Rectal Cancer with Synchronous Liver Metastases: Leave It All in? When (not) to Resect the Primary?

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Abstract

Rectal cancer with synchronous distant metastases is challenging the choice of optimal treatment. Today, it is unknown if and when the primary tumor should or should not be resected. The current literature was reviewed. Data on the safety of a primary chemotherapy approach are reported. These publications indicate that at least in selected situations without severe symptoms or complications resulting from the primary, the rectum can be left in situ without major risks for the patient. However, retrospective analyses from randomized controlled trials indicate a potential prognostic advantage for patients having the primary tumor resected. The reason for this observation is largely unknown and requires further investigation. Due to the lack of data from prospective randomized controlled trials illuminating the situation of rectal cancer with synchronous distant metastases and due to the rapid changes evolving in the field of systemic treatment of metastatic colorectal cancer, no clear conclusions can be drawn at this stage. But a practical algorithm that may reflect current European treatment patterns is presented in this article.

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1 Two Cases

The following two cases illustrate two contrary strategies for the treatment of rectal cancer with synchronous distant metastases.

1.1 Patient 1

A 42-year-old man presented with locally advanced rectal cancer. He underwent anterior resection followed by external beam radiotherapy combined with chemotherapy 8 weeks later. He relapsed within 6 months with hepatic metastases and started treatment with bevacizumab 5 mg/kg every other week plus irinotecan, infusional 5-fluorouracil, and folinic acid. During the first 4 weeks of treatment with bevacizumab, he experienced severe perianal pain requiring opioids. Digital rectal examination revealed a hard luminal mass adherent to the bowel wall. On endoscopy, wall thickening accompanied by ulcerative lesions around the anastomosis similar to the mucosal changes seen in ulcerative colitis was present (Fig. 1). MRI showed thickening of the intestinal and vesical wall in the borders of the previous pelvic irradiation. Multiple biopsies revealed no malignant areas. The specimens were consistent with mucosal damage, such as seen in ischemic colitis. Treatment with bevacizumab was stopped, and systemic analgesics and anti-inflammatory enemas were administered. The patient was still symptomatic after 5 months of follow-up. In addition, a circumscribed necrotic destruction of the bowel wall developed covered by the surrounding tissue, still without evidence of tumor. The patient recovered slowly from his symptoms and lived with metastatic disease for 5 years.

1.2 Patient 2

A 45-year-old man presented with rectal cancer in the upper rectal third (Fig. 2) with synchronous multiple lung and liver metastases (Fig. 3). He had lost 3 kg of weight and suffered from moderate diarrhea. Serum CEA was elevated to 1,727 μg/l (normal range < 5); LDH was elevated to 1,182 U/l (normal range < 220). Chemotherapy with irinotecan plus 5-fluorouracil/folinic acid (FOLFIRI) plus cetuximab was started. Apart from acneiform rash grade 3 and a severe infusion reaction at the time of the first cetuximab infusion, he tolerated chemotherapy well until 6 weeks later he presented with an acute abdomen that was caused by a rectal perforation leading peritonitis and ileus (Fig. 4). The liver metastases and the primary tumor had responded to treatment. He received an

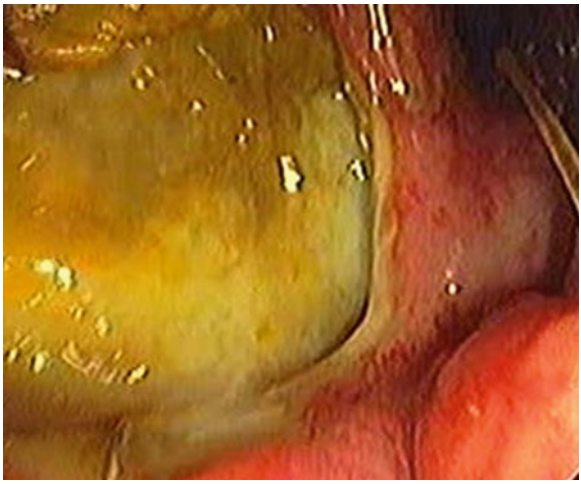

Fig. 1 Endoscopic aspect of ulcerous pseudotumor of the neorectum in patient 1 who underwent treatment with bevacizumab after previous anterior resection of the rectum and adjuvant chemoradiotherapy

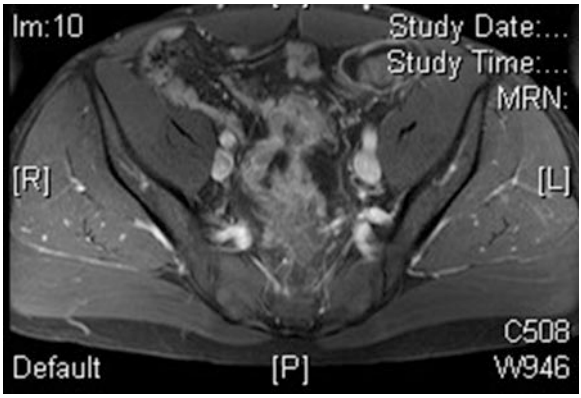

Fig. 2 Rectal cancer in the upper third in patient 2. Magnetic resonance imaging (MRI)

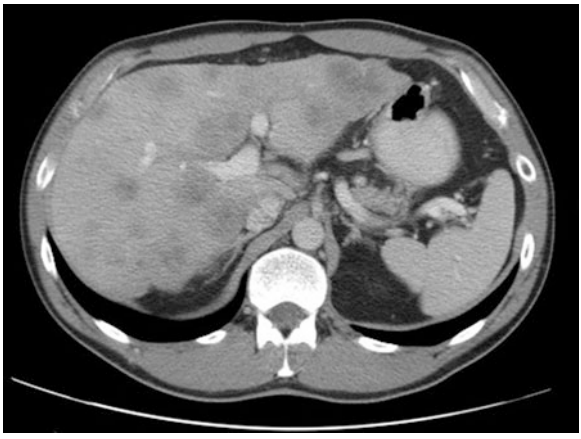

Fig. 3 Multiple liver metastases in patient 2. Computed tomography (CT)

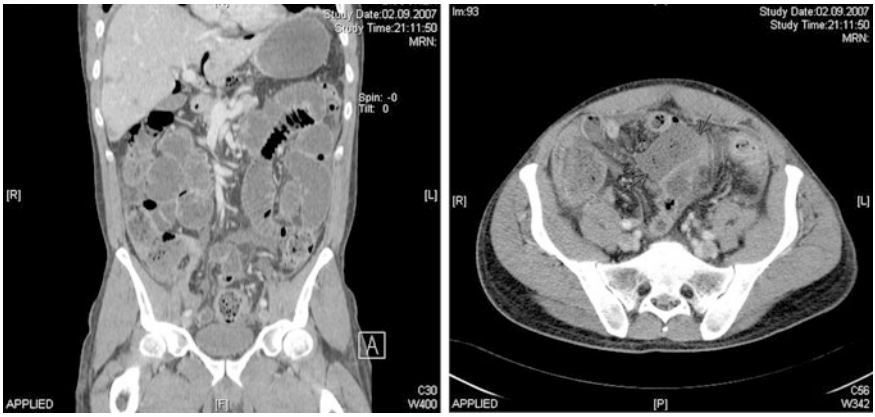

Fig. 4 CT scans of patient 2 six weeks after initiation of chemoimmunotherapy, illustrating an ileus due to peritonitis caused by a rectosigmoid perforation

anterior rectal resection and a descendostoma as an emergency operation which led to his fast recovery. Four weeks later, chemoimmunotherapy could be continued. This man lived for 4 years with his metastatic disease.

These two cases, one of which has been published previously (Lordick et al. 2006) illustrate that both strategies, i.e., primary tumor resection followed by systemic chemotherapy and primary systemic chemotherapy without resection of the primary tumor are common practice in the management of rectal cancer with synchronous distant metastases. The two cases show that both approaches can lead to complications in due course. The question is: which approach should be preferred in which situation?

2 How Do We Make a Clinical Decision?

Usually, clinicians and multidisciplinary tumor boards want to be informed about the following issues when a decision on treatment sequences in colorectal cancer with synchronous metastases has to be taken:

1. Is the primary tumor symptomatic (obstruction, bleeding, and pain)?
2. How advanced is the metastatic tumor load?
3. Can the disease be treated curatively?

In case of a symptomatic primary, the indication for early resection is more evident, but other means of controlling symptoms (e.g., colonostomy or stent insertion for obstruction, radiation for bleeding or pain) can be considered.

Massive metastatic disease, especially when associated with an inflammatory systemic reaction composed of weight loss, fever, night sweats, increase of serum acute phase proteins (C-reactive protein), or cytokines (Interleukin-6) indicate an imminent need for early and maximally active systemic treatment. Treatment of

the primary tumor is then usually postponed or will never be performed, especially when the situation deteriorates in the further course.

If cure seems achievable, different strategies are to be considered. Most centers start with systemic chemotherapy for 3 months as used in the EORTC 40983 study (Nordlinger et al. 2009). Following induction chemotherapy, a rectal-surgery-first approach must be weighed against a liver-surgery-first approach (Mentha et al. 2006). The risk of progression of resectable liver metastases during neoadjuvant chemoradiation, especially if this contains oxaliplatin, has probably been overestimated in the past (Manceau et al. 2013).

3 Is It Safe to Leave the Primary Tumor in Situ?

3.1 Cohort Studies

Dutch authors collected the outcome data of 850 patients from seven cohort studies (Scheer et al. 2008). Only patients with asymptomatic primary colorectal cancers were included. Leaving the primary tumor in situ was shown to be a relatively safe strategy: the mean complications were intestinal obstruction in 13.9 % [95 % confidence interval (CI) 9.6–18.8 %] and hemorrhage in only 3.0 % (95 % CI 0.95–6.0 %) of the patients. After resection, the overall postoperative morbidity ranged from 18.8–47.0 %. The authors conclude: "For patients with stage IV colorectal cancer, resection of the asymptomatic primary tumor provides only minimal palliative benefit, can give rise to major morbidity and mortality and therefore potentially delays beneficial systemic chemotherapy. When presenting with asymptomatic disease, initial chemotherapy should be started and resection of the primary tumor should be reserved for the small portion of patients who develop major complications from the primary tumor." However, in this publication, the proportion of patients presenting with rectal cancer is not specified and is not subject to detailed subgroup analyses.

3.2 MSKCC Series

Another more recent case series from the Memorial Sloan Kettering Cancer Center, New York, reports that from 233 patients with synchronous metastases and an unresected primary tumor, 217 (93 %) never required surgical palliation of their primary (Poultsides et al. 2009). Sixteen patients (7 %) required emergent surgery for primary tumor obstruction or perforation, 10 patients (4 %) required nonoperative intervention (stent or radiotherapy), and 213 (89 %) never required any direct symptomatic management for their intact primary tumor. Of those 213 patients, 47 patients (20 %) ultimately underwent elective colon resection at the time of metastasectomy. Of note, location of the primary tumor in the rectum, and metastatic disease burden were not associated with increased intervention rate. Also, the use of bevacizumab had no impact on complication or intervention rates.

The authors therefore concluded that "most patients with synchronous, stage IV colorectal cancer who receive up-front modern combination chemotherapy never require palliative surgery for their intact primary tumor. These data support the use of chemotherapy, without routine prophylactic resection, as the appropriate standard practice for patients with neither obstructed nor hemorrhaging primary colorectal tumors in the setting of metastatic disease."

4 The Effect of Systemic Chemotherapy on the Primary Tumor

It has been hypothesized that the effect of systemic chemotherapy on the primary tumor is not as high as on liver or other hematogenous metastases. Therefore, long-term control of the primary may not be achievable. This question has not been investigated in larger series, but a very recent study from the MSKCC gives some insight (Schrag et al. 2014). Thirty-two patients with clinical stages II–III rectal cancer participated in this single-center phase II trial. All were candidates for low anterior resection with total mesorectal excision (TME). Patients were to receive six cycles of FOLFOX, with bevacizumab included for cycles 1–4. Patients with stable/progressive disease were to have radiation before TME, whereas responders were to have immediate TME. Postoperative radiation was planned if R0 resection was not achieved. Postoperative FOLFOX-6 was recommended, but adjuvant regimens were left to clinician discretion. The primary outcome was R0 resection rate. Thirty-two (100 %) of 32 study participants had R0 resections. Two did not complete preoperative chemotherapy secondary to cardiovascular toxicity. Both had preoperative chemoradiotherapy and then R0 resections. Of 30 patients completing preoperative chemotherapy, all had tumor regression and TME without preoperative chemoradiotherapy. The pathologic complete response rate to chemotherapy alone was 8 of 32 (25 %; 95 % CI, 11–43 %). The 4-year local recurrence rate was 0 % (95 % CI, 0–11 %); the 4-year disease-free survival was 84 % (95 % CI, 67–94 %). The authors conclude that "for selected patients with clinical stages II–III rectal cancer, neoadjuvant chemotherapy and selective radiation does not seem to compromise outcomes. Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME (PROSPECT), a randomized phase III trial to validate this experience, is now open in the US cooperative group network."

This study indicates that systemic chemotherapy has a high activity in primary rectal tumors.

5 Does Resection of the Primary Tumor Confer with a Better Prognosis?

A crucial question is if resection of the primary tumor confers with a better prognosis. There is little direct evidence that this is the case in colorectal cancer. The only disease where this has been studied in randomized controlled trials is metastatic renal cell cancer (Flanigan et al. 2001; Mickisch et al. 2001). The larger of the two studies showed that the median survival of 120 eligible patients assigned to surgery followed by interferon was 11.1 months, while among the 121 eligible patients assigned to interferon alone was 8.1 months ($P = 0.05$). The difference in median survival between the two groups was independent of performance status, metastatic site, and the presence or absence of a measurable metastatic lesion. The smaller of the two studies that was recruited in the EORTC Genitourinary Group confirmed these results.

In conclusion, resection of the primary followed by systemic therapy resulted in longer survival among patients with metastatic renal cell cancer than systemic therapy alone.

5.1 SEER Data

Can the observations from renal cell cancer be transferred to metastatic colorectal cancer? Data from the Surveillance, Epidemiology and End Results (SEER) data registry of the National Cancer Institute indicate that the percentage of patients receiving resection of primary stage IV colorectal tumors is steadily decreasing from 1988 to 2000 (Cook et al. 2005). The investigators analyzed data from 26,754 patients with stage IV colorectal cancer diagnosed between 1988 and 2000. A total of 17,658 patients received resection of their primary tumor. A better overall survival was observed after primary tumor resection compared with a nonresection strategy. For rectal cancer, the difference was 16 months versus 6 months, and the 1-year-survival was 45 % versus 12 % ($p < 0.001$). Such a series, however, cannot inform us about the reasons why survival for patients having the primary tumor resected may have been longer. The authors themselves state that "The proportion of patients undergoing resection depends on patient's age and race and the anatomical location of the primary tumor. The degree to which case selection explains the treatment and survival differences observed is not known." Clearly, more detailed information from prospective trials is warranted.

5.2 CAIRO Studies

The Dutch Colorectal Cancer Group retrospectively analyzed the outcome of stage IV colorectal cancer patients with or without resection of the primary tumor treated in the phase III CAIRO and CAIRO2 studies (Venderbosch et al. 2011). In these two

studies, 258 and 289 patients had undergone a primary tumor resection and 141 and 159 patients had not. 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 versus 11.4 months [$P < 0.0001$, hazard ratio (HR) 0.61], and 6.7 versus 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 versus 13.4 months ($P < 0.0001$; HR 0.65) and 10.5 versus 7.8 months ($P = 0.014$; HR 0.78), respectively. These differences remained significant in multivariate analyses. The authors concluded: "Our results as well as data from literature indicate that resection of the primary tumor is a prognostic factor for survival in stage IV colorectal cancer patients. The potential bias of these results warrants prospective studies on the value of resection of the primary tumor in this setting."

Do the results from the CAIRO study help us to guide our decisions in rectal cancer presenting with synchronous distant metastases? Not necessarily. The publication is dealing with stage IV colorectal cancer without a special focus on the situation of synchronous metastases. Moreover, no particular focus is put on the location of the tumor. No subgroup analysis for rectal cancers has been shown.

5.3 FFCD 96-01

This is the strength of a recent French publication from the Fédération Francophone de Cancérologie Digestive (FFCD) 96-01 study (Ferrand et al. 2013). Among the 294 patients with nonresectable colorectal metastases enrolled in the FFCD 96-01 phase III trial, which compared different first-line, single-agent chemotherapy regimens, 216 patients (73 %) presented with synchronous metastases at study entry and constituted the study population. Potential baseline prognostic variables including prior primary tumor resection were assessed by univariate and multivariate Cox analyses. Among the 216 patients with stage IV colorectal cancer, 156 patients (72 %) had undergone resection of their primary tumor prior to study entry. The resection and nonresection groups did not differ for baseline characteristics except for primary tumor location: rectal cancers were more often not resected: 14 % versus 35 % ($p = 0.0006$). In a multivariate analysis, resection of the primary was the strongest independent prognostic factor for progression-free survival (PFS) (hazard ratio (HR), 0.5; 95 % confidence interval [CI], 0.4–0.8; $p = 0.0002$) and overall survival (OS) (HR, 0.4; CI, 0.3–0.6; $p < 0.0001$). Both median PFS (5.1 [4.6–5.6] versus 2.9 [2.2–4.1] months; $p = 0.001$) and OS (16.3 [13.7–19.2] versus 9.6 [7.4–12.5]; $p < 0.0001$) were significantly higher in the resection group. These differences in patient survival were maintained after exclusion of patients with rectal primary ($n = 43$). The authors conclude that "resection of the primary tumor may be associated with longer PFS and OS in patients with stage IV colorectal cancer starting first-line, single-agent chemotherapy."

Limitations of this publication, as stated by the authors themselves are: First, assessing the impact of primary colorectal cancer resection on survival was not the primary aim of the FFCD 96-01 trial, which furthermore excluded patients whose condition worsened after primary tumor resection. As such, the study must be viewed as an exploratory, hypothesis-generating, post hoc analysis of a prospective trial. Second, indications for primary resection before patient inclusion in the FFCD 96-01 trial are unknown, as the study protocol did not require to collecting such information. Thus, the analysis probably mixed patients who had primary-related symptoms or complications at diagnosis and patients who had not.

In conclusion, the Dutch and the French retrospective analyses from prospective randomized trials support the hypothesis that resection of the primary tumor in case of synchronous distant metastases may improve progression-free and overall survival. The reason for this potential difference is thus far unknown. This clinical research question merits prospective investigation.

6 Current Ongoing Studies

Two randomized controlled trials with a comparable design are currently recruiting patients in Europe: *Synchronous* is recruiting patients in Germany while *CAIRO-4* is active in the Netherlands (Rahbari et al. 2012). Both studies enroll patients with colon cancer with synchronous nonresectable metastases. The study hypotheses are based on the prognostic differences seen in the previous retrospective analyses outlined earlier. Of note, both studies exclude patients with primary rectal tumors, as the study chairs see this situation different from colon cancers. Therefore, the results of these two important studies will not finally resolve the question how to manage rectal cancer with synchronous distant metastases.

7 Practical Consequences

The published data indicate that primary chemotherapy can be administered relatively safely in asymptomatic (colo-)rectal cancer with synchronous metastases. The severity of symptoms does usually guide the strategy. If severe symptoms result from the primary tumor, local treatment (colostomy, radiation, stenting, or resection) is usually administered up-front. The choice of local treatment is tailored to the individual needs.

In patients without symptoms from the primary tumor or with far advanced metastatic disease or with severe symptoms from metastatic disease, primary systemic treatment should be given first.

Figure 5 is illustrating the strategy followed in the University Cancer Center of Leipzig (Fig. 5). This practical algorithm may reflect one of the preferred algorithms that are currently preferred in Cancer Centers in Europe.

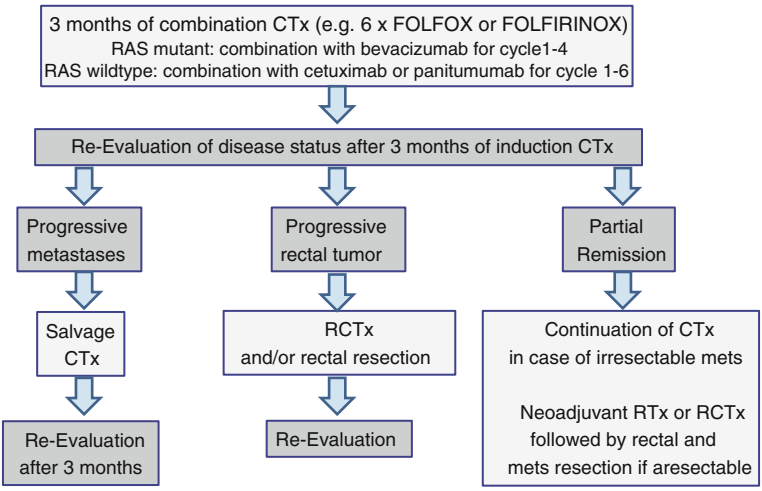

Fig. 5 Treatment algorithm of the University Cancer Center Leipzig (UCCL) for patients with asymptomatic rectal cancer with synchronous distant metastases. *Legend* CTx = chemotherapy, mets = metastases, RCTx = radiochemotherapy RTx = radiotherapy

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