemic therapy from the beginning, may attribute to lack of benefit of PTR in the current study. Since only 13% in the arm without upfront PTR required surgery

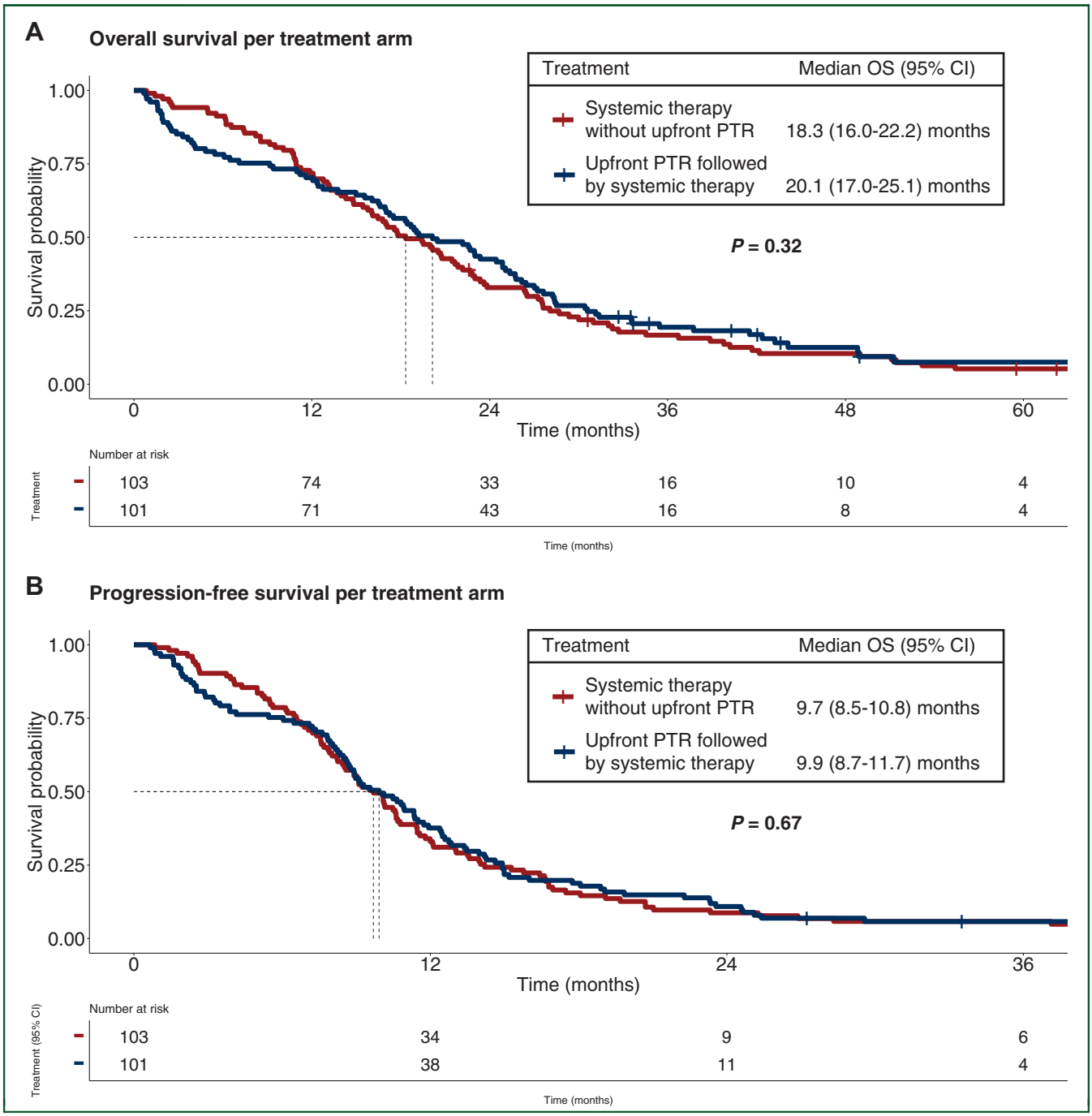

Figure 2. Overall survival (A, primary endpoint of the study) and progression-free survival (B) per treatment arm in the intention-to-treat population. Hazard ratios are not displayed, because the proportional hazards assumption of the cox regression model was violated.
CI, confidence interval; OS, overall survival; PFS, progression-free survival; PTR, primary tumor resection.

for symptom palliation, upfront PTR should not be routinely carried out, as earlier shown by others.[15]

Although it was not a primary objective, and some patients did not receive bevacizumab, our data do not support the beneficial effect of upfront PTR for bevacizumab-containing regimens that has been described by others.[17,18] Our results, therefore, do not confirm the results of retrospective series in which a survival benefit of PTR has been reported.[10,24-27] Confounding by indication could have led to the observed longer survival after upfront PTR in these studies. Patients who have favorable prognostic characteristics, such as only one organ affected by metastases and PS 0 or 1, are more likely to undergo upfront PTR in daily clinical practice.[25,27,28] Even when analyses are adjusted for confounders, concerns about residual confounding in non-randomized studies remain.[29] Furthermore, the patients who died after PTR or did not continue with systemic treatment were frequently not captured in the selection of retrospective cohorts. In addition, it is likely many retrospective analyses included

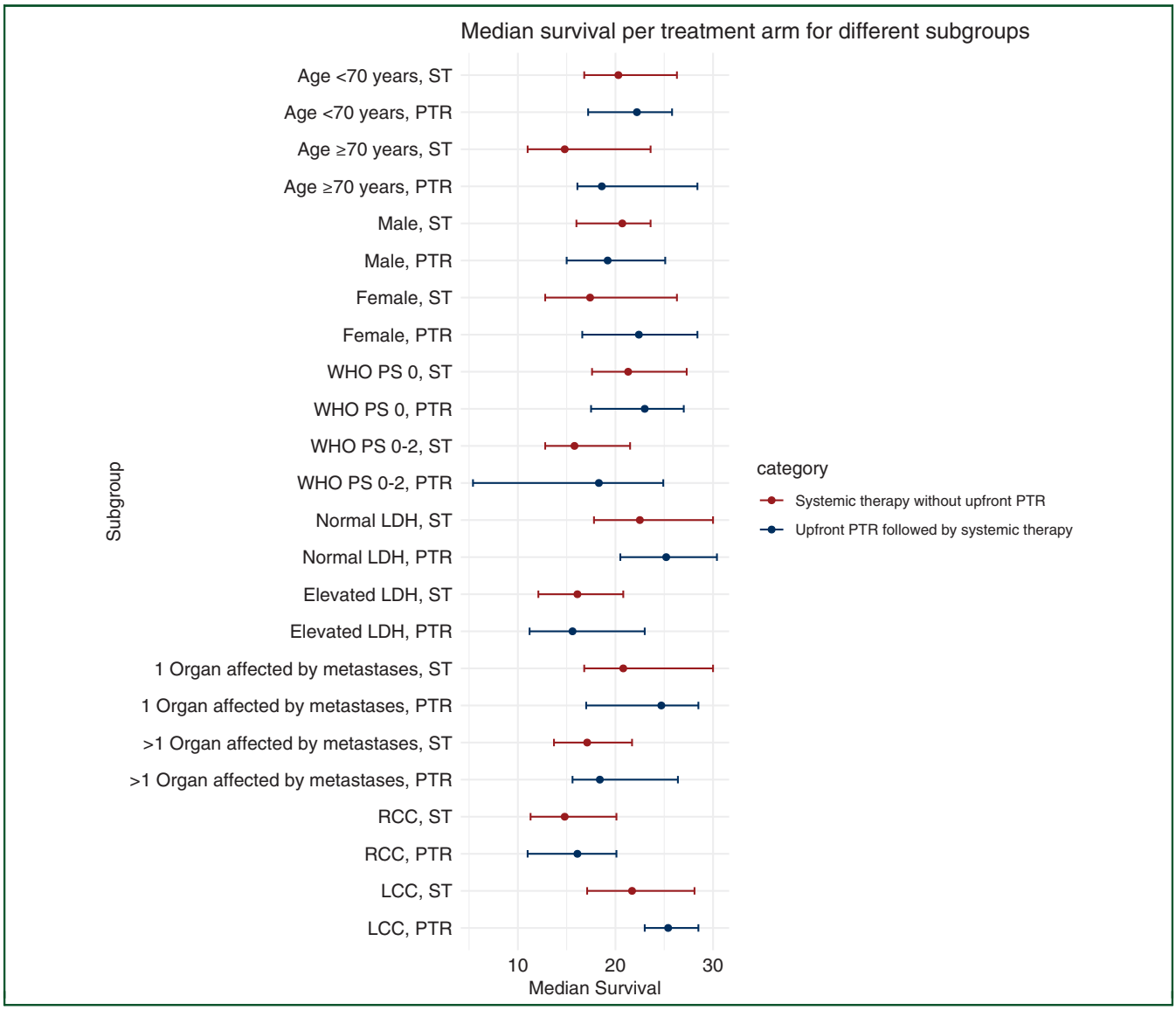

Figure 3. Median survival per treatment arm for different subgroups in the intention-to-treat population.
LCC, left-sided colon cancer; LDH, lactate dehydrogenase; PTR, primary tumor resection; RCC, right-sided colon cancer; ST, systemic therapy; WHO PS, World Health Organization performance status.

patients who underwent PTR due to symptoms of the primary tumor, which differs from the study population in CAIRO4. Recently, results of three other randomized studies on the role of PTR in mCRC patients have been presented. The Japanese iPACS study with 165 patients and the results of the German/Spanish SYNCHRONOUS study with 393 patients also showed no survival benefit of upfront PTR.[30,31] A small Korean trial with only 48 patients demonstrated a significantly higher 2-year cancer-specific survival with a trend towards a higher 2-year OS rate in favor of patients randomized to upfront PTR.[32] Two of these studies were prematurely terminated and have limited median follow-up time: the iPACS study was terminated due to futility and the Korean study was stopped due to insufficient funds and difficult accrual.[31,32]

Some differences between the aforementioned studies and CAIRO4 deserve further attention. In the SYNCHRONOUS and Korean studies, bevacizumab was not a standard component of the systemic treatment regimen.[30,32] The shorter median survival of CAIRO4 patients compared with the iPACS and Korean trials may be explained by the higher proportion of patients with relatively unfavorable prognostic characteristics. For example, in 63% of CAIRO4 patients more than one organ was affected by metastases versus 24% in the iPACS trial and 33% in the Korean trial. Although median OS in CAIRO4 is relatively short, these data cannot be adequately compared with other studies, since various systemic regimens with different effects on outcome were used in CAIRO4, and patients with potentially resectable metastases were underrepresented, as shown by the low number of patients who became eligible for local treatment of metastases.

The CAIRO4 study has several strengths. The multicenter and multinational study design allows enhanced

Table 2. Best overall response per treatment arm in the intention-to-treat population

	Systemic therapy without upfront PTR ($N = 103$)	Upfront PTR followed by systemic therapy ($N = 101$)	*P* value[a]
Best overall response, *n* (%)			0.90
Complete response	1 (1)	2 (2)	
Partial response	51 (50)	45 (45)	
Stable disease	39 (38)	33 (33)	
Progressive disease	8 (8)	8 (8)	
Not evaluable	4 (4)	13 (13[b])	

PTR, primary tumor resection.
[a]The *P* value for the best overall response is based on the Mann—Whitney *U* test. Since the Mann—Whitney *U* test is a test for ordinal data, the patients who had a best overall response that was 'not evaluable' were not included for the calculation of the *P* value.
[b]Percentages do not add up to 100% due to rounding.

generalizability of our results. Also, the fact that 87% of patients in the upfront PTR arm received subsequent systemic therapy, which is higher than the 76% in the SYNCHRONOUS study,[30] allows a fair evaluation of the role of upfront PTR. We consider the fact that we included a relatively poor prognostic group in the CAIRO4 study a strength, because it might reflect the real world more than other phase III studies.

A limitation of the CAIRO4 study was the necessity to reduce the power to 71% due to slower accrual than expected, which can partially be explained by an increase in curative treatment options in mCRC, strong and individual preferences of patients and clinicians for certain treatment options which impeded participation and the unwillingness of patients to rely on a randomization process to determine the therapy that is going to be received, especially when a surgical intervention is compared with a non-surgical intervention.[33] Furthermore, with an increasing number of different molecular subgroups such as BRAFV600E mutation and microsatellite instability (MSI), new trials were initiated including the possibility of inclusion for CAIRO4 eligible patients. Additionally, current guidelines recommend basing the specific systemic treatment regimen on RAS and BRAF molecular status, which was not included in the then-current guideline at time of initiation of the study. We do not think this influences the applicability of the CAIRO4 results, however, because bevacizumab in combination with chemotherapy is still a frequently used first-line treatment regimen. Also, we chose not to adjust for multiple testing, despite the fact that exploratory results on the 60-day mortality of CAIRO4 participants have previously been published,[20] because the current analysis is the only confirmatory analysis. Even if multiple testing would have been applied, however, this would have led to the significance level allocated to the OS endpoint in this manuscript to be at least as stringent as the 0.05 that was used and would result in the null hypothesis not being rejected irrespective of multiple testing strategy applied. Moreover, only eight patients with rectal cancer were included and the majority of patients had colon cancer, which potentially limits generalizability of the results to patients with rectal cancer. Further research on molecular tumor characteristics and a pooled analysis of randomized studies are planned, which may identify subgroups that benefit from upfront PTR.

In conclusion, CAIRO4 results show that the addition of upfront PTR to fluoropyrimidine-based chemotherapy with bevacizumab in patients with synchronous unresectable mCRC without severe symptoms of their primary tumor does not result in a survival benefit. Since these results are in line with other studies with comparable design, there appears to be no indication for upfront PTR in these patients.

Table 3. Grade 3 and grade 4 events per patient and per treatment arm in the per protocol population[a]

	Systemic therapy without upfront PTR ($N = 98$), *n* (%)	Upfront PTR followed by systemic therapy ($N = 94$), *n* (%)
Any type of AE per patient[b]		
Grade 3	63 (64)	53 (56)
Grade 4	8 (8)	8 (9)
Any grade 3/4 AE per patient		
Hematological toxicity	15 (15)	7 (7)
Thromboembolic event	6 (6)	6 (6)
Anorexia	11 (11)	4 (4)
Nausea	12 (12)	6 (6)
Vomiting	6 (6)	3 (3)
Mucositis	4 (4)	4 (4)
Diarrhea	20 (20)	9 (10)
Fatigue	15 (15)	11 (12)
Infections[c]	9 (9)	11 (12)
Hypertension	11 (11)	10 (11)
Neuropathy	3 (3)	9 (10)
Hand-foot syndrome	13 (13)	8 (9)
Abdominal pain	14 (14)	6 (6)
Ileus/obstruction	9 (9)	6 (6)
Perforation	1 (1)	0 (0)
Anastomotic leakage	1 (1)	3 (3)
Postoperative hemorrhage	1 (1)	2 (2)

In the upfront PTR arm, both adverse events after PTR and systemic therapy were included. For both treatment arms the adverse events were included until 30 days after the last study intervention.
AE, adverse event; PTR, primary tumor resection.
[a]If the same event occurred multiple times in the treatment trajectory, it was only included once in the table.
[b]If both a grade 3 and grade 4 specific event occurred, the highest grade was reported.
[c]Excluding wound infections.

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DISCLOSURE

DEWvdK reported a grant from the Dutch Cancer Society and an unrestricted grant from Hoffmann-La Roche Ltd during the conduct of the study. CJAP reports an advisory role for Nordic Pharma. JHWdW reported a grant from the Dutch Cancer Society and an unrestricted grant from Hoffmann-La Roche Ltd during the conduct of the study; grants from Medtronic paid to his institution outside the submitted work. MK reported a grant from Dutch Cancer Society and an unrestricted grant from Hoffmann-La Roche Ltd during the conduct of the study; grants from Bayer, Bristol Myers Squibb, Hoffmann-La Roche Ltd, Merck, Servier, and Pierre Fabre paid to their institution outside the submitted work; and paid advisory roles for Nordic Pharma, Merck Serono, Pierre Fabre, Servier, and Merck Sharp & Dohme outside the submitted work. GIL reported payment or honoraria for lectures/educational events from Servier and Nutricia; and support for attending meetings and/or travel from Servier. All other authors have declared no conflicts of interest.

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