Management of oligometastatic rectal cancer: is liver first?

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Abstract: Twenty percent of patients with rectal cancer present with synchronous liver metastases at the time of initial diagnosis. These patients can be treated with a curative intent, although the choice and sequence of treatment modalities are not well established and are commonly debated in multi-disciplinary tumor boards. In this article we review clinical evidence for various treatment approaches and attempt to formulate a pathway for clinicians to use in evaluating and managing these patients.

Keywords: Rectal cancer; oligometastatic; radiation therapy; surgery; review

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Introduction

In 2014, an estimated 40,000 new cases of rectal cancer will occur in the United States (1). Approximately 20% of patients with locally advanced rectal cancer will present with synchronous liver metastases at the time of initial diagnosis (2). A recent meta-analysis reported a median survival of 3.6 years after liver resection in metastatic colorectal cancer, and a median 5-year survival of 38% (3). Several retrospective analyses of carefully selected patients with solitary colorectal liver metastases reported 5-year survival rates as high as 70% following liver resection (4-6). This heterogeneous patient population thus presents with the daunting combination of a reasonable curative potential and a high risk of systemic disease progression. The optimal management of this subgroup of patients is not well established and includes surgical resection of primary disease, systemic therapy (including cytotoxic chemotherapy and/or targeted small molecule therapeutics), pelvic radiation therapy and liver-directed therapy. Appropriate use, sequencing and timing of these therapeutic modalities are not supported by randomized clinical trials in patients with synchronous oligometastatic liver disease with primary rectal cancer and are hence open to debate. We will attempt to synthesize a reasonable treatment paradigm based on clinical evidence, realizing that clinical experience and expertise of individual physicians as well as individual patient characteristics and preferences should guide the multidisciplinary team decision. Well-designed clinical trials and novel therapeutic modalities will be expected to either support or reverse our theoretical exercises.

Upfront surgery *vs.* systemic therapy

Upfront surgical resection of all gross disease, whether synchronous or staged, is a common practice at many institutions (7). Two primary arguments for this approach are both the concern for the known hepatic toxicity of prolonged courses of cytotoxic chemotherapy, with irinotecan-based regimens, in particular, contributing to the development of chemotherapy-associated steatohepatitis (CASH) and sinusoidal congestion, which increase the risk of complications at the time of liver resection. Another argument is a potential for liver disease progression on systemic chemotherapy and a possibility of losing a window of opportunity to administer a curative R0 resection for patients expressing a more aggressive malignant phenotype or one unresponsive to standard chemotherapy regimens.

A level 1 data set on this subject, the EORTC Intergroup trial 40983 randomized 364 patients with colorectal cancer and up to four liver metastases to either six cycles of FOLFOX4 before and six cycles after surgery or to surgery

alone. The initial publication (8) with a median follow up of 3.9 years revealed a statistically significant improvement in progression-free survival with the bi-modality approach. Reversible post-operative complications were higher in the chemotherapy group (25% *vs*. 16%, P=0.04), while post-operative death was similar in the two arms (1%), and only 1 out of 182 patients in the chemotherapy arm could not undergo resection due to liver damage. Twelve patients (7%) showed progressive disease on chemotherapy, with only 4 of these 12 becoming unresectable due to progression of liver lesions. The long-term results were published last year (9) and revealed no difference in overall survival (51% *vs*. 48% at 5 years). Two patients in the perioperative chemotherapy group and three in the surgery-only group died from complications of protocol surgery, and one patient in the perioperative chemotherapy group died possibly as a result of toxicity of protocol treatment. The retrospective analysis of EORTC 40983 data suggested a benefit of perioperative chemotherapy in patients with CEA values of >5 ng/mL, good performance score and body mass index <30 (10). While this is certainly a landmark study, it is difficult to draw definitive conclusions from the EORTC data regarding rectal cancer, as only 1/3 in each group had a rectal primary and in the entire cohort only 35% had synchronous disease. It is likely that different considerations should be weighed in those with synchronous disease at presentation. If there is concern for liver damage precluding resection with up-front chemotherapy, strong consideration should be given to proceeding with surgical resection as first-line therapy. Alternatively, in those who may be borderline for resection due to technical considerations, relationship of tumor(s) to critical structures, and size of the future liver remnant, chemotherapy should be the initial choice. Thus, careful planning in the multi-disciplinary setting prior to initiation of therapy is critical.

Response to chemotherapy is recognized as a predictor of outcome after resection (11,12), and patients who are offered metastatectomy in the setting of disease progression on chemotherapy have worse outcomes compared to those with radiographic response based on 5-year survival rates of 8% *vs*. 37%, as published by Adam *et al*. (13). Therefore systemic therapy prior to surgery appears to be safe, effective and can be used to select candidates with a more favorable tumor phenotype for liver metastases resection.

In the setting of oligometastatic rectal cancer, one should also consider the effect of the first treatment modality on the primary disease status. If a curative surgical approach is selected, obtaining local control becomes critical. Consider local recurrence rates of 22% for stage II and 46% for stage III patients treated on the Swedish Rectal Cancer Trial with surgery alone (14). Among patients with synchronous metastatic disease, the rates of advanced primary disease are high—for example, a contemporary series from Johns Hopkins University revealed 86% of patients had T3/T4 primary disease and approximately two-thirds had N+ disease at presentation (15). At the same time 50-60% of patients with stage II and III rectal cancer are down-staged following neoadjuvant therapy, with about 20% of patients showing a pathologic complete response (16-19).

For all the above mentioned reasons upfront surgery should not be considered standard in the setting of oligometastatic rectal cancer. The National Comprehensive Cancer Network (NCCN) have updated their 2014 guidelines version and removed upfront surgery from the standard treatment algorithm (20) for resectable synchronous metastatic rectal cancer.

Neoadjuvant therapy

The current version of NCCN guidelines offer two initial pathways for treating rectal cancer with resectable synchronous metastases—either an oxaliplatin-containing chemotherapy or pelvic radiotherapy with 5-FU-based concurrent chemotherapy. Clearly, the first pathway predominantly focuses on the systemic disease, whereas the second pathway is directed more at the pelvic disease control. The neoadjuvant approach that optimizes the therapeutic ratio should be effective for both local and systemic disease components, and be well tolerated by the patients, who must still have a performance status appropriate for an R0 surgical resection.

A retrospective analysis was carried out on 20 patients (with a total of 41 liver lesions) who underwent preoperative chemo-RT for rectal cancer with synchronous resectable liver metastases (21). All patients received a standard fractionated course of pelvic RT to 45 or 50 Gy over a period of 5 weeks, with operation performed 6 to 8 weeks later. Seven patients received FU-based-chemotherapy and 13 patients received oxaliplatin-based chemotherapy, concurrently with radiation. During oxaliplatin-RT 25 liver lesions showed the following response: 14 showed an objective tumor response, 10 were stable and 1 progressed. Among the 16 liver lesions during 5-FU-RT, 10 lesions were stable and 6 progressed. The absence of concomitant oxaliplatin-based chemotherapy was the sole predictive factor (P=0.002) of liver disease progression on imaging

during chemo-RT. There were no postoperative deaths after either rectal or hepatic surgeries in this series. Three years OS and DFS were 51% and 24%, and 6 out of 13 (46%) patients on oxaliplatin-RT developed disease recurrence *vs.* 6 out of 7 (86%) patients on 5-FU-RT (P=0.157).

Thus, the data suggests that pelvic RT with 5-FU or capecitabine might not be effective enough in controlling liver disease and preventing new distant disease recurrence. Therefore one might argue for either addition of oxaliplatin to pelvic RT or oxaliplatin-based systemic chemotherapy alone with pelvic RT omission. A prospective study enrolled 32 patients with stages II and III rectal cancer and treated with neoadjuvant FOLFOX/bevacizumab without RT. One hundred percent of patients achieved R0 resection, with 25% path CR rate and 100% local control rate at 4 years. The NCCTG phase II/III trial is now recruiting patients with stage II-III rectal cancer to either neoadjuvant FOLFOX or preoperative chemo-RT (clinicaltrials.gov NCT01515787). The results of this randomized trial will reveal whether patients could be spared radiotherapy-related toxicity without jeopardizing local control.

While the addition of oxaliplatin to pelvic RT would seem to be one of the reasonable solutions, prospective clinical trial data suggests otherwise when evaluated in the setting of non-metastatic rectal cancer. The STAR-01 trial randomized patients to 5-FU/oxaliplatin/RT *vs.* 5-FU/RT and revealed no difference in path response rate between the arms, whereas grade 3 and 4 toxicities were higher among patients randomized to oxaliplatin arm (24% *vs.* 8%, P<0.001) (22). Similar results were found in NSABP R-04 (23) and the ACCORD 12/0405-Prodige 2 trial (24). Therefore, addition of oxaliplatin to a 5-FU-based neoadjuvant chemo-RT platform is not justified in non-metastatic setting at this point. However, this might not apply to patients with oligometastatic disease, where systemic disease control is more critical and this approach may be worth the risk of additional treatment toxicity.

Another strategy of combining oxaliplatin with pelvic radiation is currently studied in a Polish Colorectal Study Group randomized Phase III trial. Patients with fixed T3/T4 or locally recurrent rectal cancer without distant metastases are randomized to either short-course RT (5 Gy ×5, given over 1 week) and 3 courses of FOLFOX 4 versus standard 50.4 Gy RT with concurrent 5-FU/leucovorin and oxaliplatin. Surgery in both groups is performed 12 weeks after the beginning of radiation. The interim analysis of the first 100 patients was recently published (25) and revealed a path CR of 21% in short-course RT arm (experimental) *vs.* 8% in the standard RT (control) arm. The experimental arm had 27% rate of post-operative complications and no post-operative mortality.

A small Korean prospective study (26) enrolled 6 patients with oligometastatic rectal cancer on upfront systemic chemotherapy with FOLFOX (with and without biologic agents) and a short-course RT (5 Gy ×5) sandwiched between chemotherapy cycles, prior to surgery. Five patients achieved R0 while all liver metastases had regressed. Prior to surgery, three patients had grade 3 toxicities, controlled by conservative therapy. With a median follow-up of 16 months, there was no locoregional recurrence, one patient developed distant metastases and no patient died. The long-term follow-up report of this experience will be important to confirm the early observations.

At present, it appears that either an oxaliplatin-based systemic therapy alone or with concurrent pelvic RT (either standard fractionated RT or a short-course RT) are reasonable neoadjuvant treatment strategies for patients with *de novo* oligometastatic rectal cancer. Ongoing and future studies that include well-defined cohorts of patients and pre-treatment tumor parameters will help provide clarity as to which strategy yields the optimal therapeutic ratio.

Synchronous (combined) *vs.* staged (sequential) surgical procedures

No randomized studies have ever evaluated the difference between two surgical approaches—synchronous (combined) approach, when liver metastases are resected at the time of TME of rectal tumor, versus a staged approach, when the two surgeries are temporally separated. Consequently, this issue is debated in multidisciplinary tumor boards on a routine basis. Hillingso and Wille-Jorgensen (27) set out to perform a systematic review on the surgical approach for synchronous liver metastases from colorectal cancer in 2007 and found conflicting evidence from available case series. Among the series they have identified, 11 studies showed a tendency towards a shorter hospital stay in the synchronous resection group, 14 studies revealed a lower total perioperative morbidity with this approach, while 15 studies identified a lower perioperative mortality with the staged approach. Eleven studies compared 5-year overall survival, which appeared to be similar in both strategies. Specific factors that have been shown to increase the rate of postoperative complications in the combined procedures were the presence of a diverting stoma, rectal location of

the primary tumor, duration of the surgery, intraoperative blood loss and the need for transfusion. A large multi-institutional retrospective study with over 600 patients revealed similar rates of mortality and severe morbidity after simultaneous colorectal resection and minor hepatectomy compared with isolated minor hepatectomy alone. However, major hepatectomy independently predicted for severe morbidity after simultaneous resections with a hazard ratio of 3.4 (P=0.008). Much debate exists regarding the optimal surgical approach (28). Furthermore, adequately powered studies comparing outcomes for major hepatectomy alone versus in combination with TME are lacking. Another important consideration is the move toward minimally invasive techniques for both the hepatic resection and TME for the primary. Many centers are moving toward these techniques, and the oncologic integrity of these approaches has been validated by several studies and consensus statements (29,30). Currently, laparoscopic techniques tend to yield shorter hospitalizations for major hepatectomy at the expense of increased operative times. Thus, staged operations may confer an overall benefit to the patient in terms of time in the operating room and lower complication rates. Patient and tumor characteristics, surgical experience and patient preference should guide the decision. At the same time, alternatives to these surgeries should also be discussed with patients, when appropriate.

Avoidance of primary rectal tumor resection in complete responders to neoadjuvant therapy

Following the success of neoadjuvant chemo-RT in anal cancer with a shift of treatment paradigm from resection to organ-preservation, led by Nigro over 30 years ago (31), several retrospective studies analyzed the outcomes after observation following complete clinical response to neoadjuvant therapy in patients with localized rectal cancer. One earlier study showed promising results with excellent DFS and OS rates at 5 years (32), but most clinicians remained skeptical of this approach (33). However, a more recent study (34) prospectively selected 21 patients with localized rectal cancer who achieved a clinical CR after chemoradiotherapy, as evaluated by magnetic resonance imaging (MRI) and endoscopy with biopsies, and followed these patients by observation for a mean follow-up of 25 months. Only one patient developed a local recurrence and had a successful salvage surgery, whereas the remaining 20 patients were alive without disease. Because of limited data and concern about the ability of imaging studies to accurately determine a pathologic response (35), the NCCN 2014 panel did not support the observation approach for patients with localized rectal cancer with complete response to neoadjuvant treatment. However, this treatment paradigm, although previously untested, could be considered for patients with known metastatic disease. These patients have a higher likelihood of systemic disease progression than patients with localized rectal cancer, and therefore the tradeoff of a lower primary disease local control for the improved quality of life might be reasonable and worthy of further investigation. Quality of life can be improved in this patient population with surgery reserved for patients with local recurrence in the absence of systemic disease progression or in the event of symptomatic local disease progression. This approach, if used, should incorporate pelvic radiation therapy as part of a neoadjuvant treatment recommendation, as the rate of local recurrence after pathological response to chemotherapy alone has not yet been studied.

Alternatives to liver surgery

It is rare for liver metastases to be permanently eradicated with systemic chemotherapy alone, even in the setting of complete radiographic response. One study revealed an 83% rate of local failure or disease persistence in sites that had initially shown a complete response to systemic chemotherapy by CT imaging (36). These results highlighted the potential pitfalls when interpreting the "disappearing metastasis" as complete response to chemotherapy. Surgery remains the standard of care even when there is a significant or complete radiologic response to up-front chemotherapy for isolated liver metastases, with 5-year overall survival rates up to 70% in selected patients. However, because of tumor size and location, over four-fifths of patients present with unresectable disease (37). Nonsurgical options have emerged and continue to constantly improve.

Radiofrequency ablation (RFA) has recently been shown to offer a 60% rate of local control beyond 12 months (38-40) and should be considered for patients who are technically unresectable or unable to tolerate an open resection. In general, lesions amenable to RFA should be no larger than 3 cm in size, not located near hilar structures, and be treated at centers with expertise in this field. Controversy persists as to whether RFA is equivalent to open or laparoscopic resection for those with appropriately sized lesions and prospective data are sorely needed. In

fact, lack of adequate evidence prompted the American Society of Clinical Oncology (ASCO) to publish a review on this topic, and the data regarding the equivalence or comparative utility of RFA relative to surgical resection was found insufficient to issue a practice guideline (41).

Non-conformal radiation therapy has a very limited role in treatment of hepatic metastases due to the high rates of radiation-induced liver disease (RILD), which develops after large percentage of liver is exposed to the radiation dose, necessary to control the metastatic disease. However, stereotactic body radiation therapy (SBRT) has emerged, which delivers radiation to a target in the body, with sufficient intensity to kill, or at least control, the underlying malignancy, while minimizing the radiation dose to adjacent normal tissues. Effectively and safely accomplishing these conflicting goals requires quantitative visualization and localization of the target lesion, complex radiation plans, continual management of the target position throughout treatment, and robust quality assurance. Detailed review of SBRT technique and clinical data has been expertly reviewed elsewhere (42). The largest series with a long-term follow-up on SBRT in colorectal liver metastases reported on 65 patients with 102 lesions treated at Princess Margaret Hospital, University of Colorado and Stanford University (43). The overall local control rate was 71%, while patients who received biologically equivalent dose (BED) of ≥79 Gy_{10}, 12-, 18- and 24-month local control rates were 86%, 80% and 71%, respectively. On the basis of the best-fit curve, a BED of 117 Gy_{10} would yield a 90% local control rate (which corresponds to a dose schedule of at least 48 Gy given in 3 fractions of 16 Gy, or its equivalent if a different number of fractions is used). In terms of toxicity of this treatment, 17% of patients experienced grade ≥2 acute (defined as within 3 months of SBRT) GI toxicity, 3% did grade ≥3 elevated liver enzymes, but none had symptomatic liver toxicity. Late toxicities were also limited, with 6% of patients experiencing grade ≥2 GI toxicities: two patients had grade 3 gastritis and two patients had grade 2 small bowel ulcers.

Further validation is needed before SBRT can be considered a standard of care for liver metastases from rectal cancer. Currently, phase I trials at University of Pittsburgh (NCT01360606) and the University of Texas (NCT01162278), plus a phase II study at the Massachusetts General Hospital (NCT01239381), are accruing patients. A phase III trial at University of Aarhus is randomizing patients with liver metastases to RFA or SBRT. Whenever possible, patients should be offered a chance to participate in prospective studies. Nevertheless, both RFA and SBRT should be considered for patients who cannot undergo liver resection.

Summary

The heterogeneous group of patients with oligometastatic rectal cancer involving the liver presents with a daunting combination of a reasonable curative potential, yet with a high risk of systemic disease progression. The optimal management of this subgroup of patients is not well established. The 2014 NCCN guidelines have removed upfront surgery as the treatment recommendation for most patients, realizing that systemic and pelvic control take precedence over surgical extirpation of liver and primary disease. As summarized in this review article, oxaliplatin-based chemotherapy with or without pelvic radiation therapy, followed by either resection of primary and liver disease or consideration of non-surgical modalities appear to be the most well-supported treatment approaches in the literature. Multidisciplinary evaluation of each patient is paramount to achieve best outcomes, with taking into account patients' preferences as well the expertise and experience of the multidisciplinary team. Future well-designed studies will shed light on how best manage this heterogeneous group of patients.

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