Reassessing the need for primary tumor surgery in unresectable metastatic colorectal cancer: overview and perspective

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Abstract: In the absence of symptoms, primary tumor resection in patients who present with unresectable metastatic colorectal cancer is of uncertain benefit. Prophylactic surgery has been traditionally considered in this setting in order to prevent subsequent complications of perforation, obstruction, or bleeding later during the treatment course, which may require urgent surgery associated with higher mortality. However, recent data have called into question the efficacy of this upfront surgical strategy. We provide a brief overview of how current combinations of systemic chemotherapy including fluorouracil, oxaliplatin, irinotecan, and targeted biologic agents have allowed improved local (in addition to distant) tumor control, significantly decreasing the incidence of late primary-related complications requiring surgery from roughly 20% in the era of single-agent fluoropyrimidine chemotherapy to almost 7% in the era of modern triple-drug chemotherapy. In addition, we attempt to highlight those factors most associated with subsequent primary tumor-related complications in an effort to identify the subset of patients with synchronous metastatic colorectal cancer who might benefit from a surgery-first approach. Finally, we discuss modern nonsurgical options available for palliation of the primary colorectal tumor and review the outcome of patients for which emergent surgery is eventually required to address primary-related symptoms.

Keywords: chemotherapy, colorectal cancer, primary tumor, stage IV

Introduction

Despite the increasing use of screening strategies, approximately 20% of patients with colorectal cancer still currently present with stage IV disease at the time of diagnosis [Edwards *et al.* 2010]. Only a select group (20–30%) of these patients will have metastatic disease amenable to curative resection; for the remaining majority the only viable option is systemic chemotherapy. Traditional surgical teaching maintains that prophylactic resection of the primary tumor in asymptomatic patients with synchronous metastatic colorectal cancer is indicated to prevent bleeding, perforation, or obstruction, complications which can occur later during the treatment course and can lead to urgent surgery which is associated with higher mortality. This approach has essentially prevailed during a former period of single-agent fluoropyrimidine chemotherapy for colorectal cancer, when the disease was felt at large to be chemorefractory.

However, there is a growing body of literature supporting a chemotherapy-first approach for patients presenting with synchronous metastatic colorectal cancer, with surgery representing a rescue option if symptoms related to the primary tumor develop [Damjanov *et al.* 2009; Poultsides *et al.* 2009]. Advocates of this deferred surgical strategy argue that surgery at diagnosis can delay or even preclude systemic chemotherapy, and that most patients will never develop symptoms and therefore could be spared an unnecessary operation. With recent advances in systemic chemotherapy and improvement in survival of stage IV colorectal cancer patients, the risks and benefits of this chemotherapy-first approach are increasingly being evaluated. In fact, combinations of infusional fluorouracil/leucovorin with oxaliplatin or irinotecan have yield response rates of 50%, disease control rates of 85%, and median survival of 20 months in prospective clinical trials [Goldberg *et al.* 2004; Tournigand *et al.* 2004].

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Furthermore, the addition of the antiangiogenic agent bevacizumab to the above combinations has been found to provide clinically meaningful improvement in response rates and survival [Saltz *et al.* 2008; Giantonio *et al.* 2007; Kabbinavar *et al.* 2005; Hurwitz *et al.* 2004]. As colorectal cancer is moving towards its designation as a chemosensitive disease, the efficacy of modern chemotherapy in providing local control in the setting of unresectable metastatic disease remains to be determined, but can be expected to be quite high.

We herein present a brief overview of the current literature on the outcome of the intact primary tumor in patients with synchronous stage IV colorectal cancer who receive upfront modern, triple-drug, oxaliplatin- or irinotecan-based combination chemotherapy without surgery as initial treatment. We focus on the difference in the incidence of primary tumor-related complications between patients receiving modern versus conventional fluorouracil-only chemotherapy. This discussion is particularly timely as two recent large epidemiological surveys in the US utilizing Surveillance Epidemiology, and End Results (SEER) data showed that in the 1990s more than two thirds of patients presenting with synchronous stage IV colorectal cancer underwent upfront surgical resection of their primary tumor [Cook *et al.* 2005; Temple *et al.* 2004]. This practice pattern appears to be based on the quantifiable incidence of late, primary tumor-related events observed in patients with synchronous, stage IV colorectal cancer primarily treated with fluoropyrimidine-only conventional chemotherapy, and in our opinion merits reevaluation in the current era of more effective chemotherapy.

Studies of fluoropyrimidine-only chemotherapy

No randomized trials are available to guide the management of the asymptomatic primary tumor in patients presenting with unresectable metastatic colorectal cancer. However, prophylactic surgery has been historically advocated for these patients based on the presumed high incidence of acute bowel obstruction or perforation that can occur later in the treatment course if the primary tumor is left *in situ*. Four cohort studies examining the outcome of the intact primary tumor in patients receiving single-agent fluoropyrimidine chemotherapy reported that these patients are exposed to a 9–29% risk of requiring subsequent urgent surgical palliation for primary tumor-related complications [Ruo *et al.* 2003; Tebbutt *et al.* 2003; Sarela *et al.* 2001; Scoggins *et al.* 1999]. These studies report both on the incidence of actual complications (bleeding, perforation, obstruction) as well the use of subsequent surgery or other nonoperative intervention to manage these complications (Table 1). Given the differing definitions of a primary tumor complication across these retrospective studies, we feel that using the performance of an intervention (operative and nonoperative) as an endpoint more accurately reflects the occurrence and severity of the complication under study. As shown in Table 1, of the 232 patients collectively examined in these four reports, the incidence of late surgical intervention necessary to palliate primary tumor-related complications reached a considerable average of 20%. In the largest one of these studies performed at Memorial Sloan-Kettering Cancer Center among 103 patients with metastatic colorectal cancer and an intact primary tumor who received fluorouracil-only chemotherapy from 1996 to

Table 1. Published series of patients with synchronous metastatic colorectal cancer receiving upfront conventional 5-fluorouracil-based chemotherapy describing the use of subsequent intervention (surgery, radiation, stent) required to palliate the intact primary tumor.

Study	Study period	N	Need for palliative surgery	Need for radiation therapy	Need for colonic stent
Scoggins <i>et al.</i> [1999]	1985–1997	23*	2 (9%)	—	—
Sarela <i>et al.</i> [2001]	1997–2000	24	6 (25%)	—	2 (8%)
Ruo <i>et al.</i> [2003]	1996–1999	103**	30 (29%)	—	—
Tebbutt <i>et al.</i> [2003]	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.

1999, a substantial 29% required late surgical palliation [Ruo *et al.* 2003]. It should be noted that this high incidence of subsequent emergent surgery in this study was noted despite the fact that 23 (22%) patients with rectal cancer received upfront radiation therapy to the primary tumor. Likewise, in the single prospective study that addresses this question, 6 (25%) of 24 patients treated with upfront fluoropyrimidine-only chemotherapy required subsequent surgical intervention for primary tumor palliation [Sarela *et al.* 2001]. Taken together, these data indicate that in the previous era of fluorouracil-only chemotherapy, approximately one in five patients with metastatic colorectal cancer treated with upfront chemotherapy required subsequent palliative surgery for symptoms related to their intact primary tumor.

Studies of modern triple-drug chemotherapy

Table 2 summarizes the findings of five recent retrospective studies on the incidence of late surgical intervention required to palliate primary tumor complications in patients treated upfront mostly with modern, oxaliplatin- or irinotecan-based, triple-drug chemotherapy [Seo *et al.* 2010; Poultsides *et al.* 2009; Muratore *et al.* 2007; Benoist *et al.* 2005; Michel *et al.* 2004]. In the authors' study, 233 patients with metastatic colorectal cancer and a confirmed intact primary tumor were treated with upfront modern combination chemotherapy from 2000 to 2006. The incidence of the subsequent use of surgery or other intervention to palliate primary tumor symptomatology was recorded. The median follow up for 22 intervention-free survivors was 22 months. The incidence of major complications involving the primary and requiring surgery was found to be low at 7% [Poultsides *et al.* 2009]. In other words, of 233 such patients,

93% never required surgical intervention for primary tumor symptomatology. Seven percent underwent emergent surgery, at a median of 7 months (range, 1–27 months) from initiation of chemotherapy. An additional 4% required non-operative intervention (stent or radiotherapy) at a median of 12 months (range, 1–36 months) from initiation of chemotherapy. As evidenced by the wide range of these intervals, operative or nonoperative intervention was necessary either early on after initiation of chemotherapy or later on, perhaps during disease progression. There was no particular trend noted for either a rapid or a delayed presentation of primary tumor complications.

Similar rates of emergent intervention were recently reported from another single-institution study [Seo *et al.* 2010]. In this study, among 83 asymptomatic patients with unresectable metastatic colorectal cancer treated with first-line combination chemotherapy from 2001 to 2008, only 5% eventually required surgery and 4% required colonic stent insertion to manage primary-related symptoms. In aggregate, these five studies reported on 401 patients and the average percentage of patients eventually requiring surgical palliation for their intact primary tumor was 7%, a number which is roughly three times lower than the 20% collectively reported in the 1990s using fluoropyrimidine-only chemotherapy (Table 1). Collectively, these data indicate that in the modern era of effective combination chemotherapy for metastatic colorectal cancer, 14 asymptomatic patients need to undergo prophylactic resection of their primary tumor in order to save one patient a subsequent operation for colonic obstruction or perforation. In the authors' opinion, this seems to be a highly ineffective strategy as it exposes a significant portion of

Table 2. Published series of patients with synchronous metastatic colorectal cancer receiving upfront modern, triple-drug, oxaliplatin- or irinotecan-based combination chemotherapy describing the use of subsequent intervention (surgery, radiation, stent) required to palliate the intact primary tumor.

Study	Study period	N	N [%] of patients receiving first-line triple-drug chemotherapy	Need for palliative surgery	Need for radiation therapy	Need for colonic stent
Michel <i>et al.</i> [2004]	1996–1999	23	19 [82%]	5 [22%]	—	—
Benoist <i>et al.</i> [2005]	1997–2002	27	18 [67%]	4 [15%]	—	—
Muratore <i>et al.</i> [2007]	2000–2004	35	35 [100%]	1 [3%]	1 [3%]	—
Poultsides <i>et al.</i> [2009]	2000–2006	233	233 [100%]	16 [7%]	3 [1%]	7 [3%]
Seo <i>et al.</i> [2010]	2001–2008	83	68 [82%]	4 [5%]	10 [12%]	3 [4%]
Total		401		30 [7%]		

these asymptomatic patients to the not trivial risks of most likely unnecessary surgery in addition to delaying potentially life-prolonging systemic chemotherapy.

Response of primary tumor to chemotherapy

It is anticipated that the beneficial effects of modern combination chemotherapy will not be confined to the metastasis, but will also apply to the primary tumor. For example, in 2006, investigators from the Royal Marsden Hospital reported on the results of a phase II trial evaluating the effect of neoadjuvant systemic chemotherapy on 77 patients with locoregionally advanced rectal cancer [Chau *et al.* 2006]. Enrolled patients received 12 weeks of capecitabine/oxaliplatin chemotherapy followed by chemoradiotherapy and total mesorectal excision. During chemotherapy, patients were assessed for evidence of rectal bleeding, pelvic pain, tenesmus, diarrhea, and constipation. The radiographic response rate by magnetic resonance imaging after 12 weeks of neoadjuvant capecitabine/oxaliplatin chemotherapy was 88%. Similarly, 86% of the patients with symptoms were noted to have symptomatic improvement. Specifically, pelvic pain/tenesmus was decreased in 71% of patients, 90% had improvement in diarrhea/constipation, 100% had reduced rectal bleeding, and 93% had weight stabilization or weight gain. The median time to symptom resolution was 32 days (just over one cycle of capecitabine/oxaliplatin). These results should be contrasted to the lower 28% radiographic and 65% symptomatic response rates in a study of neoadjuvant protracted infusion 5-fluorouracil and mitomycin-C, also in patients with rectal cancer, which has been reported by the same group previously [Chau *et al.* 2003].

In the authors' study, of the 217 (93%) patients who never required emergent surgery, 47 (20% of entire cohort) eventually underwent elective curative resection of the primary tumor and metastatic disease at a median time of 8 months from initiation of chemotherapy. In addition, eight patients (3% of entire cohort) underwent preemptive resection before the onset of symptomatology at the time of Hepatic Artery Infusion Pump placement for regional liver chemotherapy at a median time of 9 months [Poultsides *et al.* 2009]. Interestingly, 7 of the 47 (15%) curatively resected tumors and one (12%) of the 8 preemptively resected tumors demonstrated complete response to chemotherapy on pathologic

examination. Obviously, these patients represent a small, highly select group and cannot form the basis for any solid conclusions. Nonetheless, these observations underscore the potential ability of modern systemic chemotherapy to completely eradicate the primary colorectal tumor and provide considerable local control.

Mortality after emergent surgery

Immediate prophylactic surgery has been historically advocated for these patients because of concerns for substantial mortality (or need for colostomy) if emergent surgery is required. In a variety of smaller studies addressing this question [Muratore *et al.* 2007; Benoist *et al.* 2005; Michel *et al.* 2004; Sarela *et al.* 2001], this risk of perioperative death was in fact found to be extremely low (1 of a total of 16 patients, or 6%). In the authors' study, of the 16 patients who required late emergent surgery, 2 (12%) died in the postoperative period. If this number is examined using the total study population as the denominator ($n=233$, if all study patients were to undergo upfront surgery), the mortality after emergent surgery with the deferred surgical strategy would only be 2 of 233 or 0.8%. This number compares favorably with the mortality associated with elective colon resection in the metastatic setting, which ranges from 4.6% to 10% in representative series [Temple *et al.* 2004; Rosen *et al.* 2000; Scoggins *et al.* 1999; Mella *et al.* 1997; Mahteme *et al.* 1996]. Thus, recognizing the limitations of cross-study comparisons, it certainly appears that the deferred, symptom-directed surgical intervention in this setting is associated with at least comparable perioperative mortality when compared with the *a priori* surgery approach.

Predictors of primary-related complications

The identification of factors associated with future primary-related complications may be helpful in selecting these patients with metastatic colorectal cancer who might benefit from a surgery-first approach. On a multivariate analysis of 362 such patients, Tebbutt and colleagues demonstrated that the presence of peritoneal metastasis ($p=0.04$) and younger age ($p=0.001$), but not site ($p=0.21$) or resection status of the primary tumor ($p=0.06$), were the most significant factors associated with increased risk of intestinal obstruction [Tebbutt *et al.* 2003]. On the other hand, prophylactic primary tumor resection has been previously recommended selectively for patients with low metastatic burden presumed to be at high risk of obstruction because of their

relatively long survival [Rosen *et al.* 2000]. Most relevant studies, however, have failed to establish a correlation between advanced disease stage and the incidence of late primary tumor complications [Sarela *et al.* 2001; Scoggins *et al.* 1999]. Similarly, the authors' study examined several markers representative of tumor burden (two or more sites of metastasis, carcinoembryonic antigen [CEA] >200 ng/ml, alkaline phosphatase >250 IU/l, lactate dehydrogenase [LDH] >200 IU/l, albumin <3 g/dl) and found no statistically significant association between these variables and the need for late primary tumor-directed intervention [Poultides *et al.* 2009]. Unfortunately, there appears to be no specific clinicopathologic variable at presentation that can reliably predict the incidence of a future primary-related complication in this patient cohort.

Similarly, location of the primary tumor in the rectum, as opposed to the colon, was not associated with a higher incidence of late, emergent intervention in the authors' analysis [Poultides *et al.* 2009]. Specifically, primary tumors located in the rectum compared with tumors located in the colon required similar rates of operative (6% *versus* 7%, $p=0.94$) and overall (15% *versus* 9%, $p=0.19$) emergent intervention. This finding is particularly relevant, as the management of synchronous metastatic rectal cancer in the US during the previous decade has traditionally included the prophylactic use of surgery in up to 45–62% of patients and or radiotherapy in 12% of patients [Cook *et al.* 2005; Temple *et al.* 2004], mainly secondary to concerns that the unresected primary tumor can lead to significant future symptomatology in the pelvis. Our experience with 78 patients with synchronous stage IV rectal cancer, who were not stented, radiated or operated upon initially, but received upfront modern, triple-drug, combination chemotherapy, suggests that only 6% required surgery and an additional 9% required nonoperative intervention (stent or radiotherapy) to palliate primary tumor symptomatology. In our opinion, this low incidence of late, symptom-directed intervention does not justify routine use of prophylactic surgery or radiotherapy in this setting.

Bevacizumab

Bevacizumab has been associated with a 1–2% incidence of gastrointestinal perforation in prospective clinical trials [Kozloff *et al.* 2009; Saltz *et al.* 2008; Giantonio *et al.* 2007;

Hurwitz *et al.* 2004]. In addition, in the prospective, multicenter BRiTE registry [Kozloff *et al.* 2009] of 1953 patients with metastatic colorectal cancer, patients with an intact primary tumor had a slightly increased risk of gastrointestinal perforation (3.0%) as opposed to patients who had undergone previous resection of their primary tumor (1.7%). However, in these trials bevacizumab-related perforations were observed throughout the entire gastrointestinal tract and frequently not involving the site of the primary tumor. Therefore, resecting the primary would not eliminate the risk of perforation. In the authors' study, approximately half of the patients received bevacizumab ($n=112$, 48%) and of the five perforations observed, all at the site of the primary tumor, only two occurred while on bevacizumab therapy; one patient experienced perforation 6 months after the last administration of bevacizumab, whereas two patients were naive to this agent. Although the small number of patients who developed this complication precludes definitive conclusions, bevacizumab did not appear to increase the rate of perforation in our experience.

Palliation of intestinal complications by nonsurgical methods

External beam radiation therapy has a proven record of being useful in palliating perineal pain and bleeding in some patients with rectal cancer [Myint, 2000]. Furthermore, with the use of stereotactic methods higher doses of radiation can be delivered with lower toxicity to adjacent organs. In addition, advances in gastrointestinal endoscopy have permitted the successful delivery of self-expandable metal stents in patients with colorectal obstruction using colonoscopic and/or fluoroscopic guidance. Endoscopic laser ablation can be used to facilitate subsequent endoluminal stenting of near-obstructing tumors. When considering colonic stenting, the clinician should keep in mind that the procedure may be technically challenging in very distal rectal or very proximal colonic tumors. In addition, in recent large series [Fernandez-Esparrach *et al.* 2010; Small *et al.* 2010] as well as previous systematic reviews [Watt *et al.* 2007], colonic stents can be associated with a complication rate of 25–50%, the most common being migration (5–22%), occlusion due to tumor ingrowth (9–17%), and perforation (3–9%). Furthermore, the Dutch Stent-in I multicentre trial that randomized patients with incurable colorectal cancer to surgery or stenting had to be terminated prematurely because of four stent-related delayed perforations resulting in

3 deaths among 10 patients [Van Hooft *et al.* 2006]. In the authors' study of 233 patients, endoluminal stenting was successful in seven patients (3%), but repeat stent insertion was required in three, because of tumor ingrowth. In addition, three of the seven patients who eventually underwent diverting colostomy creation had a previous failed stent insertion, but none experienced a stent-related perforation [Poultides *et al.* 2009]. Nonetheless, stent placement has been found to improve quality of life scores in prospective studies of patients with malignant colorectal obstruction [Nagula *et al.* 2010], and remains a useful option for the symptomatic palliation of these patients, particularly when declining performance status precludes surgical intervention.

The effect of an emergent operation on survival

Although several retrospective analyses suggest that patients with stage IV colorectal cancer who undergo prophylactic resection of the primary tumor live longer, most of these reviewed data prior to the advent of modern polychemotherapy and are subject to considerable selection bias, as patients who were considered able to undergo surgery likely had better performance status and overall prognosis than those who were not [Stillwell *et al.* 2010]. Another potential issue worthy of discussion is whether this initial nonoperative strategy is associated with a detrimental effect on survival when emergent surgery is required. In the authors' study [Poultides *et al.* 2009], the median time to operative and nonoperative intervention was 7 and 12 months, respectively, and median survival after intervention was 6 and 7 months, respectively. Median survival from initiation of chemotherapy for patients who did not require intervention was 13 months, which is comparable with survival from initiation of chemotherapy for the 26 patients who eventually needed intervention (by addition of time to procedure and survival after procedure). A direct comparison of survival after initiation of chemotherapy between patients who did and did not undergo late intervention is not statistically valid, as intervention is a metachronous event and not established at time zero. However, when included as a time-varying covariate in a Cox regression model, the need for emergent intervention did not correlate with overall survival ($p=0.81$). These data suggest that the need for late intervention, despite being a potential marker of aggressive tumor biology

and/or chemoresistance, does not appear to be associated with shorter survival when this is measured from initiation of chemotherapy.

Future prospective studies

Based on the paucity of prospective data on this particular controversy in oncology [Kemeny, 2006; Petrelli, 2006], the National Surgical Adjuvant Breast and Bowel Project has formulated Protocol C-10, entitled 'A Phase II Trial of 5-Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) Chemotherapy Plus Bevacizumab for Patients with Unresectable Stage IV Colon Cancer and Synchronous Asymptomatic Primary Tumor' [National Surgical Adjuvant Breast and Bowel Project (NSABP), 2010]. The primary endpoint is the rate of primary tumor-related events (obstruction, perforation, fistula, hemorrhage) necessitating surgery. The secondary aim is to determine the rate of specific events related to the intact primary tumor requiring hospitalization or a major intervention. The trial is powered to determine outcomes relative to the primary tumor with an incidence of events less than 25% considered a therapeutic success. The trial opened in March 2006 and was recently closed after accruing the goal of 90 patients. The results are eagerly awaited.

Conclusion

Prophylactic resection of the asymptomatic primary tumor in patients who present with unresectable metastatic colorectal cancer has been traditionally considered necessary to avoid local complications during subsequent chemotherapy. However, recent and more rigorous data have emerged estimating that the need for surgery to manage complications derived from the intact primary tumor in patients with unresectable metastatic colorectal cancer receiving upfront systemic chemotherapy has roughly decreased from 20% in the era of single-agent fluoropyrimidine chemotherapy to 7% in the current era of newer combination chemotherapy. Upfront prophylactic resection of the asymptomatic primary tumor risks surgical complications that may postpone administration of modern chemotherapy, which has been proven to offer not only systemic but also local disease control. In addition, recent advances in the endoscopic palliation of patients with obstructed or bleeding colorectal tumors can further reduce the need for surgery. These findings support our institutional policy of nonoperative initial management of the

asymptomatic primary tumor in patients with synchronous stage IV colorectal cancer. This policy allows prompt initiation of systemic therapy, is associated with a low incidence of late, symptom-directed intervention and should be regarded as routine standard practice for patients with synchronous metastatic colorectal cancer without overt obstruction or hemorrhage.

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Conflict of interest statement

None declared.

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