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Sixty-Day Mortality of Patients With Metastatic Colorectal Cancer Randomized to Systemic Treatment vs Primary Tumor Resection Followed by Systemic Treatment

The CAIRO4 Phase 3 Randomized Clinical Trial

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IMPORTANCE The role of primary tumor resection (PTR) in synchronous patients with metastatic colorectal cancer (mCRC) who had unresectable metastases and few or absent symptoms of their primary tumor is unclear. Studying subgroups with low postoperative mortality may identify patients who potentially benefit from PTR.

OBJECTIVE To determine the difference in 60-day mortality between patients randomized to systemic treatment only vs PTR followed by systemic treatment, and to explore risk factors associated with 60-day mortality.

DESIGN, SETTING, AND PARTICIPANTS CAIRO4 is a randomized phase 3 trial initiated in 2012 in which patients with mCRC were randomized to systemic treatment only or PTR followed by systemic treatment with palliative intent. This multicenter study was conducted by the Danish and Dutch Colorectal Cancer Group in general and academic hospitals in Denmark and the Netherlands. Patients included between August 2012 and December 2019 with histologically proven colorectal cancer, unresectable metastases, and a primary tumor with few or absent symptoms were eligible.

INTERVENTIONS Systemic treatment, consisting of fluoropyrimidine-based chemotherapy with bevacizumab vs PTR followed by fluoropyrimidine-based chemotherapy with bevacizumab.

MAIN OUTCOMES AND MEASURES The aim of the current analysis was to compare 60-day mortality rates in both treatment arms. A secondary aim was the identification of risk factors for 60-day mortality in the treatment arms. These aims were not predefined in the study protocol.

RESULTS A total of 196 patients were included in the intention-to-treat analysis (112 [57%] men; median [IQR] age, 65 [59-70] years). Sixty-day mortality was 3% (95% CI, 1%-9%) in the systemic treatment arm and 11% (95% CI, 6%-19%) in the PTR arm (P = .03). In a per-protocol analysis, 60-day mortality was 2% (95% CI, 1%-7%) vs 10% (95% CI, 5%-18%; P = .048). Patients with elevated serum levels of lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and/or neutrophils who were randomized to PTR had a significantly higher 60-day mortality than patients without these characteristics.

CONCLUSIONS AND RELEVANCE Patients with mCRC who were randomized to PTR followed by systemic treatment had a higher 60-day mortality than patients randomized to systemic treatment. Especially patients randomized to the PTR arm with elevated serum levels of lactate dehydrogenase, neutrophils, aspartate aminotransferase, and/or alanine aminotransferase were at high risk of postoperative mortality. Final study results on overall survival have to be awaited.

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Visual Abstract

Invited Commentary

Supplemental content

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A majority of patients (55%-71%) with synchronous metastatic colorectal cancer (mCRC) have few or no symptoms from the primary tumor.[1-3] Although primary tumor resection (PTR) is indicated in case of bleeding, obstruction, and perforation, the need for PTR in patients with an asymptomatic primary tumor remains unclear.[4] The National Comprehensive Cancer Network advises against performing PTR in patients with colorectal cancer (CRC) without symptoms of the primary tumor and synchronous unresectable metastases but emphasizes that data from randomized clinical trials (RCTs) are needed.[5]

Important arguments in the debate concerning the role of PTR in asymptomatic synchronous unresectable mCRC are focused on possible benefits and hazards of PTR. For example, observational data indicate a survival benefit in favor of patients with mCRC treated with PTR.[6,7] Moreover, a prematurely terminated RCT (NCT01978249) that investigated the role of PTR in mCRC (n = 48) found a significantly improved 2-year cancer-specific survival after PTR.[8] However, PTR is associated with a 30-day postoperative mortality of approximately 4.5% vs almost 0% after systemic treatment in patients with mCRC.[9,10]

Recently, the results of the iPACS trial,[11,12] in which systemic treatment was compared with PTR followed by systemic treatment, were published. The study was prematurely terminated owing to medical futility (n = 165). The iPACS results suggest there is no indication for PTR,[12] but a comparison of early mortality and morbidity in both treatment arms according to intention to treat was lacking. Studying subgroups with low postoperative mortality may identify patients who potentially benefit from PTR. Sixty-day mortality is frequently used as an outcome measure to evaluate safety of systemic therapy.[13] Therefore, we report the 60-day mortality and morbidity of patients with an asymptomatic primary tumor participating in the CAIRO4 trial, in which patients were randomized to either systemic treatment only or PTR followed by systemic treatment.

Key Points

Question Is there a difference in 60-day mortality after randomization between systemic treatment only vs primary tumor resection followed by systemic treatment in patients with metastatic colorectal cancer treated with palliative intent?

Findings In this phase 3 randomized clinical trial, 60-day mortality in 99 patients randomized to systemic treatment was significantly lower compared with 97 patients randomized to surgery. Within the surgery arm, 60-day mortality was highest for patients with elevated levels of serum lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, neutrophils, and/or right-sided tumor.

Meaning Caution should be exercised while considering primary tumor resection in patients who have preoperative elevated serum lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and/or neutrophil levels.

Methods

Study Design

The CAIRO4 study is an international, multicenter, randomized phase III trial initiated by the Dutch Colorectal Cancer Group and the Danish Colorectal Cancer Group. Accrual started in July 2012 and was completed in January 2021 in Denmark and the Netherlands. The study was approved by the Medical Research Ethics Committee (Arnhem-Nijmegen) and was conducted in accordance with the Declaration of Helsinki.[14]

Study Population

A total of 45 centers participated in the study. The study design has been previously described in detail,[15] and the trial protocol is available in Supplement 1. Patients 18 years or older with histologically confirmed CRC, unresectable metastases, no severe signs or symptoms of the primary tumor, and a resectable tumor based on radiologic imaging and World Health Organization performance status between 0 and 2 were eligible. Patients were excluded if they had a comorbidity that potentially jeopardized the intervention, had a second primary malignant neoplasm 5 years or less before randomization, or required neoadjuvant (chemo)radiation. An amendment was implemented to allow inclusion of patients with a resectable primary rectal tumor who did not require neoadjuvant (chemo)radiotherapy. Data on race and ethnicity were not collected.

Randomization

After confirmation of eligibility and signed informed consent, patients were randomized centrally (1:1) and were allocated for systemic treatment only vs PTR followed by systemic treatment. Randomization was performed using minimization techniques, stratifying for the following prognostic criteria: number of metastatic sites (1 vs more), serum lactate dehydrogenase (LDH) (normal vs elevated), World Health Organization performance status (0 or 1 vs 2), institution, and location of the primary tumor (right-sided vs left-sided primary tumor, demarcation at the proximal end of the splenic flexure). Patients, physicians, data managers, and researchers were aware of the allocated treatment.

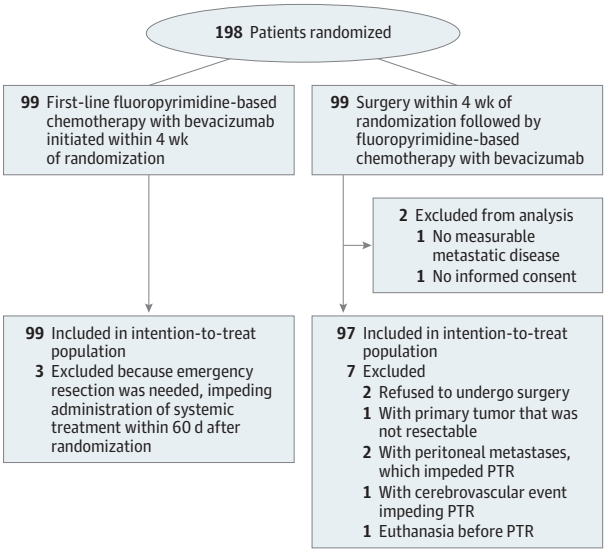
Interventions

Systemic treatment consisted of first-line fluoropyrimidine-based chemotherapy with bevacizumab to be initiated within 4 weeks of randomization. The alternative treatment arm consisted of PTR to be performed within 4 weeks of randomization, which was followed by fluoropyrimidine-based chemotherapy with bevacizumab until progression or unacceptable toxicity. Salvage therapy on progression of disease was left to the discretion of the local investigator.

Outcomes and Sample Size

The primary outcome of the CAIRO4 study is overall survival in the intention-to-treat population. Secondary outcomes include progression-free survival and quality of life.[15] In the current analysis, the primary aim was to compare the 60-day mortality between the 2 treatment arms. The secondary aims were

Figure. Flowchart



PTR indicates primary tumor resection.

Table 1. Baseline Characteristics

Characteristic	No. (%)	
	Systemic treatment (n = 99)	PTR followed by systemic treatment (n = 97)
Male	50 (51)	62 (64)
Female	49 (50)	35 (36)
Age, median (IQR), y	65 (57-70)	64 (59-70)
WHO performance status		
0-1	97 (98)	95 (98)
2	2 (2)	2 (2)
Charlson Comorbidity Index		
0-1	87 (88)	86 (89)
>1	12 (12)	11 (11)
Location of primary tumor		
Right	46 (47)	49 (51)
Left	53 (54)[a]	48 (50)[a]
>1 Affected organs by metastases	60 (61)	61 (63)
Liver involvement	84 (85)	87 (90)
Liver-only disease	28 (28)	29 (30)
Elevated serum lactate dehydrogenase level[b]	57 (58)	58 (60)

Abbreviations: PTR, primary tumor resection; WHO, World Health Organization.

[a] Percentages may not add up to 100% owing to rounding.

[b] Elevated as defined by the local hospital.

to explore the association between patient/biochemical characteristics and 60-day mortality within each treatment arm. Additional aims were to compare adverse events (AEs), including surgical AEs and hospitalization time between the 2 treatment arms within 60 days after randomization. The analysis of outcomes within 60 days after randomization was not predefined in the study protocol. AEs were classified according to the Common Terminology Criteria for Adverse Events version 4.0.[16] Only AEs with grade 3 or higher were registered. Hospitalization time was defined as time between admission and discharge.

Statistical Methods

The analysis was conducted according to the intention-to-treat approach. To address the primary research question of the comparison of the 60-day mortality in both treatment arms, a Fisher exact test was used. For the secondary research questions, Fisher exact test was used to compare categorical variables and a Kruskal-Wallis test for continuous variables. Characteristics of patients within each treatment arm who remained alive 60 days after randomization were compared with patients who died. Missing values were excluded from this analysis. A per-protocol analysis was performed as a subanalysis.

For all analyses, a 2-sided *P* value below .05 was considered significant. We did not correct for multiple testing and results should not be considered as confirmatory. Statistical analyses were conducted in R version 3.6.3 (R Foundation).

Results

Study Participants

Of 198 patients randomized between August 2012 and December 2019, 60-day mortality data was analyzed, with a total of 99 patients in each treatment arm. Two patients in the PTR treatment arm were excluded from the analysis. In 1 patient who underwent PTR, no evidence of metastatic disease could be established. Another patient was discovered to be erroneously registered as a study participant before study investigations had been started (**Figure**). No patients were excluded from the systemic treatment arm. Follow-up was completed until at least 60 days after randomization for all 196 participants (112 men [57%] and 84 women [43%]).

Baseline characteristics were well balanced between treatment arms, except for sex, with a larger proportion of men being allocated to the PTR arm (**Table 1**). The median (IQR) time between randomization and start of allocated therapy was 7 (5-11) days in the systemic treatment arm and 17 (11-22) days in the PTR arm. Of 99 patients allocated to the systemic treatment arm, 96 (97%) received systemic treatment within 60 days after randomization. In the systemic treatment arm, 76 patients (77%) received 3 or more cycles of systemic therapy within 60 days. Six patients (6%) in the systemic treatment arm underwent PTR within 60 days owing to symptoms necessitating resection of the primary tumor. One patient (1%) preferred PTR but was allocated to the systemic treatment arm.

In the PTR arm, a laparoscopic approach was performed in 68 patients (73%) (eTable 1 in Supplement 2). Seven patients (7%) did not undergo PTR within 60 days owing to death before PTR (n = 2), refusal of surgery and preference of systemic therapy (n = 2), peritoneal disease detected during laparoscopy that impeded PTR (n = 2), or unresectable primary tumor (n = 1). Histology of the resected tumors revealed a pT4 tumor in 35 patients (39%). In the PTR arm, 66 (68%) received systemic treatment within 60 days after randomization. Six patients (6%) received 3 or more cycles of systemic therapy

Table 2. Sixty-Day Mortality per Patient Characteristic and Study Arm According to Intention-to-Treat Analysis[a]

Characteristic	Systemic therapy arm			PTR + systemic therapy arm		
	Total (n = 99)	Deceased, No. (%) [95% CI] (n = 3)	*P* value[b]	Total (n = 97)	Deceased, No. (%) [95% CI] (n = 11)	*P* value[b]
Sex						
Male	50	1 (2) [0-10]	.62	62	5 (8) [3-18]	.20
Female	49	2 (4) [1-14]		35	6 (17) [8-33]	
Age, median (IQR)	65 (57-70)	65 (63-65)	.81	64 (59-70)	60 (59-65)	.52
BMI						
<18.5-25	31	1 (3) [0-16]	>.99	38	6 (16) [7-30]	.33
>25	68	2 (3) [1-10]		59	5 (8) [4-18]	
WHO performance score						
0-1	97	3 (3) [1-9]	>.99	95	11 (12) [7-20]	>.99
2	2	0 (0) [0-66]		2	0 (0) [0-66]	
Charlson Comorbidity Index						
0-1	87	3 (3) [1-10]	>.99	86	8 (9) [5-17]	.11
>1	12	0 (0) [0-24]		11	3 (27) [10-57]	
Location of primary tumor						
Right	46	3 (7) [2-18]	.10	49	9 (18) [10-31]	.051
Left	53	0 (0) [0-7]		48	2 (4) [1-14]	
No. of affected organs by metastases						
1	39	1 (3) [0-13]	>.99	36	3 (8) [3-22]	.74
>1	60	2 (3) [1-11]		61	8 (13) [7-24]	
Liver involved						
Yes	84	3 (4) [1-10]	>.99	87	10 (11) [6-20]	>.99
No	15	0 (0) [0-20]		10	1 (10) [1-40]	
Liver only						
Yes	28	1 (4) [0-18]	>.99	29	2 (7) [2-22]	.50
No	71	2 (3) [1-10]		68	9 (13) [7-23]	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PTR, primary tumor resection; WHO, World Health Organization.

[a] Each characteristic was compared within a treatment arm for patients who died within 60 days after randomization vs patients who survived after 60 days.

[b] For categorical variables, a Fisher exact test was used to compare the proportion of patients with a certain characteristic who survived after 60 days to patients who died within 60 days in 1 of the treatment arms. For continuous variables, a Kruskal-Wallis test was used.

within 60 days. The median (IQR) time between surgery and start of systemic treatment in the PTR arm was 29 (25-35) days.

Outcomes

Within 60 days from randomization, there were 3 deaths (3%; 95% CI, 1%-9%) in the systemic treatment arm and 11 deaths (11%; 95% CI, 6%-19%) in the PTR arm (*P* = .03). Of patients who died within 60 days in the systemic treatment arm, 1 died due to progression of disease, 1 due to gastrointestinal toxicity related to systemic treatment, and another as a consequence of colonic perforation before start of systemic treatment (eTable 2 in Supplement 2). Of patients randomized to PTR who died within 60 days, 2 patients (18%) died before PTR: 1 due to a cerebrovascular injury and another due to euthanasia. Five patients died after PTR but before start of systemic therapy: 4 (36%) due to rapid disease progression after PTR and 1 (9%) due to surgical complications resulting in a combination of distributive and obstructive shock. Four patients died after PTR and systemic therapy: 2 (18%) due to toxicity related to systemic treatment, 1 due to sepsis without neutropenia, and another due to unknown reason. Per-protocol analysis showed 2 patients (2%; 95% CI, 1%-7%) in the systemic treatment-only arm and 9 patients (10%; 95% CI, 5%-18%) in the PTR arm died within 60 days after randomization (*P* = .048). The 30-day postoperative mortality in patients randomized to the PTR arm who actually underwent PTR was 4 of 90 (4.4%).

None of the patient characteristics (excluding biochemical markers) were associated with significantly increased 60-day mortality within the treatment arms (**Table 2** and eTable 3 in Supplement 2). In the PTR arm, 9 of 49 patients (18%; 95% CI, 10%-31%) with right-sided colon cancer died within 60 days, whereas only 2 of 48 patients (4%; 95% CI, 1%-14%) with left-sided colon cancer died (*P* = .051). Of 39 patients who underwent a right hemicolectomy, 7 (18%; 95% CI, 9%-33%) died within 60 days (eTable 1 in Supplement 2).

For patients randomized to the systemic treatment arm, serum albumin was the only biochemical marker that was significantly different between patients who died within 60 days after randomization and patients who survived beyond 60 days (2 of 10 patients with hypoalbuminemia [20%; 95% CI, 6%-51%] died within 60 days; *P* = .04; **Table 3**). Four of 19 patients in the PTR arm (21%; 95% CI, 8%-43%) with hypoalbuminemia died within 60 days (*P* = .09).

Table 3. Sixty-Day Mortality and Different Blood Test Results per Study Arm According to Intention-to-Treat Analysis[a]

Characteristic	Systemic therapy			PTR + systemic therapy		
	Total (n = 99)	Deceased, No. (%) [95% CI] (n = 3)	*P* value[b]	Total (n = 97)	Deceased, No. (%) [95% CI] (n = 11)	*P* value[b]
Hemoglobin						
Normal (13.9-17.2 g/dL)	24	0 (0) [0-14]	>.99	25	2 (8) [2-25]	.72
Anemia (<13.9 g/dL)	75	3 (4) [1-11]		72	9 (13) [7-22]	
Leukocytes						
Normal (4000-10 000/μL)	64	1 (2) [0-8]	.28	59	4 (7) [3-16]	.10
Elevated (>10 000/μL)	35	2 (6) [2-19]		38	7 (18) [9-33]	
Neutrophils[c]						
Normal (1600-8300/μL)	75	1 (1) [0-7]	.31	64	4 (6) [2-15]	.04
Elevated (>8300/μL)	15	1 (7) [0-30]		15	4 (27) [11-52]	
Thrombocytes[c]						
Thrombocytopenia (<150 ×10^3/μL)	1	0 (0) [0-95]	>.99	2	0 (0) [0-66]	>.99
Normal (≥150 ×10^3/μL)	97	3 (3) [1-9]		95	11 (12) [7-20]	
Serum creatinine						
Normal (≤1018 mg/dL)	90	3 (3) [1-9]	>.99	92	10 (11) [6-19]	.46
Elevated (>1018 mg/dL)	7	0 (0) [0-35]		5	1 (2) [1-62]	
Serum albumin[c]						
Hypoalbuminemia (<3.5 g/dL)	10	2 (20) [6-51]	.04	19	4 (21) [8-43]	.09
Normal (3.5-5.0 g/dL)	72	1 (1) [0-7]		61	4 (7) [3-16]	
Serum bilirubin level[c]						
Normal (0.18-1.23 mg/dL)	95	3 (3) [1-9]	>.99	90	10 (11) [6-19]	>.99
Elevated (>1.23 mg/dL)[d]	1	0 (0) [0-95]		3	0 (0) [0-56]	
Alkaline phosphatase[c]						
Normal (0-120 U/L)	53	0 (0) [0-7]	.08	49	3 (6) [2-17]	.19
Elevated (>120 U/L)[d]	41	3 (7) [3-19]		45	7 (16) [8-29]	
Aspartate aminotransferase[c]						
Normal (≤35 U/L)	48	2 (4) [1-14]	.50	43	0 (0) [0-8]	<.001
Elevated (35 U/L)[d]	37	0 (0) [0-9]		41	9 (22) [12-37]	
Alanine aminotransferase[c]						
Normal (≤45 U/L)	88	3 (3) [1-10]	>.99	72	3 (4) [1-12]	.002
Elevated (>45 U/L)[d]	10	0 (0) [0-28]		23	7 (30) [16-51]	
Serum lactate dehydrogenase						
Normal	42	1 (2) [0-12]	>.99	39	1 (3) [0-13]	.046
Elevated[e]	57	2 (4) [1-12]		58	10 (17) [10-29]	
Carcinoembryonic antigen[c]						
Normal (0-3 ng/mL)	7	0 (0) [0-35]	>.99	8	1 (24) [1-47]	>.99
Elevated (>3 ng/mL)	85	3 (4) [1-10]		77	8 (10) [5-19]	

Abbreviations: PTR, primary tumor resection; ST, systemic therapy.

SI conversion factors: To convert alanine aminotransferase to microkatals per liter, multiply by 0.0167; albumin to grams per liter, multiply by 10; alkaline phosphatase to microkatals per liter, multiply by 0.0167; aspartate aminotransferase to microkatals per liter, multiply by 0.0167; bilirubin to millimoles per liter, multiply by 17.104; carcinoembryonic antigen to micrograms per liter, multiply by 1; creatinine to millimoles per liter, multiply by 88.4; hemoglobin to grams per liter, multiply by 10; leukocyte to ×10^9 per liter, multiply by 0.001; neutrophils to ×10^9 per liter, multiply by 0.001; thrombocytes to ×10^9 per liter, multiply by 1.

[a] Each laboratory value was compared within 1 of the treatment arms for patients who died within 60 days after randomization vs patients who survived after 60 days.

[b] Fisher exact test to compare the proportion of patients with a certain characteristic who survived after 60 days to patients who died within 60 days after randomization within 1 of the treatment arms.

[c] Missing values in ST and PTR treatment arms: neutrophils: 27 missing values (ST: 9; PTR: 18); platelets: 1 missing value (ST); serum bilirubin: 5 missing values (ST: 3, PTR: 2), 2 patients in PTR arm with a value between 0 and 0.12 mg/dL; alkaline phosphatase: 8 missing values (ST: 5; PTR: 3); aspartate aminotransferase: 27 missing values (ST: 14; PTR: 13); alanine aminotransferase: 3 missing values (ST: 1; PTR: 2); creatinine: 2 missing values (ST); albumin: 33 missing values (ST: 17; PTR: 16); and carcinoembryonic antigen: 19 missing values (ST: 7; PTR: 12).

[d] Maximum of 5 times the upper limit of normal if liver metastases are present; if no liver metastases were present, a maximum of 3 times the upper limit of normal.

[e] Elevated as defined by the laboratory of the local hospital.

Within the group randomized to PTR, several biochemical markers were significantly different between patients who died and who survived beyond 60 days (Table 3 and eTable 4 in Supplement 2). LDH levels were elevated in 58 patients of whom 10 (17%; 95% CI, 10%-29%) died (*P* = .046). Of 15 patients with elevated neutrophil levels, 4 (27%; 95% CI, 11%-52%) died (*P* = .04). Nine of 41 patients (22%; 95% CI, 12%-37%) with elevated aspartate aminotransferase levels died

($P < .001$). Alanine aminotransferase was elevated in 23 patients, of whom 7 (30%; 95% CI, 16%-51%) died within 60 days ($P = .002$). Of 39 patients in the PTR arm with 2 or 3 of the aforementioned biochemical (LDH, aspartate aminotransferase, alanine aminotransferase, neutrophils) and/or patient characteristics (right-sided tumor), 5 patients (13%; 95% CI, 6%-27%) died within 60 days. There were 14 patients with 4 or 5 characteristics, and 6 patients (43%; 95% CI, 21%-67%) died within 60 days. None of the 44 patients with 1 characteristic or no unfavorable characteristics died within 60 days.

AEs Within 60 Days

The number of patients with AEs with grade 3 or 4 within 60 days after randomization was 30 (30%; 95% CI, 22%-40%) and 22 (23%; 95% CI, 15%-32%) in the systemic treatment and PTR arm, respectively ($P = .25$). The most common AEs in the systemic treatment arm included diarrhea (9 [9%]) and pain (8 [8%]). In the PTR arm, infections (6 [6%]; excluding wound infections), pain (4 [4%]), and wound infections (3 [3%]) were the most frequent AEs. One grade-4 event was reported in the systemic treatment arm, which was caused by neutropenia. Three grade-4 events were observed in the PTR arm: acute kidney insufficiency, thromboembolic event, and postoperative hemorrhage.

Hospitalizations Within 60 Days

The number of hospitalized patients within 60 days after randomization, excluding patients admitted to the day care ward, was 18 (19%) in the systemic treatment arm and 94 (97%) in the PTR arm. Most patients in the systemic treatment arm required treatment for toxicity (7 [39%]) or symptoms necessitating surgical intervention (6 [33%]). Apart from surgery (92 [98%]), the most common reasons for hospitalization in the PTR arm were postoperative complications (8 [9%]). The median (IQR) hospitalization time was 0 (0) in the systemic treatment-only arm and 6 (5-13) days in the PTR arm ($P < .001$).

Discussion

The debate about the role of PTR in patients with mCRC who have unresectable metastases and an asymptomatic primary tumor remains ongoing. Although data from a 2021 RCT did not demonstrate a beneficial effect on overall survival,[12] the short-term results (defined as mortality 60 days after randomization) of PTR vs systemic therapy in RCTs have not been compared, to our knowledge. We demonstrated that the 60-day mortality of patients randomized to PTR followed by systemic therapy was significantly higher than 60-day mortality of patients randomized to systemic treatment only. Moreover, risk factors for increased postoperative mortality were identified.

The 30-day postoperative mortality according to per-protocol analysis was 4.4% in our study. This was comparable with the 4.5% determined in a meta-analysis of patients with mCRC who underwent PTR, the 3.8% reported in a Korean RCT (NCT01978249), and the 4% observed in the iPACS trial.[8,9,12] The postoperative mortality in mCRC seems higher than the 30-day mortality of 2.4% observed in patients with stage 1-3 disease between 2011 to 2016 in Dutch clinical practice.[17] Explanations might be increased systemic inflammation and worse nutritional status in patients with metastatic disease.[18-21] Systemic inflammation facilitates progression of disease,[22,23] and poor nutritional status is associated with impaired wound healing and immune dysfunction, possibly resulting in higher postoperative mortality.[24,25]

The 60-day mortality rate of 3% after randomization for patients who received systemic treatment was comparable with the 3.7% reported in a pooled analysis of patients with mCRC in 4 RCTs.[13] In our study, we observed a 60-day mortality of 11% in patients who were randomized to PTR. In the iPACS trial, the mortality rate in the PTR arm was especially high during the 2 months after randomization compared with the systemic treatment arm.[12] However, accurate comparison of our results to iPACS and the Korean RCT is difficult because 60-day mortality was not reported. Moreover, the participants in these RCTs had limited tumor load compared with the participants in our study.[8,12] Of note is that of the deaths occurring in the PTR arm in our study, only 1 was directly related to surgery and 4 deaths were related to progression of disease shortly after surgery. Possibly progression occurred due to absence of systemic treatment.

An exploratory analysis of which subgroups in the PTR arm had an increased risk of death within 60 days after randomization indicated that these patients more frequently had elevated LDH, aspartate aminotransferase, alanine aminotransferase, and/or neutrophil serum levels. Of note, 60-day mortality seems to increase if multiple abnormal biochemical characteristics were present simultaneously before surgery. Several explanations might be given for these observations. First, these biochemical characteristics are regarded as markers of tumor burden and degree of malignancy.[26-30] Possibly, patients with these elevated biomarkers had considerable tumor load and were therefore at risk of experiencing rapid progression after PTR. Second, each biochemical characteristic is individually known to be associated with worse prognosis.[30,31] The association between elevated neutrophil levels and worse survival can be seen in the light of an increased systemic inflammatory response, which is associated with increased mortality.[29,32] Possibly, this systemic inflammatory response cannot be reduced by removing the primary tumor in patients with extensive metastatic disease due to the large remaining tumor load.[29] In contrast, patients with normal biochemical characteristics might form a subgroup with low 60-day mortality and potential long-term benefit from PTR.

Although not statistically significant in the PTR arm, right-sided colon cancer ($P = .051$) and hypoalbuminemia ($P = .09$) may be clinically relevant risk factors for 60-day mortality owing to several reasons. First, the limited number of events (n = 11) might impede statistically significant observations. A larger percentage of patients in the PTR arm with right-sided colon cancer died within 60 days after randomization (11%) compared with patients with left-sided colon cancer (4%). This was similar for hypoalbuminemia (21%) vs normal se-

rum albumin (7%). Second, both characteristics have previously been identified as prognostically unfavorable in mCRC.[33-36] Population-based data from the Netherlands and the United States suggest that primary tumor location might have predictive value for the effect of PTR. During the first 3 months after PTR, the mortality rate was demonstrated to be high in patients with right-sided colon cancer compared with patients with left-sided colon cancer who underwent PTR.[37]

The number of AEs within 60 days after randomization was comparable within both treatment arms. As expected, a smaller proportion of patients in the PTR arm (66%) was exposed to systemic treatment within 60 days than in the systemic treatment arm owing to, for example, the waiting time until surgery and the recovery interval between surgery and systemic treatment administration. This might have favorably influenced the number of AEs in the PTR arm. The number of AEs with grade 3 and 4 observed (23%) within 60 days after randomization was similar to the 21% postoperative AEs reported in iPACS.[12]

Strengths and Limitations

To our knowledge, this is the first trial studying the role of PTR in synchronous patients with mCRC in which 60-day mortality has been analyzed according to intention-to-treat principle. The generalizability of our results is enhanced by the multicenter and multinational design. However, the current sample size and number of events is limited for accurate testing of the interaction between patient/biochemical characteristics and treatment arm. Another limitation is that not all patients underwent their allocated treatment, although the difference in 60-day mortality was also observed in the per-protocol analysis. Furthermore, we observed a larger proportion of men in the PTR arm than in the systemic treatment arm. A pooled analysis of 26 RCTs has shown that men have a worse prognosis compared with women, although the difference is small.[38]

Conclusions

In conclusion, patients randomized to PTR followed by systemic treatment experienced a higher 60-day mortality than patients randomized to systemic treatment only. Patients with elevated serum LDH, aspartate aminotransferase, alanine aminotransferase, and/or neutrophil levels may be poor candidates for undergoing PTR and delaying systemic therapy. Caution is warranted in patients with multiple unfavorable characteristics. In the future, pooling of data of different RCTs is necessary to confirm these observations and to study whether careful patient selection can potentially identify patients who benefit from PTR.[8,12,39-43] The final results on overall survival of the CAIRO4 and other trials should be awaited to assess the definite role of PTR in patients with CRC who have synchronous metastases and a primary tumor with few or absent symptoms.

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