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The Management of the Primary Tumor in Patients with Metastatic Colorectal Cancer

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Abstract

Over the past decade, the role of surgery in stage IV colorectal cancer (CRC) has evolved, yet the optimal surgical management of the primary tumor in patients with metastatic CRC that is not amenable to curative resection is unknown. A high rate of surgical resection of the primary tumor has been reported in patients with unresectable metastatic disease. Resection of the primary tumor in patients with metastatic CRC is often performed to deal with presenting primary tumor symptoms and or to prevent future primary tumor complications. Nevertheless, with access to novel agents and their efficacy in the primary tumor as well as lack of major complications related to an intact primary tumor, surgery is less commonly performed today. Although the data regarding survival advantages of resection of the primary tumor are inconsistent, overall the evidence suggests potential survival benefit of removal of the primary tumor in patients with both symptomatic and asymptomatic primary tumors even with access to more effective combination chemotherapy. However, the published literature favoring surgery mostly comprises retrospective observational studies. Consequently, the survival benefit related to surgery has been attributed to selection bias, and in the absence of randomized controlled trial no definite conclusion can be drawn. Currently, two randomized controlled trials are enrolling patients to answer this important question in the management of metastatic CRC.

Keywords: Primary tumor resection, stage IV colorectal cancer, palliative surgery, survival, metastatic colorectal cancer, primary tumor, colon cancer, rectal cancer, symptomatic tumor, chemotherapy

1. Introduction

The role of surgery in stage IV colorectal cancer (CRC) has evolved over the past two decades. Surgery has become an important treatment component in the management of patients with metastatic CRC [1–3]. Between 30 and 38% of patients diagnosed with stage IV CRC will undergo one or more major surgical procedures [4]. The known 5-year survival rate after liver and lung metastasectomy has been reported to be 25 to 51% and 30 to 73%, respectively [5]. Although administration of systemic therapy in patients with stage IV CRC may convert unresectable into resectable disease, in a majority of patients, the metastatic disease is not resectable. For most patients with advanced CRC, systemic chemotherapy is the primary treatment and the focus of management is on how best to palliate the symptoms and to prolong survival (**Figure 1**) [1]. With the availability of several novel agents and increasing use of liver-directed therapies, the median overall survival of patients with metastatic CRC has improved from 6 months with best supportive care alone to 30 months with the use of combination therapy [6].

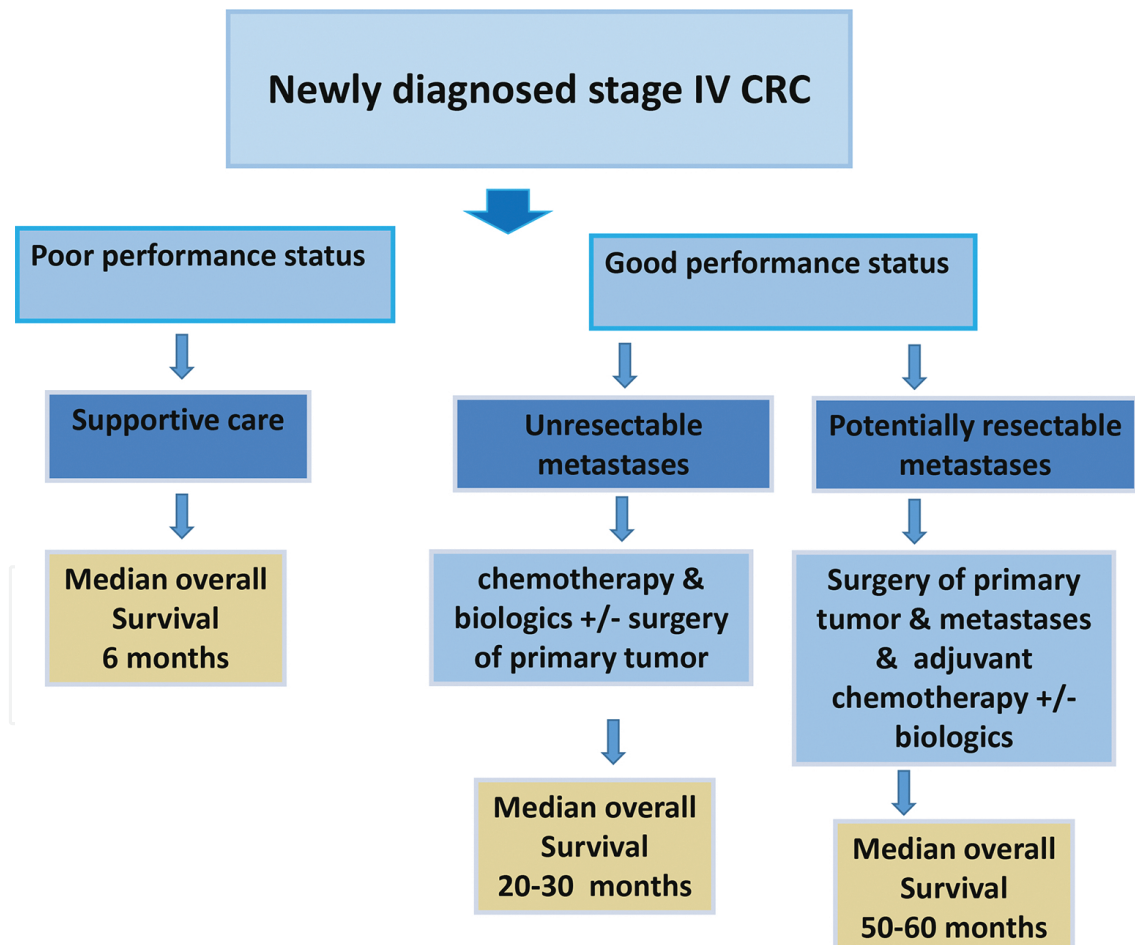


Figure 1. Framework of management of patients with stage IV CRC. Most patients are primarily treated with chemotherapy, nevertheless, a selected group of patients can be cured with primary tumor resection and metastasectomy. Currently, the role of resection of primary tumor in patients with unresectable metastatic disease is not well defined (Adapted with permission from Ahmed et al. [1]).

Even though enormous progress has been made in the treatment of patients with CRC within the past three decades, the optimal management of patients with metastatic disease not amenable to curative therapy who present without severe primary tumor-related symptoms has remained controversial. Resection of the primary tumor in patients with metastatic CRC is often performed to deal with presenting primary tumor symptoms and/or to prevent future primary tumor complications. Potential advantages of resection of the primary tumor in stage IV CRC are prevention of obstruction and major bleeding, better pain control, and potential reduction in serious adverse effects related to novel targeted therapy such as bleeding and perforation. Conversely, the newer generation chemotherapy in combination with targeted therapy has been associated with response rate of 40–60% [7]. Complications following resection of the primary tumor in patients with advanced CRC can delay or prevent initiation of systemic therapy and thereby precludes benefit associated with it. There is no evidence that response rates of the primary tumor are inferior to that of the metastases.

Recent data suggest that resection of the primary tumor in patients with stage IV CRC has been associated with a lower mortality risk [8]. Nevertheless, most studies failed to adjust for important prognostic variables such as performance status. In this chapter we will review the evidence regarding the benefit of resection of the primary tumor, limitations of the current evidence and future directions.

2. Argument for surgery

Resection of the primary tumor by lowering the tumor burden may maximize the benefit of chemotherapy and increase the potential for surgery with a curative intent. Evidence from other solid tumors such as renal cell cancer supports resection of the primary tumor in patients with metastatic disease. Two well-designed randomized trials demonstrated significant survival benefit for patients with metastatic renal cancer undergoing nephrectomy prior to systemic therapy. For example, Flanigan et al. reported median overall survival times of 11.1 compared with 8.1 months and Mickisch et al. of 17 versus 7 months in favor of nephrectomy [9, 10]. Surgical resection of the primary tumor in metastatic CRC may prevent complications caused by the primary tumor that may subsequently require emergency interventions which are associated with increased peri-operative mortality and unfavorable long-term outcome. Stillwell and others have shown that patients who were initially treated with chemotherapy were 7.3 times more likely to have a complication from the primary tumor and, when operated for such complications, were more likely to have a poor postoperative outcome [11–13].

3. Argument against surgery

Over the past decade, several highly active systemic agents, both cytotoxic and biologic, have become available for the treatment of patients with metastatic CRC. As a result, the median survival of patients with stage IV CRC has increased from 9 to 12 months with fluorouracil alone to up to 24 to 30 months with sequential modern cytotoxic and biologic treatments [1].

There remains concern of primary tumor-related complications during systemic therapy particularly with a risk of perforation when combining anti-VEGF (vascular endothelial growth factor) therapy to cytotoxic agents [14]. Recent studies, however, have demonstrated that combination chemotherapy and biological agents can be safely administered in patients with metastatic CRC with an in situ primary tumor [12, 15, 16]. A recent phase II trial utilizing bevacizumab containing regimen reported 14% primary tumor complications rate [17]. The author concluded that the survival is not compromised by leaving the primary colon tumor intact.

4. Evidence from the literature

The evidence regarding benefit of primary tumor resection, in patients with stage IV CRC and unresectable metastatic lesions is not conclusive. The published literature about survival advantages of removal of primary tumor is inconsistent; while some suggest benefit of surgery [8], others have failed to demonstrate survival benefit of non-curative resection of the primary tumor [18, 19].

Cirrochi and others performed a systematic review of seven non-randomized eligible studies involving 1086 patients. Of 1086 patients, 722 (66.4%) underwent primary tumor resection, and 364 (33.6%) were managed with chemotherapy alone [18]. The author concluded that resection of the primary tumor in asymptomatic patients with metastatic CRC was not associated with a consistent improvement in overall survival. Furthermore, primary tumor resection did not significantly reduce the risk of complications from the primary tumor. Another review by Scheer and others that specifically focused on complication rates of the primary tumor did not support surgery. Based upon the data on 850 patients from 7 papers published from 1999 to 2006 when first-line chemotherapy was administered in patients with unresectable stage IV CRC, obstruction and intestinal hemorrhage were observed in 13.9% and 3% of the patients, respectively. On the other hand, when upfront surgery of the primary tumor was performed, complications rates were 18.8–47%. Of note, two of 7 studies in this review did not have a surgical intervention group [19].

Our research group conducted a systematic review and meta-analysis of the current literature [8]. Of total of 3379 reports, 15 retrospective observational studies were selected with patients population of 12456 (**Table 1**) [12, 13, 20–31]. Six studies were exclusively done in minimally symptomatic patients and 10 studies met the criteria of using new generation anti-cancer therapy. All included studies were retrospective observational studies. No study met the criteria for good quality study using ‘validity scoring for observational study’ for any outcome of interest. Overall, 26% patients had rectal tumor, 21.9% in the resection group compared with 31% in the control. For the primary outcome “overall survival” 9 of 15 studies were of low quality and remaining 6 were fair quality. Among 12,456 patients, 8620 (69%) underwent surgery with a median overall survival of the 15.2 months (range: 10–30.7) compared with 11.4 months (range: 3–22) of the non-resection group. Quantitative meta-analysis utilizing the data of all 15 studies revealed that the primary tumor resection was associated with a significant improvement in survival compared with no surgery with a hazard ratio (HR) of 0.69 (95%

confidence interval [CI]: 0.61–0.79). Nine studies reported surgical mortality rate. Mean 30 days post-operative mortality rate in the intervention group was 4.9% (95% CI: 0–9.7%). Only seven studies reported non-fatal surgical complications including anastomotic leak, surgical wound infection and other complications. The mean surgical morbidity rate was 25.9% (95% CI: 20.1–31.6). Mean primary tumor complications rate & non-surgical procedures rate in the control group were 29.7% (95% CI: 18.5–41.0) and 27.6% (95% CI: 15.4–39.9), respectively. No study provided quality of life data. In a sub-group analysis involving studies during the period of modern chemotherapy, the median overall survival of group with surgery was 18.7 months (range: 11–30.7) compared with 12.85 months (range: 5.8–22) in the control group. The HR for survival of the subgroup treated with irinotecan and or oxaliplatin based chemotherapy was 0.68 (95% CI: 0.56–0.83) favoring the surgical intervention compared with HR of 0.73 (95% CI: 0.59–0.90) of the group treated with older regimen. Likewise, in a separate sub-group analysis of studies restricted to minimally symptomatic tumor from the primary tumor, the median overall survival of group with surgery was 18.5 months (range: 14.5–23) versus 13.15 months (range: 5.8–22) in the control group. The HR for survival of minimal symptomatic patients was 0.67 (95% CI: 0.48–0.94) favoring the intervention group compared with HR of 0.75 (95% CI: 0.67–0.84) of symptomatic patients. A substantial low quality studies, publications bias and selected reporting were the major limitations of the review. Consequently, the survival benefit related to surgery has been attributed to selection bias and selection of younger and healthier patients with good performance status.

To address some of the limitations reported in the literature our research group conducted a cohort study to evaluate survival benefit of surgery (**Table 2**) [32]. The study population was comprised of adult patients with histologically documented adenocarcinoma of colon and rectum, intact primary tumor and evidence of metastases, diagnosed between the period of 1992 and 2005, in the Canadian province of Saskatchewan. In this large population based cohort study individual medical records were reviewed to retrieve information about important prognostic variables including performance status. A total 1378 eligible patients with median age of 70 years were identified. Five hundred and forty four (39.5%) patients were symptomatic. Nine hundred and forty four (68.5%) patients underwent resection of the primary tumor. Of 1378 patients, 29.5% had rectal or recto-sigmoid tumor (rectal, 20.1%, recto-sigmoid, 9.4%). Among 1378 patients, 42.3% received chemotherapy and 45.1% received 2nd generation (irinotecan and/or oxaliplatin based) therapy. Patients who underwent primary tumor resection and received chemotherapy had median overall survival of 18.3 months (95% CI: 16.6–20) compared with 8.4 months (95% CI: 7.1–9.7) if they were treated with chemotherapy alone ($p < 0.0001$). In a subgroup of patients who were treated with second generation chemotherapy, median survival of patients who underwent surgical resection of primary tumor was 24.6 months (95% CI: 20.2–29.0) versus 11.0 months (95% CI: 7.8–14.3) if they did not have surgery. Due to imbalance between the two groups with respect to important prognostic variables such as chemotherapy, metastasectomy, and performance status a Cox proportional multivariate analysis was performed. The analysis revealed that resection of the primary tumor was independently correlated with better survival after adjustment for important clinical and pathological variables. For example, use of chemotherapy (HR 0.47, 95% CI: 0.41–0.54), primary tumor resection (HR 0.49, 95% CI: 0.41–0.58), second line chemotherapy (0.47, 95% CI:

0.45-0.64), and metastasectomy (HR 0.54, 95% CI: 0.45-0.64) were correlated with superior survival whereas older age, poor performance status, low albumin, elevated bilirubin, elevated alkaline phosphatase, anemia, leukocytosis, colonic primary, and grade 3 tumor were correlated with inferior survival. The tests for interactions between the surgical resection of primary tumor and second line therapy or more than 2 metastatic sites, were significant suggesting greater benefit of surgery in patients who received further line of therapies or who had limited metastases. Since patients who undergo metastasectomy have potential to achieve long term survival, a secondary analysis, after excluding patients who underwent metastasectomy was performed. In the secondary analysis, surgical resection of primary tumor significantly correlated with better survival (adjusted HR of 0.43; 95% CI: 0.41–0.52).

Study and year of publication	Study design	Study duration	N	Patients	Co-interventions	Outcomes
Aslam et al. 2010 [26]	Retrospective multi-centers observational study	1998–2007	T: 647 I: 366 C: 281	Minimally symptomatic	Chemotherapy I: 63%, C: 36%	Median OS 14.5 (I) vs. 5.8 (C) months (p<0.05); post-operative mortality (I) 7%
Benoist et al. 2005 [12]	Retrospective single institutional case-control study	1997–2002	T: 59 I: 32 C: 27	Asymptomatic or minimally symptomatic	Chemotherapy I: 94%, C: 100%; metastasectomy I: 16%, C: 22%	Median OS 22 (I) vs. 23 (C) months (p=NS); post-operative mortality (I) 0%
Chan et al. 2010 [27]	Retrospective population based study	2000–2002	T: 411 I: 286 C: 125	Symptomatic & asymptomatic	Chemotherapy I: 61%, C: 58%; metastasectomy I: 10%, C: 0%	Median OS 14 (I) vs. 6 (C) months (p<0.05)
Evans et al. 2009 [28]	Retrospective single institutional observational study	1999–2006	T: 97 I: 45 C: 52	Symptomatic & asymptomatic	Chemotherapy I: NP, C: 42%	Median OS 11 (I) vs. 7 (C) months (p=NS); post-operative mortality (I) 16%
Galizia G et al. 2008 [24]	Retrospective single institutional observational study	1995–2005	T: 65 I: 42 C: 23	Asymptomatic or minimally symptomatic	Chemotherapy I: 100%, C: 100%; metastasectomy I: 12%, C: 4%	Median OS 15.2 (I) vs. 12.3 (C) months (p=0.003); post-operative mortality (I) 0%
Karoui M et al. 2011 [21]	Retrospective multi-centers observational study	1998–2007	T: 208 I: 123 C: 85	Symptomatic & asymptomatic	Chemotherapy I: 100%, C: 99%; metastasectomy I: 23%, C: 29%	Median OS 30.7 (I) vs. 21.9 (C) months (p=0.004)
Konyalian et al. 2007 [29]	Retrospective single institutional cohort study	1991–2002	T: 109 I: 62 C: 47	Symptomatic & asymptomatic	Chemotherapy I: 71%, C: 60%	Median OS 12.5 (I) vs. 4.6 (C) months (p<0.05); post-operative mortality (I) 5%
Michel et al. 2004 [30]	Retrospective single institutional observational study	1996–1999	T: 54 I: 31 C: 23	Asymptomatic or minimally symptomatic	Chemotherapy I: 97%, C: 100%; metastasectomy I: NP, C: 9%	Median OS 21 (I) vs. 14 (C) months (p=NS); post-operative mortality (I) 0%
Ruo et al. 2003 [13]	Single institutional retrospective observational study	1996–1999	T: 230 I: 127 C: 130	Asymptomatic or minimally symptomatic	Chemotherapy I: NP, C: 83%	Median OS 16 (I) vs. 9 (C) months (p<0.05); post-operative mortality (I) 2%
Scoggins et al. 1999 [22]	Single institutional retrospective observational study	1985–1997	T: 89 I: 66 C: 23	Symptomatic & asymptomatic	NP	Median OS 14.5 (I) vs. 16.6 (C) months (p=NS)
Seo et al. 2010 [31]	Single institutional retrospective observational study	2001–2008	T: 277 I: 144 C: 83	Asymptomatic or minimally symptomatic	Chemotherapy I: 100%, C: 100%	Median OS 22 (I) vs. 14 (C) months (p=NS); post-operative mortality (I) 0%
Tebutt et al. 2003 [23]	Single institutional retrospective observational study	1990–2000	T: 362 I: 208 C: 82	Symptomatic & asymptomatic	Chemotherapy I: 100%, C: 100%; metastasectomy I: 2%, C: 1%	Median OS 14 (I) vs. 8.2 (C) months (p=NS)
Temple et al. 2004 [25]	Population based study using SEERS & Medicare data	1991–1999	T: 9011 I: 6464 C: 2542	65 years or older symptomatic & asymptomatic	Chemotherapy I: 47%, C: 31%; metastasectomy I: 5.2%, C: 1.3%	Median OS 10 (I) vs. 3 (C) months (p<0.05); post-operative mortality (I) 9%
Venderbosch et al. 2011 (CAIRO) [20]	Retrospective multi-centers cohort of a RCT	2003–2004 (recruited period)	T: 399 I: 258 C: 141	Symptomatic & asymptomatic	100% chemotherapy in both groups	Median OS 16.7 (I) vs. 11.4 (C) months
Venderbosch et al. 2011 (CAIRO 2) [20]	Retrospective multi-centers cohort of a RCT	2005–2006 (recruited period)	T: 488 I: 289 C: 159	Symptomatic & asymptomatic	100% chemotherapy in both groups	Median OS 20.7 (I) vs. 13.4 (C) months

C=control group; I=intervention group; N=number; NP=not provided; NS=not significant; OS=overall survival; RCT=randomized controlled trial; T=total.

Table 1. Summary of studies that evaluated benefit of resection of primary tumor and were included in a systematic review and meta-analysis.

Study & year of publication	Study design	Study duration	N	Patients	Co-interventions	Outcomes*
Ahmed et al. 2013 [32]	Retrospective Population based cohort study	1992–2005	T: 1378 I: 944 C: 434	Symptomatic & asymptomatic	Chemotherapy I: 50%, C: 20% metastasectomy I: 19.4%, C: 3.5%	Median OS 18.3 (I) vs. 8.4 (C) months (p<0.001); post-operative mortality (I) 6.6%
Ahmed et al. 2015 [33]	Retrospective Population based cohort study	1992–2005	T: 834 I: 521 C: 313	Asymptomatic or minimally symptomatic	Chemotherapy I: 53%, C: 28%; metastasectomy I: 20.5%, C: 2.9%	Median OS 19.7 (I) vs. 8.4 (C) months (p<0.001); post-operative mortality (I) 4.8%
Ahmed et al. 2015–2016 [34]	Retrospective Population based cohort study	2006–2010	T:569 I:313 C:256	Symptomatic & asymptomatic	Chemotherapy I: 64%, C: 50%; metastasectomy I: 26%, C: 3%	Median OS 27 (I) vs. 14 (C) months(p<0.001); post-operative mortality (I) 5%

C=control group; I=intervention group; N=number; OS= overall survival; T=total.

Table 2. Summary of three population based cohort studies that used individual patients' data and evaluated survival benefit of surgery of primary tumor by controlling the important prognostic variables in stage IV CRC

Our study suggests that resection of the primary tumor in patients with stage IV CRC improves survival, independent of age, performance status, co-morbid illness and chemotherapy. Nevertheless, the study was inclusive of symptomatic patients who tend to get benefit from palliative resection of the primary tumor, we therefore conducted a sub-group analysis involving a cohort of patients with asymptomatic or minimally symptomatic primary tumor to confirm survival benefit of surgery (**Table 2**) [33]. A total of 834 patients with median age of 70 years were identified. Among them, 521 (63%) patients underwent surgery and 43.3% received chemotherapy. Patients who underwent surgery had median overall survival of 19.7 months (95% CI: 16.9–22.6) compared with 8.4 months (95% CI: 6.9–10.0) if they did not have surgery (p<0.0001). The study once more confirmed the survival benefit of surgery after adjustment of other important prognostic variables in a multivariate analysis. Among various prognostic variables, 5FU-based chemotherapy (HR 0.43; 95% CI: 0.36–0.53), surgery of primary tumor (HR 0.47; 0.39–0.57), metastasectomy (HR 0.48; 0.38–0.62), and 2nd line chemotherapy (HR 0.72; 0.58–0.92) were correlated with superior survival. Test for interaction between ≥1 metastatic sites and surgery was significant suggesting a larger benefit of surgery in patients with stage IVA disease.

4.1. Benefit of surgery in patients treated with combination chemotherapy and biologics

Our data revealed the potential benefit of resection of the primary tumor regardless of underlying symptoms and that patients with asymptomatic or minimally symptomatic primary tumor who underwent surgery had similar survival benefit with overall 53% reduction in mortality after adjustment for older age, comorbid illness, poor performance status, disease burden, chemotherapy, and metastasectomy. Of note, a larger benefit of surgery was noted in patients with stage IVA disease. However, only about 43% of patients were treated with systemic therapy. Among the treated patients about 45% received irinotecan- or oxaliplatin-based (FOLFIRI or FOLFOX) chemotherapy. Moreover, less than 5% received a biological agent. It is not known if similar benefit can be achieved with the use of more effective systemic therapy. Our research group undertook a study to validate our findings in a cohort of patients with stage IV CRC who were diagnosed during the period of modern systemic therapy. A cohort of 569 patients with stage 4 CRC diagnosed during 2006–2010 in the province of Saskatchewan was evaluated (**Table 2**) [34]. Their median age was 69 years (59–95), 57.3%

Variables	HR (95% confidence interval)
Use of any chemotherapy	
Yes	0.33 (0.26–0.43)
No	1
Metastasectomy	
Yes	0.43 (0.31–0.58)
No	1
Surgical resection of primary tumor	
Yes	0.44 (0.35–0.56)
No	1
Second-line treatment	
Yes	0.50 (0.35–0.70)
No	1
Third-line treatment	
Yes	0.58 (0.41–0.83)
No	1
Serum alkaline phosphatase >120 U/l	
Yes	1.50 (1.20–1.78)
No	1
Grade III tumors	
Yes	1.33 (1.10–1.62)
No	1
Leukocytosis	
Yes	1.32 (1.05–1.66)
No	1
Stage IVb CRC	
Yes	1.31 (1.10–1.56)
No	1
ECOG performance status >1	
Yes	1.30 (1.04–1.57)
No	1

HR=hazard ratio; ECOG=Eastern Cooperative Oncology Group.

Table 3. Prognostic variables that correlate with survival in stage IV CRC in a multivariate analysis [34])

received chemotherapy, 91.4% received FOLFIRI or FOLFOX and 67% received a biologic agent. Median overall survival (OS) of patients who underwent surgical resection of primary tumor and received chemotherapy was 27 months compared with 14 months of the non-resection group ($p < 0.0001$). Median OS of patients who received all active agents and had surgery was 39 months (95% CI: 25.1–52.9). Patients with asymptomatic primary tumor who underwent surgery and received systemic therapy had a median OS of 34 months (95% CI: 26.6–43.4) compared with median OS of 14 months (95% CI: 11.1–17.0) if they did not have surgery ($p < 0.001$). Median duration of hospital stay of was 9 days (interquartile range: 7–13). Overall, 30 days mortality rate of the group who underwent surgery was 5.4%. Fifteen of 171 (8.8%) patients with symptomatic disease compared with 2 (1.4%) of 142 patients with asymptomatic or minimally symptomatic disease died within 30 days of surgery ($p = 0.003$). Post-operative complications rates were not mutually exclusive and were as followed: post-operative wound infection, 7.3%, non-wound infection, 4.8%, anastomotic leak, 2.2%, wound dehiscence, 1.9%, bleeding, 1.6%, and pulmonary embolism, 1.8%.

On multivariate analysis, surgery of primary tumor, HR: 0.44 (95% CI: 0.35–0.56), use of chemotherapy, HR: 0.33 (95% CI: 0.26–0.43), metastasectomy, HR: 0.43 (95% CI: 0.31–0.58), second line therapy, HR: 0.50 (95% CI: 0.35–0.70), and third line therapy, HR: 0.58 (95% CI: 0.41–0.83) were correlated with superior survival (**Table 3**). After adjustment for other prognostic variables, only the interaction between surgical resection of primary tumor and subsequent line of therapy was significant suggesting a differential benefit of removal of primary tumor in patients who received other lines of therapies. In a subgroup of 345 patients with asymptomatic or relatively asymptomatic primary tumors, surgery was significantly correlated with better survival with HR 0.32 (95% CI: 0.22–0.45).

Other studies also supports potential advantage of resection of primary tumor in patients who are treated with modern chemotherapy regimens. A retrospective analysis of CAIRO study that compared combination versus sequential chemotherapy demonstrated a significantly better median OS of 16.7 months in patients who underwent resection of primary tumor compared with 11.4 months with no surgery (HR 0.61, 95% CI: 0.49–0.76) [20]. Likewise, a pool analysis of four French phase 3 trials involving 850 patients indicated survival benefit of surgery [35]. More than two third of patients were treated with FOLFIRI or FOLFOX and about 12% received bevacizumab.

Since the publication of our meta-analysis, the resection of the primary tumor has become one of the key issues in the management of stage 4 CRC. Several recent studies have addressed this question in patients with symptomatic or minimally symptomatic tumors [36–39]. Ishihara and others retrospectively evaluated 1982 patients with stage 4 CRC from 1997 to 2007 [36]. Among the whole patient population, primary tumor resection significantly improved survival (HR: 0.46, 95% CI 0.32–0.66). However, primary tumor resection did not significantly improve survival in patients treated in the first 5 years of the study, patients aged > 65 years, female patients, patients with right-sided colon cancer, and patients without nodal involvement. Gresham et al. [37] evaluated 517 patients with stage 4 CRC. Among them, 378 (73%) patients underwent palliative resection of their primary tumor. Palliative resection was associated with a longer median OS (17.9 vs. 7.9 months) and more favorable adjusted HR for

death (0.56, 95 % CI: 0.40–0.78). In a propensity score-matched analysis, prognosis was also more favorable in the resected group ($p = 0.0017$). Tarantino and others used the Surveillance, Epidemiology, and End Results (SEER) database from 1998 to 2009 and identified 37,793 patients with stage IV CRC. Of those, 23,004 (60.9%) underwent palliative primary tumor resection. The primary cancer resection was associated with a significantly improved OS (HR: 0.40, 95% CI: 0.39–0.42) and cancer-specific survival (HR: 0.39, 95% CI: 0.38–0.40) [38]. Yun and others assessed 416 patients with asymptomatic unresectable stage IV CRC from year 2000 to 2008 [39]. Among 416 patients, 218 (52.4%) underwent palliative resection of the primary tumor. Their data revealed that palliative resection was not associated with a significant increase in survival compared with non-resection. Clancy and others performed an updated meta-analysis of 21 eligible studies involving a total of 44,226 patients [40]. Resection of the primary tumor in patients with unresectable metastases compared with chemotherapy alone was associated with a lower mortality risk (odds ratio [OR] 0.28; 95% CI: 0.165–0.474; $P < 0.001$), translating into a difference in mean survival of 6.4 months in favor of resection (95% CI: 5.025–7.858). Patients who underwent resection of the primary tumor were more likely to have liver metastasis only (OR 1.551; 95% CI: 1.247–1.929), were less likely to have ≥ 2 metastasis (OR 0.653; 95% CI: 0.508–0.839), and were less likely to have rectal cancer (OR 0.495; 95% CI: 0.390–0.629).

5. Time trend in surgery of the primary tumor

In spite of uncertain survival benefit, a high rate of surgical resection has been reported in patients with unresectable metastatic disease. Nevertheless, with access to novel agents and their efficacy in the primary tumor as well as lack of major complications related to an intact primary tumor, surgery is less commonly performed [16, 17, 41]. Hu and others performed a retrospective cohort study using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results CRC registry involving 64,157 patients diagnosed with stage IV colon or rectal cancer from January, 1988, through December, 2010. Of the 64,157 patients, 43,273 (67.4%) had undergone primary tumor resection [42]. The annual rate of primary tumor resection significantly decreased from 74.5% in 1988 to 57.4% in 2010, and a significant annual percentage change occurred between 1998–2001 and 2001–2010 (-0.41% vs -2.39%). Among various prognostic variables age younger than 50 years, female sex, being married, higher tumor grade, and presence of colon tumors were correlated with primary tumor resection.

6. Mechanisms of potential survival advantages of surgery

The underlying mechanism of potential survival benefit related to the removal of primary tumor is mostly hypothetical. It is well recognized that surgical resection of primary tumor with or without debulking of metastatic lesions, in some malignant diseases such as ovarian and renal cell cancer, has been associated with better survival [43, 10]. Non-curative resection of the primary tumor in patients with advanced cancer may prevent local tumor complications

and improve disease control by simply reducing the tumor bulk. The host-tumor interaction plays an important role in cancer progression [44]. It is plausible that the primary tumor may secrete cytokines that promote tumor growth and reduce response to cytotoxic agents [46]. Turner and others examined the effect of primary tumor resection on systemic inflammation and survival in patients with stage IV CRC using the neutrophil-lymphocyte ratio (NLR) as a biomarker of systemic inflammation [46]. The reversal of an elevated NLR following the primary tumor resection was associated with significantly improved OS (hazard ratio, 0.53).

Hence, resection of the primary tumor by affecting the tumor-host relationship may slow the cancer progression. Furthermore, removal of primary tumor may restore the host immune system and may improve response to systemic therapy [47].

7. Limitations of the published literature

Most studies obtained data retrospectively. Many studies failed to provide baseline prognostic information of resection and non-resection groups while others showed significant imbalance in baseline characteristics of the two groups and did not make adjustment for that. Only few studies provided detail information about the use and type of chemotherapy in each group. In addition, to our knowledge no study have adjusted for BRAF mutation which has been reported in about 5-11% stage IV CRC and is an important prognostic marker [48]. Although our cohort studies were good quality studies, imbalance of several known and unknown prognostic variables between the two groups suggests bias [32–34]

8. Future directions

At least two randomized clinical trials are currently evaluating the survival benefit of removal of primary tumor in patients with metastatic CRC [49, 50]. The SYNCHRONOUS trial is a multicenter German study comparing resection of the primary tumor and systemic therapy to systemic therapy alone in patients with metastatic colon cancer which is not amenable to curative therapy [49]. The investigators estimated that resection of the primary tumor will prolong survival from 20 to 26 months. In addition to survival, the study is evaluating short- and long-term safety of both treatment strategies, subsequent curative procedures, and patients' quality of life. In this trial, 694 patients (347 per group) will be enrolled to test the hypothesis that removal of the primary tumor has been associated with superior survival.

The CAIRO trial is a multicenter Dutch trial which is evaluating benefit of resection of the primary tumor in patients with synchronous unresectable metastatic CRC [50]. Patients with synchronous metastatic colon cancer with asymptomatic or minimally symptomatic primary tumor will be randomized to systemic treatment or resection of the primary tumor followed by systemic treatment. Unlike SYNCHRONOUS, trial patients with colon or rectal cancer are included in this study. A total of 360 patients will be enrolled to detect a difference in median overall survival of 13 compared with 19 months.

9. Conclusions

Although evidence suggests possible survival benefits with surgery despite the availability of effective chemotherapeutic agents, due to a lack of prospective clinical trials, no firm conclusions can be drawn with respect to whether surgical resection of the primary tumor should be routinely offered to all patients with newly diagnosed metastatic CRC. Currently, two randomized controlled trials are evaluating this important question in the management of metastatic CRC. If the magnitude of survival benefits is confirmed in future randomized clinical trials, surgical resection of the primary tumor could potentially be a more cost effective intervention compared with novel systemic therapy in the management of stage IV CRC.

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