

## Prognostic Value of Resection of Primary Tumor in Patients with Stage IV Colorectal Cancer: Retrospective Analysis of Two Randomized Studies and a Review of the Literature

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### ABSTRACT

**Background.** In patients with metastatic colorectal cancer (mCRC) with an asymptomatic primary tumor, there is no consensus on the indication for resection of the primary tumor.

**Methods.** A retrospective analysis was performed on the outcome of stage IV colorectal cancer (CRC) patients with or without resection of the primary tumor treated in the phase III CAIRO and CAIRO2 studies. A review of the literature was performed.

**Results.** In the CAIRO and CAIRO2 studies, 258 and 289 patients had undergone a primary tumor resection and 141 and 159 patients had not, respectively. In the CAIRO study, a significantly better median overall survival and progression-free survival was observed for the resection compared to the nonresection group, with 16.7 vs. 11.4 months [ $P < 0.0001$ , hazard ratio (HR) 0.61], and 6.7 vs. 5.9 months ( $P = 0.004$ ; HR 0.74), respectively. In the CAIRO2 study, median overall survival and progression-free survival were also significantly better for the resection

compared to the nonresection group, with 20.7 vs. 13.4 months ( $P < 0.0001$ ; HR 0.65) and 10.5 vs. 7.8 months ( $P = 0.014$ ; HR 0.78), respectively. These differences remained significant in multivariate analyses. Our review identified 22 nonrandomized studies, most of which showed improved survival for mCRC patients who underwent resection of the primary tumor.

**Conclusions.** Our results as well as data from literature indicate that resection of the primary tumor is a prognostic factor for survival in stage IV CRC patients. The potential bias of these results warrants prospective studies on the value of resection of primary tumor in this setting; such studies are currently being planned.

For most patients with metastatic colorectal cancer (mCRC), there are no curative options, but a benefit in median overall survival (OS) can be achieved with palliative systemic treatment.<sup>1</sup> This treatment currently consists of cytotoxic chemotherapy and targeted therapy. The 5-year OS for patients who are diagnosed with distant metastases ranges 10–20%.<sup>2–4</sup> The median OS is improved when patients are exposed to all available cytotoxic drugs during the course of their disease.<sup>5</sup> Because the disease of only a subset of patients will respond to systemic treatment, we need predictive and prognostic markers that will permit us to select patients who may experience the

optimal benefit of available treatments. Currently available biomarkers are not predictive for the efficacy of chemotherapy, and for targeted therapy, only *KRAS* mutation status is predictive for response to anti-epidermal growth factor receptor therapy, with *BRAF* mutation status being a candidate prognostic marker.<sup>6–8</sup>

Patients with colorectal cancer (CRC) with stage IV disease may manifest various symptoms of their primary tumor and/or metastases, and a palliative resection of the primary tumor before the initiation of systemic treatment is frequently performed.<sup>9</sup> This indication is obvious in patients with a symptomatic primary. However, in patients with few or absent symptoms, the indication for resection is under debate, and its effect on survival and quality of life is still uncertain.<sup>10–12</sup> The possible influence of a palliative resection of the primary tumor on survival has never been properly assessed, and most randomized studies in mCRC do not even report whether a resection of the primary tumor has been performed.<sup>13,14</sup>

We here report a retrospective analysis of two phase III studies on the prognostic and predictive value of resection of the primary tumor in stage IV mCRC patients.<sup>15,16</sup> Data on the toxicity of systemic treatment in resected versus nonresected patients are presented. We review the literature on this issue and discuss our data in relation to the results of this review.

## METHODS

### *CAIRO Studies*

Data of metastatic CRC patients included in two phase III studies (CAIRO and CAIRO2) of the Dutch Colorectal Cancer Group were used (ClinicalTrials.gov NCT00312000 and NCT00208546). Details of these studies have been published elsewhere.<sup>15–18</sup>

Patients with stage IV disease (metastatic disease at diagnosis) were classified as having undergone a resection (resection group) or no resection (nonresection group) of the primary tumor before randomization in the study. Patients who had undergone a resection of the primary tumor after randomization and patients who had an incomplete resection of the primary tumor before randomization were included in the nonresection group. To assess the prognostic value of resection, we analyzed the total group of patients in each study with stage IV disease and compared the outcome of the resection group with the nonresection group. To assess the predictive value of resection, we analyzed the interaction of resection with the outcome of first-line treatment per treatment arm in each study. Toxicity was scored according to U.S. National Cancer Institute Common Toxicity Criteria, version 2.0.

### *Statistical Methods*

Ineligible patients were excluded from the analysis. The progression-free survival (PFS) was calculated from the date of randomization to the first observation of disease progression or death from any cause. OS and PFS curves were estimated by the Kaplan-Meier method and compared by the log rank test. Multivariate analysis of survival was performed by the Cox proportional hazard model. The comparison of factors between groups (resection vs. non-resection) was performed by chi-square, Fisher's exact, or Mann-Whitney tests, where appropriate. All tests were two-sided, and *P* values of less than 0.05 were considered statistically significant. All analyses were performed by SAS 9.1 and S-plus 6.2 software.

### *Literature Search Strategy, Inclusion Criteria, and Data Extraction*

We reviewed the literature on the prognostic and/or predictive value of resection of the primary tumor in mCRC patients with unresectable distant metastases. The primary outcomes of interest were OS, toxicity, and morbidity. A search was conducted of Medline, PubMed, and the Cochrane Library from January 1980 to December 2010 with an English-language restriction.

Original publications were selected if the abstract contained safety and efficacy data for patients with and without resection of the primary tumor. In case of duplicate publications, the most recent and/or most complete study was included. We excluded cohorts of patients with mCRC who were candidates for potentially curative metastasectomy, and publications that included only rectal cancer or merely focused on the surgical procedure.

## RESULTS

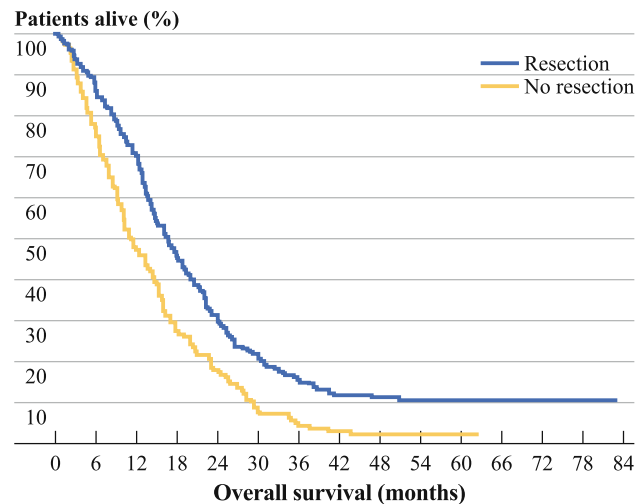
### *CAIRO Study*

*Patient Characteristics* Of the 803 eligible patients with advanced CRC disease in the CAIRO study, 399 patients had stage IV disease at inclusion. Of these patients, 258 were placed in the resection group and 141 patients in the nonresection group. Patients in the nonresection group more often had abnormal baseline serum lactate dehydrogenase (LDH), more often had predominant extrahepatic metastases, more often had a primary tumor located in rectosigmoid or rectum, and received fewer cycles of chemotherapy (Table 1). At baseline, none of the patients had grade 3–4 nausea, vomiting, or ileus toxicity. Only two patients in the nonresection group had grade 3–4 diarrhea toxicity at presentation (*P* = 0.06).

**TABLE 1** Characteristics of 399 stage IV CRC patients on the CAIRO study with resection and nonresection of primary tumor

Characteristic	Resection group (n = 258)	Nonresection group (n = 141)	P value
Sex			0.086
Male	159 (62%)	99 (70%)	
Female	99 (38%)	42 (30%)	
Age, years			0.138
Median	63	60	
Range	34–81	27–82	
LDH serum			<0.0001
Normal	164 (64%)	49 (35%)	
Abnormal	94 (36%)	92 (65%)	
Performance status			0.382
0	161 (62%)	78 (55%)	
1	84 (33%)	55 (39%)	
2	13 (5%)	8 (6%)	
Predominant localization of metastases			0.005
Liver	233 (81%)	113 (81%)	
Extrahepatic	23 (9%)	26 (19%)	
Localization of the primary tumor			0.005
Colon	183 (71%)	78 (55%)	
Rectosigmoid	16 (6%)	15 (11%)	
Rectum	56 (22%)	48 (34%)	
Multiple tumor	3 (1%)	0 (0%)	
Metastatic sites involved			0.067
1	119 (46%)	50 (36%)	
>2	137 (53%)	90 (64%)	
Unknown	2 (1%)	0 (0%)	
Treatment arm			0.517
Sequential	123 (48%)	72 (51%)	
Combination	135 (52%)	69 (49%)	
No. of cycles			0.004
Median (range)	8 (0–53)	6 (0–18)	

**Prognostic Value of Resection of the Primary Tumor** A significantly better median OS and PFS was observed for patients in the resection versus the nonresection group, with 16.7 vs. 11.4 months [ $P < 0.0001$ ; hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.49–0.76] (Fig. 1), and 6.7 vs. 5.9 months ( $P = 0.004$ ; HR 0.74, 95% CI 0.60–0.91), respectively. A multivariate analysis was performed that included baseline serum LDH, predominant localization of metastases, performance status, localization of the primary tumor, and chemotherapy schedule. Resection of the primary tumor was prognostic for OS and borderline

**FIG. 1** OS (months) for resection vs. nonresection of the primary tumor in the CAIRO study

prognostic for PFS in patients with only one metastatic site ( $P = 0.016$ , HR 0.63, 95% CI 0.43–0.92, and  $P = 0.069$ , HR 0.57, 95% CI 0.30–1.25), but not in patients with two or more metastatic sites ( $P = 0.276$ , HR 0.88, 95% CI 0.70–1.11, and  $P = 0.444$ , HR 1.10, 95% CI 0.87–1.38).

**Predictive Value of Resection of the Primary Tumor** The primary objective of the CAIRO study was to evaluate sequential versus combination chemotherapy. No significant interaction with sequential versus combination treatment in respect to median OS was observed for patients in the resection group (16.2, 95% CI 13.5–29.4 vs. 17.6 months, 95% CI 14.8–20.1) and the nonresection group (9.8, 95% CI 7.9–11.8, vs. 14.9 months, 95% CI 10.8–16.4) ( $P = 0.769$ ).

**Toxicity** We assessed a possible interaction for patient symptoms that may have been related to the presence of the primary tumor—that is, nausea, vomiting, ileus, diarrhea, and fatigue.

In first-line treatment, none of the instances of grade 3–4 toxicity occurred significantly more frequently in the nonresection group compared to the resection group. When all treatment lines were considered, the incidence of grade 3–4 vomiting and ileus in the overall study population occurred significantly more frequently in the nonresection compared to the resection group, with 11% vs. 5% for vomiting ( $P = 0.053$ ) and 7% vs. 2% for ileus ( $P = 0.019$ ), respectively. In the sequential treatment arm, nausea and fatigue occurred significantly more frequently in the nonresection compared to the resection group; 13% vs. 5% ( $P = 0.054$ ) and 33% vs. 18% ( $P = 0.014$ ), respectively. In the combination treatment arm, only grade 3–4 ileus occurred significantly more frequently in the

nonresection compared to the resection group, 10% vs. 3% ( $P = 0.029$ ).

### CAIRO2 Study

**Patient Characteristics** Of the 736 eligible mCRC patients in the CAIRO2 study, 448 patients had stage IV disease at inclusion. Of these patients, 289 were assigned to the resection group and 159 patients to the nonresection group. Patients in the nonresection group were more often men, were younger, more often had abnormal baseline serum LDH, had a worse performance status, and more often had liver plus other metastases and a larger number of metastatic sites compared to the resection group (Table 2). At baseline, none of the patients presented with grade 3–4 nausea, vomiting, or ileus toxicity. Only one patient in the nonresection group had grade 3–4 diarrhea toxicity at presentation ( $P = 0.178$ ).

**Prognostic Value of Resection of the Primary Tumor** A significantly better median OS and PFS were observed for patients in the resection versus the nonresection group, with 20.7 vs. 13.4 months ( $P < 0.0001$ ; HR 0.65, 95% CI 0.52–0.80) (Fig. 2), and 10.5 vs. 7.8 months ( $P = 0.015$ ; HR 0.78, 95% CI 0.64–0.95), respectively.

In the multivariate analysis that included sex, age, baseline serum LDH, performance status, localization of metastases, localization of primary tumor, number of metastatic sites involved, and treatment arm, resection of the primary tumor remained an independent prognostic factor for median OS ( $P = 0.010$ ; HR 0.73, 95% CI 0.58–0.93), but not for PFS ( $P = 0.130$ ; HR 0.84, 95% CI 0.68–1.05).

**Predictive Value of Resection of the Primary Tumor** The primary objective of the CAIRO2 study was to evaluate the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab. No significant interaction with treatment was observed in respect to median OS for patients in the resection group (21.6, 95% CI 17.6–27.8 vs. 20.2 months, 95% CI 17.1–22.2) and the nonresection group (13.4, 95% CI 11.7–18.4 vs. 13.8 months, 95% CI 10.9–17.8) ( $P = 0.612$ ).

### Toxicity

We assessed a possible interaction for patient symptoms that may have been related to the presence of the primary tumor—that is, nausea, vomiting, ileus, diarrhea, and fatigue.

For the overall study population, grade 3–4 nausea, vomiting, ileus, and fatigue toxicity occurred significantly more frequently in the nonresection compared to the resection group, 9% vs. 3% for nausea ( $P = 0.004$ ), 9% vs.

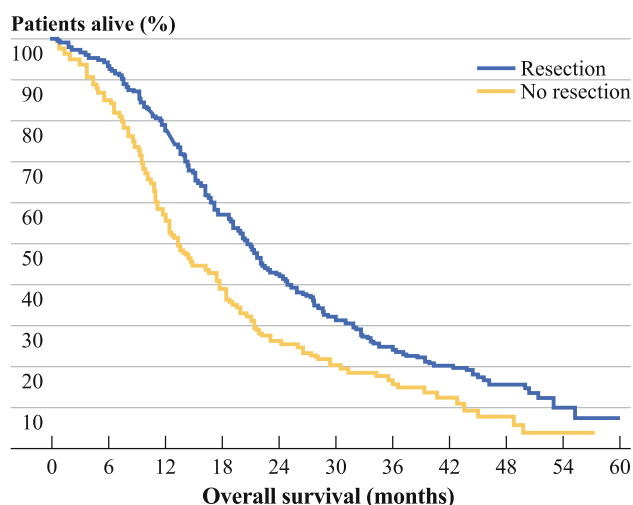
**TABLE 2** Characteristics of 488 stage IV CRC patients on the CAIRO2 study with resection and nonresection of primary tumor

Characteristic	Resection group ( <i>n</i> = 289)	Nonresection group ( <i>n</i> = 159)	<i>P</i> value
Sex			0.011
Male	155 (54%)	105 (66%)	
Female	134 (46%)	54 (34%)	
Age, years			0.008
Median	62.2	59.5	
Range	34.7–80.0	31.4–77.7	
LDH serum			<0.0001
Normal	172 (60%)	44 (28%)	
Abnormal	115 (40%)	115 (72%)	
Performance status			0.001
0	184 (64%)	76 (48%)	
1	104 (36%)	83 (52%)	
Localization of metastases			0.001
Liver	114 (39%)	51 (32%)	
Liver + other	138 (48%)	99 (62%)	
Extrahepatic	34 (12%)	4 (3%)	
Locally advanced	0 (0%)	2 (1%)	
Unknown	3 (1%)	3 (2%)	
Localization of primary tumor			0.121
Colon	128 (51%)	71 (48%)	
Rectosigmoid	76 (31%)	37 (25%)	
Rectum	45 (18%)	39 (27%)	
Metastatic sites involved			0.011
1	132 (46%)	52 (34%)	
>2	153 (54%)	102 (66%)	
Treatment arm			0.787
CB	142 (49%)	76 (48%)	
CBC	147 (51%)	83 (52%)	
No. of cycles			0.410
Median (range)	9 (0–76)	9 (1–52)	

CB chemotherapy + bevacizumab (arm A), CBC chemotherapy + bevacizumab + cetuximab (arm B)

4% for vomiting ( $P = 0.043$ ), 8% vs. 3% for ileus ( $P = 0.019$ ), and 23% vs. 13% for fatigue ( $P = 0.004$ ), respectively.

In the treatment arm without cetuximab, grade 3–4 nausea, vomiting, and fatigue occurred significantly more frequently in the nonresection group compared to the resection group, 13% vs. 4% for nausea ( $P = 0.015$ ), 15% vs. 4% for vomiting ( $P = 0.003$ ), and 21% vs. 11% ( $P = 0.046$ ) for fatigue, respectively. In the treatment arm with cetuximab, only grade 3–4 fatigue occurred significantly more frequently in the nonresection group compared to the resection group; 25% vs. 14% ( $P = 0.042$ ).



**FIG. 2** OS (months) for resection vs. nonresection of the primary tumor in the CAIRO2 study

### Review of the Literature

The literature search identified 22 nonrandomized, single-center studies (Tables 3 and 4). Twenty-one studies were retrospective, and one study concerned a case-matched cohort analysis.<sup>13,19–39</sup> Two studies were restricted to patients without symptoms of their primary tumor.<sup>23,25</sup>

Definition of nonresection was defined either as surgical intervention without resection (group 1; 12 studies; Table 3) or as no surgical intervention (group 2; 12 studies; Table 4). In both groups, resection was defined as a resection of the primary tumor. Two studies used both definitions for nonresection, and therefore we present the results of these studies in the analysis of both groups.<sup>24,29</sup>

In group 1, the median OS was statistically significantly better in resected versus nonresected patients in 8 of 12 studies.<sup>13,19,21,27,28,35,37,38</sup> The conclusion of most of these studies was that resection should be performed if feasible, in particular in symptomatic patients (Table 3).<sup>13,21,27,29,30,32,35,37</sup> Two studies presented a subgroup analysis in asymptomatic patients, and although patients who underwent resection had a significantly better median OS compared to patients without resection, both studies suggested that nonresection of the primary tumor is a valid treatment choice in this setting.<sup>35,37</sup> This was supported in one study by a multivariate analysis that identified chemotherapy as the only prognostic factor for OS in asymptomatic patients, and in the other by the fact that the advantages of primary tumor resection in asymptomatic patients are outweighed by perioperative mortality.<sup>35,37</sup> The postoperative mortality was higher in the nonresection group (0–36%) compared to the resection group (3–16%) in 5 of 12 studies. The incidence of postoperative

morbidity ranged 3–50% in the resection group versus 0–38% in the nonresection group.

In group 2, 6 of 12 studies demonstrated an improved median OS in the resection compared to the nonresection group (Table 4).<sup>20,22,25,26,29,33</sup> In three studies a subset of patients was reported to be asymptomatic in relation to their primary tumor,<sup>33,34,39</sup> of which the largest study showed a significant benefit in OS for patients with a resection of the primary tumor.<sup>33</sup> The postoperative mortality ranged 0–16%, and the postoperative morbidity ranged 10–34.7% (Table 4). In 8 of 12 studies, both the resected and nonresected groups received chemotherapy.<sup>20,22,23,25,26,31,36,39</sup> Tebbutt et al.<sup>36</sup> suggested that most patients who do not require surgical intervention for complications of their primary tumor at the time of diagnosis can be safely treated with chemotherapy because no increase of intestinal complications was observed.

### DISCUSSION

To our knowledge, this is the first retrospective analysis of two phase III studies investigating the prognostic and predictive value of resection of the primary tumor in patients with stage IV CRC treated with systemic therapy. We identified resection of the primary tumor as a prognostic factor for OS. Resection was not predictive in relation to the outcome of treatment that was used in these studies. We observed a higher incidence of toxicity in the nonresected group, in particular in the CAIRO2 study.

It seems plausible that a resection was performed or at least attempted in patients who had symptoms that demanded urgent surgical treatment. However, a major limitation of our study is that the decision to resect the primary tumor was made before study entry, and thus we have no information about the reasons for nonresection, such as irresectability of the primary tumor, poor condition of the patient, symptomatic metastases requiring priority for systemic treatment, or absence of symptoms of the primary tumor. Obviously, these concern arguments of a highly different nature and may define different patient populations. For instance, the fact that patients in the nonresection group more often had an elevated serum LDH and a larger number of metastatic sites may have shifted the decision of the treating physician toward nonresection. However, when these variables were included in a multivariate analysis, resection of the primary tumor remained a prognostic factor in the CAIRO2 study and in the subgroup of patients with one metastatic site in the CAIRO study.

What can we learn from our review on this subject? The studies that we identified were of nonrandomized design, performed in a single center, and retrospective of nature, with only one exception. Taken together, the data were in

**TABLE 3** Studies in which resection was defined as resection of the primary tumor and nonresection was defined as surgical intervention without resection (i.e., enterostomy, bypass, stenting)

Author	Years of study	Resection	No. of patients	OS (months)	<i>P</i> value	Postoperative mortality (%)	<i>P</i> value	Morbidity (%)	<i>P</i> value	Chemotherapy (%)
Makela et al. <sup>30a</sup>	1974–1983	Resection	66	15	NA	5	–	24	–	In total 22
		Nonresection	30	7		17		23		
Liu et al. <sup>29a</sup>	1986–1991	Resection	57	11	NA	9	–	10	–	–
		Nonresection	6	3		17		NA		
Konyalian et al. <sup>27a</sup>	1991–2002	Resection	62	13	<0.0001	5	–	19	–	58
		Nonresection	47 <sup>b</sup>	5		6		6		
Beham et al. <sup>21a</sup>	1993–2003	Resection	46	18	<0.001	4	–	7	–	85
		Nonresection	21	8		0		0		
Costi et al. <sup>13a</sup>	1994–2003	Resection	83	9	<0.001 <sup>f</sup>	8	0.397	29	0.366	0
		Nonresection	47	4		15		38		
Law et al. <sup>28a</sup>	1996–1999	Resection	150	7	<0.001	7	0.01	18	–	14
		Nonresection	30	3		21		In total		
Mik et al. <sup>32a</sup>	1996–2000	Resection	52	21	NA	–	–	50	0.041	53.8
		Nonresection	82	14		–		23.1		
Stelzner et al. <sup>35a</sup>	1995–2001	Resection	128	11.4	<0.0001	12	0.784	NA	–	In total 99
		Nonresection	58 <sup>c</sup>	4.6		10		NA		
<i>Asymptomatic only</i>		Resection	82	11.7	0.0002	9	0.401	NA	–	In total 99
		Nonresection	25	5.2		4		NA		
Yun et al. <sup>37a</sup>	1994–2004	Resection	283	15.3	<0.001 <sup>g</sup>	3	–	3	–	In total 56
		Nonresection	93	5.3		–		–		
<i>Asymptomatic only</i>		Resection	95	15.1	0.072 <sup>g</sup>	–	–	NA	–	In total 55 <sup>h</sup>
		Nonresection	36	6.1		–		–		
Evans et al. <sup>24</sup>	1999–2006	Resection	45	11	0.2056	16	–	NA	–	–
		Nonresection	52	7		36		NA		
Aslam et al. <sup>19</sup>	1998–2007	Resection	366	14.5	<0.005	7.6	–	32	–	63
		Nonresection	281 <sup>d</sup>	5.83		NA		NA		
Frago et al. <sup>38</sup>	2004–2008	Resection	12	39.1 <sup>e</sup>	0.008	8.3	–	41.6	–	100
		Nonresection	43	1.0 <sup>e</sup>		6.1		11.1		

<sup>a</sup> Study that concluded that resection should be performed if feasible

<sup>b</sup> Including 24 patients without intervention

<sup>c</sup> Including 16 patients without intervention

<sup>d</sup> A total of 168 patients received symptomatic and supportive treatment and 128 required surgical intervention

<sup>e</sup> Overall 2-year survival rate

<sup>f</sup> For patients with only technical resectable disease in both groups, also significant

<sup>g</sup> Multivariate analysis

<sup>h</sup> Only chemotherapy was prognostic for OS in the asymptomatic group of patients

favor of a resection of the primary tumor in patients with symptomatic lesions. In asymptomatic patients, the results are less clear, although the median OS was improved in resected patients in most studies. An important limitation of these studies is that few if any data on the use of systemic therapy were presented, which, given its impact on survival, makes it difficult to assess the relative contribution of resection to outcome.

The two main objectives in the management of patients with irresectable mCRC are to improve or maintain the

quality of life and to prolong survival. The treatment strategy in patients with stage IV disease and a symptomatic primary tumor usually consists of initial resection of this tumor, followed by palliative systemic treatment. In patients with few or absent symptoms of the primary tumor, arguments both in favor and against initial resection have been presented. The most dominant argument in favor of initial resection is the prevention of complications of the primary tumor with subsequent prolongation of symptom-free survival and OS.<sup>29,40,41</sup> Furthermore, Stillwell et al.

**TABLE 4** Studies in which resection was defined as resection of primary tumor and nonresection was defined as no intervention

Author	Years of study	Resection	No. of patients	OS (months)	<i>P</i> value	Postoperative mortality (%)	<i>P</i> value	Morbidity (%)	<i>P</i> value	Chemo therapy (%)
Liu et al. <sup>29a</sup>	1986–1991	Resection	57	11	NA	9	–	10	–	–
		Nonresection	5	2		NA				
Ruo et al. <sup>33a</sup>	1996–1999	Resection	127 <sup>b</sup>	16	<0.001	2	–	21	–	–
		Nonresection	103	9		NA		83		
Kaufman et al. <sup>26a</sup>	1998–2003	Resection	115	22	<0.0001	NA	–	NA	–	51
		Nonresection	69	3		NA		30		
Scoggins et al. <sup>34</sup>	1985–1997	Resection	66	14.5	0.59	5	–	30	–	–
		Nonresection	23 <sup>b</sup>	16.6		NA		100		
Tebbutt et al. <sup>36</sup>	1990–1999	Resection	280	14	0.08 <sup>c</sup>	NA	–	13 <sup>d</sup>	–	100
		Nonresection	82	8.2		NA		All in trials		
Michel et al. <sup>31</sup>	1996–1999	Resection	31	21	0.718	0	–	NA	–	97
		Nonresection	23	14		NA		100		
Benoist et al. <sup>39</sup>	1997–2002	Resection	32	23	NA	0	–	19	–	100 <sup>b</sup>
		Nonresection	27 <sup>b</sup>	22		NA		100 <sup>e</sup>		
Galizia et al. <sup>25a</sup>	1995–2005	Resection	42	15.2	0.03	0	–	21.4	–	100
		Nonresection	23	12.3		NA		100		
Bajwa et al. <sup>20</sup>	1999–2005	Resection	32	14	0.005	3	–	25	–	100
		Nonresection	35	6		NA		100		
Chan et al. <sup>22</sup>	2000–2002	Resection	286	14	<0.001	–	–	–	–	61
		Nonresection	125	6		–		58		
Evans et al. <sup>24</sup>	1999–2006	Resection	45	11	<0.0001	16	–	NA	–	–
		Nonresection	57	2		NA		–		
Seo et al. <sup>23</sup>	2001–2008	Resection	144	22	0.076 <sup>c</sup>	0	–	34.7	–	100
		Nonresection	83	14		NA		100		

<sup>a</sup> Study that concluded that resection should be performed if feasible

<sup>b</sup> Asymptomatic patients

<sup>c</sup> Multivariate analysis

<sup>d</sup> Obstruction primary tumor

<sup>e</sup> No differences in toxicity

found that patients initially treated with chemotherapy were 7.3 times more likely to have a complication from the primary tumor, and when operated for such complications, they were more likely to have a poor postoperative outcome.<sup>33,39,42</sup>

In the United States, most patients with mCRC undergo a resection of the primary tumor.<sup>9</sup> This is in contrast to the situation in the Netherlands, where a trend toward a non-resection approach has been observed.<sup>43</sup> This trend might be due to the availability of new active drugs and to a more adequate selection of patients for surgery.<sup>44</sup> Another argument in favor of resection of the primary tumor is the more accurate staging of disease because extrahepatic metastases may be better identified by visual exploration of the peritoneal cavity.<sup>25,31</sup> Circumstantial evidence comes from data that show an increased growth rate of liver metastases on resection of the primary tumor, as determined by an increased vascular density, proliferation rate, and metabolic

growth rate.<sup>45–47</sup> These data suggest that the outgrowth of metastatic disease may at least partly be controlled by the primary tumor. However, clinical data to support this concept are lacking. The most important argument against an initial resection of the primary tumor is that the survival benefit of resection has not been demonstrated, and that the morbidity and mortality associated with surgery should therefore be avoided.<sup>28,34,48</sup> Poultsides et al.<sup>49</sup> concluded that most patients with synchronous advanced CRC who receive up-front systemic therapy never require palliative surgery for their primary tumor, and that systemic therapy can be safely administered to these patients. We challenge their conclusion for two reasons. First, the median OS in their patient population with intact primary was only 13 months, while median OS times of 22–24 months are currently achieved for unselected mCRC patients. Second, we observed a higher incidence of toxicity in the non-resection group compared to the resection group, especially in

the CAIRO2 study. Patients in the nonresection group experienced more nausea, vomiting, and ileus, which might be related to the primary tumor.

Scheer et al.<sup>50</sup> concluded that for patients with synchronous metastatic disease and an asymptomatic primary tumor, initial chemotherapy was the treatment of choice because resection of the primary tumor provides only minimal palliative benefit, can give rise to major morbidity and mortality, and therefore may delay potentially beneficial chemotherapy.

This possible detrimental effect of a delay in systemic treatment caused by initial resection is not supported by the survival benefit, as shown in the CAIRO studies. However, a selection bias in this respect cannot be excluded because patients experiencing serious morbidity after resection obviously did not qualify for the CAIRO entry criteria and were therefore not included.

Taken together, the fact that the CAIRO results are derived from clinical studies with predefined inclusion criteria, treatment regimens, and follow-up schedules in our opinion provides stronger evidence for the prognostic value of resection of the primary tumor in CRC patients with stage IV disease compared with the data from the studies as presented in our review. However, in all studies presented to date, a selection bias cannot be excluded. Therefore, prospective studies on this topic are warranted; these are currently being planned.

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