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Resection of the primary tumor in stage IV colorectal cancer: when is it necessary?

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Introduction

Approximately 20% of patients with colorectal cancer present with metastatic disease, which can be challenging to manage (1). Within this subpopulation, there are many different clinical scenarios, leading to a potentially complex decision-making process for selecting a treatment plan. Despite considerable advances in the treatment of metastatic colorectal cancer, in the majority of cases the disease is not curable. Therefore, the goal of treatment for most patients is to extend survival and improve the quality of life. Treatment options are tailored to the patient's performance status, comorbidities, disease burden, and the presence or absence of symptoms such as bowel obstruction (2).

For patients with minimal primary-tumor symptoms and acceptable performance status, the standard treatment according to the National Comprehensive Cancer Network guidelines is systemic chemotherapy, which has been shown to increase survival (3, 4). Over the last 10 years, the overall survival (OS) rate has improved from 9 to 24 months (and in some series up to 36 months) which is possibly the result of the addition of multiagent chemotherapy (5,6). First line chemotherapy with FOLFOX or FOLFIRI (folinic acid, fluorouracil, irinotecan) produces major responses in the majority of previously untreated patients (7).

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Systemic therapy alone rarely cures the disease; however, in patients with resectable disease, effective chemotherapy combined with complete resection of metastatic disease maximizes the possibility of a cure.

In this context, several important questions arise. Is the metastatic disease resectable? If so, should the resection be synchronous or staged and, if staged, in what order? If the metastatic disease is not resectable, is resection of the primary tumor indicated? These and related questions are matters of considerable debate, reflecting the complexity of the management of metastatic colorectal cancer. In this chapter, we review the published literature with the goal of developing an evidence-based approach to managing various clinical scenarios associated with metastatic colorectal cancer.

Evaluation

The evaluation of colorectal cancer is based on the principles of accurate staging and multidisciplinary treatment planning. After a thorough history is taken and a physical examination is performed, the disease is staged. Accurate staging includes tissue diagnosis; carcinoembryonic antigen measurement; and cross-sectional imaging of the chest, abdomen, and pelvis. In addition, rectal cancer requires rectal MRI and/or endorectal ultrasound for local staging. Several imaging modalities, including MRI, CT, and PET are available to identify metastatic disease and facilitate differentiation from other conditions such as hemangiomas, focal nodular hyperplasia, or cysts in patients with liver metastases. Carcinoembryonic antigen levels greater than 20 ng/mL warrant a high degree of suspicion for systemic disease (8).

Symptomatic Primary Tumor

One of the more disagreed upon treatment decisions in metastatic colorectal cancer relates to the appropriate time and indication for resection of the primary tumor. Traditionally, “symptomatic” primary tumors warranted resection, but in reality, the degree of symptoms is variable, and tumors that are mildly symptomatic may become less troublesome after systemic therapy.

Without question, perforated primary tumors with associated peritonitis warrant exploration and resection when feasible. In cases of complete bowel obstruction, the need for urgent or emergency surgery is also straightforward. However, the incidence of this presentation is difficult to measure, as cases of complete obstruction are commonly reported together with cases of partial obstruction. Patients with partial or complete bowel obstruction represent between 8 and 29% of all patients with colorectal cancer (9). Patients with a complete obstruction typically have either stage III or stage IV disease (10). Complete colonic obstruction requires urgent intervention by stenting, resection, or diversion to relieve this life-threatening condition, which can otherwise lead to perforation, peritonitis, or sepsis. Severe, massive bleeding from the tumor site, though less common, is another indication to pursue resection. Surgical intervention is performed using oncological principles as long as the preoperative circumstances allow it (11). The risks and benefits of primary anastomosis

must be discussed in detail, so that the patient understands the risks of anastomotic leak, including death or possible delay in the initiation of chemotherapy (12).

Asymptomatic Primary Tumor with Resectable Metastatic Disease

Excluding the scenarios described above, the management of the primary tumor in patients with stage IV colorectal cancer depends on whether the metastatic disease is resectable. The most common site of colorectal cancer metastasis is the liver. Approximately 25% of patients with colorectal cancer present with liver metastasis at the time of diagnosis (13). Among patients with stage IV colorectal cancer, those with liver metastasis have the greatest chance of complete resection and cure. In borderline resectable cases, induction chemotherapy may improve the likelihood of resection. The EORTC CLOCC trial (14) was the first prospective randomized trial to demonstrate a survival benefit from resection/ablation plus chemotherapy vs. systemic treatment alone. The 8-year OS was 36% for the combination treatment and 9% for systemic therapy alone. Furthermore, progression-free survival was 16.8 and 9.9 months, respectively. For patients with apparently resectable disease, induction chemotherapy may be omitted (this decision making process is outside the scope of this chapter).

Staged Resection

Historically, the preferred operative approach for stage IV colorectal cancer with liver metastasis began with resection of the primary tumor, followed by chemotherapy and then liver resection 2 to 3 months later. The proponents of this strategy based their argument on the hypothesis that the primary tumor may seed metastatic disease in an ongoing manner. Furthermore, there was concern that the primary tumor would progress to complete colonic obstruction, perforation, or hemorrhage. Additionally, complications from colorectal resection such as anastomotic leak may be exacerbated by the perioperative effects of hepatic resection. It is believed that the low-flow state or temporary changes in portal blood circulation could affect oxygenation of the bowel anastomosis (15).

On the other hand, there are arguments for not resecting the primary tumor first. One such argument is based on the fact that induction chemotherapy with fluorouracil-based regimens can produce a significant response in both the primary tumor and hepatic metastases. Another argument is that complications associated with resection at the primary site can delay further treatment and thereby promote metastasis progression. Given that the presence of systemic metastasis is one of the main determinants of survival, many physicians prioritize the treatment of metastatic lesions (16).

Simultaneous Resection

With the recent advances in liver resection techniques and the associated perioperative care, outcomes for patients who undergo simultaneous resection of the primary tumor and the metastasis have improved. Cumulative morbidity and mortality rates have been similar to or better than those for patients who have undergone staged procedures (17, 18).

Some authors recommend that the simultaneous approach be used only when the liver resection is minor, since major liver resections are thought to be associated with relatively

high morbidity (19). However, recent data indicate that combining a major liver resection with resection of the primary colorectal tumor is safe, leading to more centers favoring the simultaneous approach (20). Silberhumer et al. (21) reported that the 1- and 5-year OS rates for simultaneous resection were similar to those for the staged approach (90.5 vs. 92.6% at 1 year and 38.5 vs. 38.9% at 5 years, respectively). The 5-year rates of disease-free survival were also similar (25.3 vs. 24.3%, respectively). In a multicenter analysis, Mayo et al. (22) also found that the staged approach and the simultaneous approach produced similar oncological outcomes.

As shown in Table 1, many other studies found no significant differences between simultaneous resection and staged resection (regardless of whether the primary tumor or the metastasis was resected first). The choice of the approach should therefore be based on the expertise available at different institutions.

Asymptomatic Primary Tumor with Unresectable Metastatic Disease

Traditionally, prophylactic resection of the primary tumor in asymptomatic patients with unresectable metastatic disease has been performed for many patients, with the goal of avoiding late complications such obstruction, perforation, or hemorrhage. Most of the evidence supporting this strategy is from the era of fluoropyrimidine monotherapy, which was the standard of care during the 1990s. In those years, more than two-thirds of patients with synchronous colorectal cancer metastasis underwent upfront resection of the primary tumor, with the goal of preventing future hypothetical complications and eliminating chemoresistance thought to be associated with the primary tumor (23,24). However, there was little evidence to support this approach, as the few studies on outcomes in patients with an intact primary tumor treated with fluoropyrimidine monotherapy showed that the risk of needing urgent palliative resection was 9–29% (Table 2).

Ruo et al. (25) reported that of 103 patients treated with fluorouracil monotherapy between 1996 and 1999, 30 required surgical palliative intervention, even though 23 patients with rectal cancer received radiation therapy upfront (Table 2). Another, prospective study showed a similar rate of palliative surgical intervention (25%) in 24 patients treated with fluoropyrimidine monotherapy (26) (Table 2). We can conclude from these studies that approximately four in five patients with metastatic colorectal cancer treated upfront with single-agent chemotherapy will not experience primary-tumor-associated complications requiring palliative surgical intervention.

Some recent findings support primary tumor resection in patients with unresectable colorectal cancer metastasis, including patients treated with FOLFOX or FOLFIRI in addition to biologic agents. In a Canadian study of patients with stage IV colorectal cancer diagnosed during 2006–2010 (30), 199 patients who received chemotherapy underwent upfront resection, and 127 other patients who also received chemotherapy did not undergo upfront resection. Ninety-one percent of patients received FOLFIRI or FOLFOX, and 67% received a biologic agent. The median OS was 27 months in the resection group and 14 months in the nonresection group. These findings appear to suggest that primary tumor resection may improve outcomes. However, the longer OS could be a result of selection bias:

54% of the patients in the nonresection group had stage IVb disease compared to 40% in the resection group, and performance status in the nonresection group was poorer (48%) than in the resection group (25%).

A meta-analysis of 21 studies including 44,226 patients (31) found that patients with metastasis who underwent resection of the primary tumor had a lower risk of death than patients who received chemotherapy alone, with a difference in mean OS of 6.4 months (95% confidence interval, 5.0–7.9; $P < 0.001$). However, selection bias may have played a significant role in these findings as well. Patients who underwent resection were more likely to have colon rather than rectal cancer, and most of the resection patients had a single metastasis confined to the liver.

A pooled post hoc analysis of four randomized trials including 816 patients (32–36) (Table 3) found that primary tumor resection was independently associated with longer OS (median, 19.2 vs. 13.3 months) in multivariate analysis (Kaplan-Meier curve).The association of OS with resection of the primary tumor did not differ significantly between the trials or between the types of chemotherapy received. Selection bias seems to be the most common limitation across the four studies. For example, in one of the trials (32) the decision to resect the primary tumor was made prior to randomization. Also, no tumorspecific mutation markers (e.g., RAS or BRAF) were available when these studies were conducted, which in addition to other unmeasured factors, may explain the lower survival in the nonresection group. Finally, despite the adjustments for known potential confounders, it remains likely that resections were more likely to be performed in patients with better prognoses, leading to longer OS.

A retrospective analysis of two randomized trials conducted by the Dutch Colorectal Cancer Group (CAIRO and CAIRO-2) compared 547 patients who underwent a primary tumor resection and 310 patients who received upfront chemotherapy (37–39). As a prognostic factor, primary tumor resection was associated with a significantly longer median OS (CAIRO, 16.7 vs. 11.4 months; CAIRO-2, 20.7 vs. 13.4 months). A similar association was found for progression-free survival. The patients in the two trials received capecitabine, oxaliplatin, and irinotecan regimens as well as biologic therapy. Selection bias appears to have affected the results of these studies also, as the patients who underwent resection had on average better performance status and lower disease burden than nonresection patients, and the proportion of patients with colon, rather than rectal, cancer was higher in the resection group. In contrast, Poultsides et al. (40) reported a median OS of 18 months among 233 patients who did not undergo initial resection of the primary tumor, which is comparable to the median OS for resection patients in the meta-analysis.

In summary, retrospective studies that argue for resection of an asymptomatic primary tumor in patients with metastatic colon cancer must be interpreted with caution, as they are compromised by selection bias and therefore cannot be used to conclude that upfront resection is beneficial. Prospective randomized clinical trials such as CAIRO 4, CAIRO 5 and GRECCAR 8 are currently being conducted in Europe to explicitly address this question.

Chemotherapy as Initial Treatment

With the advent of fluorouracil-based combination regimens, survival and the quality of life have improved in patients with metastatic colorectal cancer. In the United States, Asia, and Europe, many centers are avoiding futile interventions by resecting only symptomatic primary tumors (41). Matsumoto et al. (42) reported that approximately 75% of patients with metastatic colorectal cancer can be spared surgery for an asymptomatic primary tumor (42). Another study suggested that in 68–91% of the patients, resection of the primary tumor is not required (43).

Poultsides et al. (40) also addressed this issue when they reported the frequency of interventions necessary to palliate the primary tumor among 233 patients receiving upfront combination chemotherapy without prophylactic surgery. Ninety-three percent of the patients did not experience primary-tumor-associated complications requiring surgery. In the remaining 7%, surgery was performed at a median of 7 months (range, 1–27 months) after initiation of chemotherapy. In addition, 4% of the 233 patients required nonoperative intervention (stenting or radiotherapy) at a median of 12 months (range, 1–36 months) after initiation of chemotherapy. Given the wide range of time points, no specific trend in the timing of primary tumor complications can be discerned. Nevertheless, the overall need for intervention was very low. Seo et al. (44) reported a similar, 5% rate of emergency surgical interventions in 83 patients treated with first-line chemotherapy between 2001 and 2008. Four percent of the patients in that study needed colonic stenting to manage primary-tumor-related symptoms.

Some authors have argued for upfront resection of the primary tumor based on bevacizumab-associated bowel perforation. Bevacizumab, an antiangiogenic agent, has been found in prospective clinical trials to be associated with a 1–2% incidence of gastrointestinal perforation (45–48). The multicenter BRiTE registry study found that in patients with an intact primary tumor, the risk of perforation was higher than in patients in whom the primary tumor had been resected (3 vs. 1.7%) (45). These findings indicate that resection of the primary tumor does not eliminate the risk of perforation. Interestingly, perforations were seen not just at the primary tumor site but throughout the entire gastrointestinal tract. In another study, half of the patients received bevacizumab (n = 112); of the five patients with perforations at the primary tumor site, only two received bevacizumab at the time of the perforation (40).

A phase II, prospective, single-arm study of primary systemic chemotherapy with mFOLFOX-6 and bevacizumab in patients with unresectable stage IV colorectal cancer also found that an asymptomatic primary tumor may not need to be resected (49). Eighty-six patients from 29 institutions were evaluated. With a median follow-up of 20.7 months, the majority of the patients were managed successfully without the need to resect the primary tumor. The median OS was 19.9 months, and the primary-tumor-associated morbidity rate was 16.3% at 24 months. The authors concluded that this is an acceptable complication rate and that prophylactic resection is therefore unnecessary. Since the risk of perforation associated with bevacizumab is to some extent counterbalanced by the risk of anastomotic

leak after resection, the risk of bevacizumab-associated perforation should not be used as the sole justification for upfront resection.

Nonsurgical Approaches

Emergency operations for colorectal cancer are associated with high complication rates and often result in irreversible stomas, which have significant quality-of-life implications. One study found that surgery was associated with a complication rate of 30% and a hospital mortality rate of 8.5% (50). When faced with a symptomatic, obstructing tumor in the setting of unresectable metastatic disease, clinicians must consider whether the morbidity of surgery can be avoided with less invasive techniques. Endoluminal therapy has the advantage of shorter hospital stay and less morbidity than resection or diversion.

Both laser therapy and fulguration have been utilized to palliate primary tumors. Laser therapy has been shown to be appropriate for rectosigmoid cancers. In one study, there was an 85% success rate and a 2% complication rate in a series of 272 patients (51). In that series, patients had functional improvement for an average of 10.1 months. One of the major disadvantages of laser therapy is that it is time intensive and requires multiple treatments. Fulguration, another endoluminal technique, can also reduce the size of a distal tumor that is not amenable to resection and provide symptomatic relief.

Over the past 20 years, due to mixed results obtained with laser therapy and fulguration, colonic stents have become the preferred endoluminal therapy for obstructing or near-obstructing tumors. Colonic stents were first introduced in 1991 and have proven to be useful in patients who have unresectable metastatic disease or who need decompression of obstructed bowel as a bridge to resection (52). Some authors argue that stenting should not be performed for palliative decompression in patients receiving or expected to receive antiangiogenic therapy (e.g., bevacizumab) (53), but this argument remains speculative.

One of the advantages of colonic stenting is that the procedure can be done under sedation. In addition to their effectiveness for rectosigmoid tumors, colonic stents have been shown to be effective for tumors in the ascending and transverse portions of the colon (54). However, since colonic stenting requires special expertise, which is not universally available, resection remains an appropriate treatment for tumors obstructing the right colon.

Stenting is often not feasible for tumors obstructing the rectum, as it may result in pain, tenesmus, and incontinence. Furthermore, due to the anatomy of the rectum, possible distal stent migration can result in significant symptoms, and this risk usually precludes rectal stenting. Some initial studies on colonic stenting reported high rates of stent-associated perforation, and one of the earlier randomized controlled studies was closed early due to a high perforation rate (55). However, a more recent study reported a relatively low perforation rate of 5.2% (56). This low rate may be due to better patient selection, improved technique, and/or the knowledge gained from early missteps.

In sum, endoluminal therapy, particularly colonic stenting, is an important alternative for treatment of obstructing or near-obstructing colorectal tumors when surgery is not desirable. Nevertheless, surgery remains the first-line treatment if an obstruction causes systemic

toxicity with suspicion for peritonitis, bowel ischemia, or high-grade bowel obstruction with massive colonic distention.

Conclusion

The decision of whether to resect the primary tumor in patients with stage IV colorectal cancer is multifactorial, and includes the presence of symptoms and the resectability of metastatic disease. With the advent of modern therapeutic regimens, resection of the primary tumor does not appear to provide a survival benefit if the patient is asymptomatic. For symptomatic primary tumors, options include resection, diversion, and endoluminal therapy.

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Key Points

1. The cornerstones in the management of metastatic colorectal cancer are accurate staging and multidisciplinary treatment planning
2. Treatment options are tailored to the patient's burden of disease, performance status, goals of care, and expected survival
3. Staged resection, with either colon or liver resection first, and synchronous resection are options for the management of resectable liver metastases
4. Unresectable metastases with an asymptomatic primary tumor should be initially managed with systemic chemotherapy, avoiding futile interventions
5. Additional therapies for local control at the primary tumor site include colonic stenting, fulguration, and laser therapy

Synopsis

The management of metastatic colorectal cancer requires accurate staging and multidisciplinary evaluation, leading to a consensus treatment plan with the ultimate goal of increasing survival and improving the quality of life, while taking into consideration the patient's performance status, disease burden, and goals of care. Since the introduction of multidrug chemotherapeutic regimens, the overall survival of patients with metastatic colorectal cancer has improved. Many patients with unresectable disease are undergoing surgery for asymptomatic primary tumors as initial treatment despite evidence that in most patients it is a futile intervention. Available palliative measures for local control of the primary tumor include colonic stents, laser therapy, and fulguration.

Table 1

Studies comparing simultaneous resection vs staged resection

Author	Year	N	Simultaneous n=	Staged n=	Rate of simultaneous resection (%)	Major Hepatectomy in simultaneous vs staged resection (%) *	Morbidity simultaneous /staged (%)	Mortality simultaneous/staged (%)
Weber et al (57)	2003	97	35	62	36	11 (31)	23/32	0/0
Martin et al (17)	2003	240	134	106	56	34 (72)	49/67	2.2/2.8
Tanaka et al (19)	2004	91	41	50 **	47	6 (15)	28/16	0/0
Capussotti et al (58)	2007	127	70	57	55	24 (34)	35.7/36.8	0/0
Turrini et al (59)	2007	119	57	62	48	NA	21/31	3.5/5
Reddy et al (60)	2007	610	135	475	28	36 (27)	36.3/38.6	1/0.5
Martin et al (20)	2009	230	70	160	30	32 (33)	56/55	1.4/1.9
Luo et al (18)	2010	405	129	276	31	44 (34)	47.3/54.3	1.5/2
Abbott et al (61)	2012	144	60	84	42	20 (33)	38.3/40.5	3.3/1.2
Yoshioka et al (62)	2014	150	127	23	85	18 (14)	61.4	0
Silberhumer et al (21)	2016	429	320	109	74.6	58 (43)	NA	0

*Major Hepatectomy was defined as hepatic resection of three or more Couinaud's segments

**13 patients were excluded, because they underwent 2-stage hepatectomy procedures

N/A Not available

Data from Yoshioka R, Hasegawa K, Mise Y, et al. Evaluation of the safety and efficacy of simultaneous resection of primary colorectal cancer and synchronous colorectal liver metastases. Surgery 2014;155:478–85.

Table 2

Published series of palliation of the primary tumor after upfront fluorouracil-based chemotherapy

Study	Study period	N	Need for palliative surgery	Need for radiation therapy	Need for colonic stent
Scoggins et al (27)	1985–1997	23*	2 (9%)	—	—
Sarela et al (26)	1997–2000	24	6 (25%)	—	2 (8%)
Ruo et al (25)	1996–1999	103*	30 (29%)	—	—
Tebbutt et al (28)	1990–2000	82	8 (10%)	11 (13%)	
Total		232	46 (20%)		

*10 of 23 patients received upfront radiation therapy to the primary tumor.

**23 of 103 patients received upfront radiation therapy to the primary tumor

Data from Poultsides GA, Paty PB. Reassessing the need for primary tumor surgery in unresectable metastatic colorectal cancer: overview and perspective. Ther Adv Med Oncol 2011;3:35–42.

Table 3

Characteristics of the four randomized trials

	FFCD-9601	FFCD-2000–05	ML-16987	ACCORD-13
Accrual period	1997–2001	2002–2006	2003–2004	2006–2008
Line	First line	First line	First line	First line
Phase	III	III	III	II
Number of patients	294	410	306	145
Primary endpoint	Progression free survival	Progression free survival after second line	Overall response rate	Six months progression free survival
Treatment allocated by randomization (number of patients on this arm)	LV5FU2 (N=74) LV5FU2 with low dose LV (N=75) Bolus 5FU (N=73) Raltitrexed (N=72)	LV5FU2 followed by FOLFOX at progression then third line FOLFIRI(N=205) FOLFOX followed by FOLFIRI at progression (N=205)	FOLFOX (N=150) XELOX (N=156)	Bevacizumab+FOLFIRI (N=73) Bevacizumab+XELIRI (N=72)
More than one metastatic site	39%	57%	52%	51%
At least one unresectable site*	35%	41%	42%	28%
Subsequent Surgery	4% had surgery	3% curative intent resection	No data available	14% curative intent resection

FU, fluorouracil. LV, leucovorin

LV5FU2: bolus and infusional FU and LV

FOLFOX: oxaliplatin plus bolus and infusional FU and LV

FOLFIRI, irinotecan plus bolus and infusional FU and LV

XELOX: capecitabine and oxaliplatin, XELIRI:capecitabine and irinotecan

FFCD: Federation Francophone de Cancerologie Digestive, ACCORD: Actions Concertees dan les cancers ColoRectaux et Digestifs.

*Defined by the presence of metastasis in one of the following sites: bone, retroperitoneal nodes, supraclavicular nodes, brain, pleura, peritoneum.

Data from Faron M, Pignon JP, Malka D, et al. Is primary tumor resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomized trials. Eur J Cancer. 2015;51:166–76.