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Local Therapies in Advanced Colorectal Cancer

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Introduction

Approximately 25% of patients with colorectal cancer (CRC) present with metastatic disease at initial diagnosis, while almost 50% will ultimately develop distant metastases at some point during their lifetime.[1,2] For the majority of patients, metastatic disease is confined to the liver and/or lungs.[3,4] Advances in systemic therapy and use of hepatic resection for select patients have resulted in dramatic improvements in outcomes for patients with metastatic CRC (mCRC).[5] While surgical resection remains the gold standard for treatment of local disease in the liver and lungs, additional therapies are now available for treatment of metastatic sites with evolving data on their safety and efficacy. This review will provide an overview of local therapies for mCRC and highlight some of the current developments and controversies in managing this select group of patients.

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Local Therapy for Liver Metastasis

The liver is the primary site of metastasis in patients with mCRC.[6] Evidence regarding the optimal treatment modality for management of mCRC to the liver is based largely on retrospective reviews. Given the limitations of retrospective series, summary data of local therapy to the liver, which is presented in Table 1, is suspect because of near-universal selection bias in the trials on which these meta-analyses are based. For this reason, we have listed the ranges of local control and/or response rates, where possible, in the included individual studies rather than the outcome of each overall meta-analysis, as a single local control number fails to capture the complexity of these comparisons. In most centers, the practice pattern in the era of these studies has been that surgical resection is the first choice, given favorable outcomes, and other modalities are only used when resection is infeasible due to tumor location, inadequate hepatic reserve, or patient comorbidity. Therefore, it is difficult to compare survival rates in a meaningful way.

Prospective data does exist on the benefit of interventional radiology (IR) ablation to all areas of inoperable hepatic disease. EORTC-40004, a randomized phase II trial in patients with liver-limited mCRC with <10 lesions, demonstrated that radiofrequency ablation (RFA) with or without surgery when added to standard of care systemic therapy resulted in improved overall survival (OS) as compared to standard of care systemic therapy alone (HR 0.58, 95% CI [0.38, 0.88]; P=0.01).[7,8] Thus, when surgical resection is not an option, typically percutaneous or open RFA or microwave ablation (MWA) is the next choice of treatment modality. Stereotactic ablative radiotherapy (SABR) is a non-invasive ablative option for patients with liver metastasis that uses specialized immobilization and highly conformal beams to deliver high doses of radiation per fraction to the tumor target. SABR has been shown to be a safe and effective treatment for CRC liver metastases with local control rates approaching 90% in modern series.[9] Given the larger body of available literature with surgery and IR ablation, SABR is typically reserved for patients deemed ineligible for these treatments. Limited comparison of treatment modalities has been performed and remains an area of controversy which will hopefully be answered by the ongoing prospective COLLISION trial (NCT03088150) which is a comparison of surgical resection and thermal ablation. Pragmatically, it is likely that selection of treatment modality will depend on a variety of factors including overall disease burden, patient fitness, and metastasis location.

There are several intra-arterial therapy options for management of liver metastases including transarterial radioembolization (TARE), transarterial chemoembolization (TACE), and hepatic artery infusion (HAI) pump therapy. TARE is often reserved for patients with liver-only disease not eligible for curative intent resection or ablation, however, its exact role in the treatment of patients with CRC liver metastases remains undefined. A number of phase III trials have investigated the role of TARE in mCRC liver-confined disease with the combined analysis of these trials showing no difference in OS or progression-free survival (PFS) when combining TARE with first-line FOLFOX compared to FOLFOX alone with increased toxicity observed in the TARE group.[10] However, patients receiving TARE did have a lower incidence of in-liver progression as compared to patients receiving systemic therapy alone.

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The delivery of regional systemic therapy to the liver either via TACE or HAI pump for liver-confined mCRC remains unclear but is evolving as more centers are considering these therapies. There is mixed data on the benefit of TACE in mCRC patients with one small limited study showing no benefit, while a second small prospective study showed an OS benefit of drug-eluting beads with irinotecan over systemic FOLFIRI.[11,12] Initial prospective trials comparing the use of HAI therapy to systemic therapy showed promising outcomes, but the control arms consisted of inferior systemic therapy regimens by current standards.[13,14] A small case-control study which included patients treated with modern systemic therapy showed improved OS in patients treated with combination systemic therapy plus HAI vs. systemic therapy alone.[15] Memorial Sloan Kettering reported on 2,368 consecutive patients who underwent complete resection of CRC liver metastases.[16] The median overall survival was 67 months with HAI (n=785) vs. 44 months without HAI (n=1,583) (P<0.001) despite more advanced disease in the HAI group.[16] When restricting the analysis to 1295 patients treated with modern systematic chemotherapy this survival benefit persisted (median OS 72 vs. 51 months, P<0.001). These data are concordant with results of a phase III randomized study that reported improved 2-year OS (86% vs. 72%, P=0.03) and 2-year survival free of hepatic recurrence (90 vs. 60%, P<0.001) and a strong trend towards improved 2-year PFS (57% vs. 42%, P=0.07) with HAI, in patients with metastatic CRC who underwent complete resection of liver metastases randomized to systemic 5-FU/leucovorin with or without HAI.[17] Currently, the benefit of HAI therapy in the era of modern systemic therapy and outside large, specialized tertiary care centers remains an open question. The major barrier to wider adoption is the complexity of surgery to place a HAI pump, which requires multidisciplinary skill and experience.[16]

Factors that in some studies correlate with higher success rates across treatment modalities include the presence of 3 or fewer liver lesions, CEA level 200 ng/mL or less prior to local treatment, tumor diameter 3 cm or less, and tumors that are not near major vascular structures.[18] Patient performance status has an effect in some studies, likely because it can limit treatment choices, which may therefore be a reflection of inferior systemic therapy paired with the local treatment. It is extremely difficult to control the confounding factor of peri-procedural chemotherapy in these patients as doing so would result in unusably small cohorts.

What we can glean from the data presented in Table 1, which represents only a sample of available studies investigating the role of local therapy to the liver in mCRC, is that local control is worth pursuing in this patient population. In patients with liver-only disease in whom further distant metastasis can be prevented with systemic therapy, delivering high-quality local therapy greatly increases the chances of controlling all disease. Although 5-year OS rates remain low, the mean OS following diagnosis of metastases has climbed continuously since about 1985, and liver-directed therapies play an important role in that improvement.[19]

Local Therapy for Lung Metastasis

The lungs are the most common site of extra-abdominal disease in patients with mCRC.[6] Surgical resection of pulmonary metastases may lead to improved disease control and

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prolonged OS based on largely retrospective series with several recent publications summarized in Table 2.[20–23] Randomized evidence to determine the efficacy of lung metastasectomy has been limited to the PulMiCC trial, a randomized phase III noninferiority trial of patients with resectable CRC lung metastases randomized to observation vs. surgical metastasectomy.[24] The trial was closed early due to poor accrual with only 93 patients out of a planned 300 randomized. The 5-year OS was 30% for control and 36% for the metastasectomy patients. A number of meta-analyses have been performed to identify prognostic factors following lung metastasectomy for CRC.[25–28] Poor prognostic factors which have been identified include: a shorter disease-free interval between primary tumor resection and development of lung metastases, the presence of multiple lung metastases, positive hilar and/or mediastinal lymph nodes, elevated pre-surgical CEA, presence of *KRAS* mutation, and prior liver metastases.[25–28] Reported rates of 5-year OS for patients with resected lung metastases range from 27–68% in reported series.[25]

Non-surgical options have also been utilized for the management of pulmonary metastases with select series summarized in Table 2. The RAPTURE study was a prospective, single-arm, multicenter trial evaluating use of RFA for patients with non-small cell lung cancer or lung metastases with up to 3 tumors per lung each ≤3.5 cm in diameter.[29] The trial included 106 patients total with 53 patients with mCRC. Treatment was completed in 99% of patients although a pneumothorax requiring intervention was a major complication in 27 of the procedures. A confirmed complete response of treated mCRC tumors for a duration of at least 1 year was 90% with a 1 and 2-year OS of 89% and 66%, respectively, and a 1 and 2-year cancer-specific survival of 91% and 68%, respectively. A large prospective database study from two French centers reported on use of RFA to treat lung metastases with over half of the 566 patients with CRC lung metastases.[30] For the mCRC patients, 3-year OS was 76% for colon and 65% for rectal, 3-year PFS was 17% for colon and 8.6% for rectal, and 3-year local treatment failure was 16.2% for colon and 30.7% for rectal. For the mCRC patients, metastasis size >2 cm and ≥3 metastases were associated with worse OS. Toxicity of treatment was a concern with 67% of procedures resulting in a pneumothorax with a chest tube required in 58% of pneumothorax cases.

SABR has also been shown to be an effective treatment for pulmonary metastases from CRC with select published series summarized in Table 2. Overall, local control rates of 80–90% at 1 year have been reported with minimal toxicity.[31–33] Data from several series have shown that CRC lung metastases treated with SABR have a higher rate of local failure compared to other histologies and improved local control can be achieved by delivering a higher biologically effective dose.[34,35] While no prospective clinical trials have evaluated SABR with surgery for the treatment of CRC lung metastases, a retrospective exploratory analysis suggests that OS within 2 years of treatment is similar following surgery or SABR.[36] A recent meta-analysis suggested comparable OS outcomes in recent series when comparing surgical to non-surgical interventions for patients with colorectal lung metastases likely due to improved systemic therapies and local therapies such as RFA and SABR.[37]

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Other Sites

Additional sites of metastases that are less common, but are still amenable to local therapy include ovarian, adrenal gland, and retroperitoneal lymph nodes. Ovarian metastases occur in a minority of women (≤ 10%) with mCRC and are generally associated with poor OS.[38] However, favorable outcomes have been shown following resection of all macroscopic disease based on a large series from Memorial Sloan Kettering.[38] The incidence of isolated adrenal metastases in patients with mCRC is also low with isolated case reports and limited series describing favorable outcomes following adrenalectomy.[39] Similarly, para-aortic lymph node involvement occurs in fewer than 2% of CRC cases.[40] A systematic review of 18 retrospective studies demonstrated an improvement in OS in mCRC patients with isolated either synchronous or metachronous para-aortic lymph node involvement treated with surgical resection compared to non-surgical therapy including chemotherapy or chemoradiation.[40] While bone metastases were once rarely observed in patients with mCRC, improvements in systemic therapy have resulted in prolonged OS and a change in pattern of metastases with bone metastases occurring late in the disease course.[41] While patients with bone metastases are unlikely to have prolonged survival following local therapy, palliation of symptoms oftentimes will warrant local treatment. While standard multifraction external beam radiation therapy is a proven therapy for palliation of bone metastases, recent data suggest that single fraction SABR may result in higher rates of pain response and should be considered in patients expected to have a relatively long survival.[42]

Local Therapy for Multiple Sites

A limited number of prospective studies have been performed which investigate the role of local therapy for patients with mCRC with both intra- and extrahepatic disease. In the single arm phase II Dutch M1 trial, 50 patients with potentially resectable or ablatable metastases in the liver (84%), lungs (10%), or both (6%) were treated with short course radiotherapy (25 Gy in 5 fractions) followed by capecitabine, oxaliplatin, and bevacizumab and subsequent resection of the primary tumor and all metastatic sites.[43,44] Complete surgical resection was feasible in 72% of patients. After a median follow-up of 8.1 years, 32% of patients were alive with 28% disease-free. The median OS was 3.8 years. A phase II Canadian study evaluated metastasectomy for patients with both intrahepatic (any number) and extrahepatic (up to three foci) disease.[45] Of the 26 patients enrolled, resection of all sites was completed in 77% of patients. The median OS from the time of metastasectomy was 38 months with a 3-year OS of 53%. Major complications (Clavien grade ≥3) occurred in 19% of patients. A recent nationwide prospective intervention study from Finland enrolled 1086 patients with treatable mCRC.[46] Multiple metastatic sites were reported in 46% of patients and in 76% of patients during disease trajectory. Three hundred and ninety-nine patients underwent 690 curative resections or local ablative therapies, which included liver and lung thermoablation and/or SABR. Overall, 414 liver, 112 lung, 57 peritoneal, and 107 other metastasectomies were performed. The 5-year OS rates were 60%, 40%, and 6% in patients treated with gross surgical excision (i.e. R0/R1 resection), surgical debulking (i.e. R2 resection) or local ablative therapy, and systemic therapy, respectively.

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Advances in radiation therapy planning and delivery have led to the utilization of SABR for the treatment of a number of different body sites. SABR-COMET is a phase II trial randomizing patients with 1–5 metastatic lesions and a controlled primary to palliative standard of care treatment or the addition of SABR to all metastatic sites.[47,48] Of 99 patients included in the study, 18 had mCRC with the majority of treated sites located in the bone or lungs. The 5-year OS was 17.7% in the standard of care alone arm and 42.3% in the SABR arm, P=0.006. The 5-year PFS was 0% in the standard of care arm and 17.3% in the SABR arm, P=0.001. The rate of grade ≥2 adverse events due to treatment was 9% in the standard of care arm and 29% in the SABR arm, P=0.03. A single arm phase II trial evaluated SABR for patients with oligometastatic cancer with a recent report of the subset of treated mCRC patients.[49] Five-year local control and OS were 83% and 45%, respectively, with 3.2% late grade 3+ toxicity.

Discussion

The use of local therapy in patients with oligometastatic CRC has improved outcomes, however, multiple questions remain regarding identification of appropriate candidates for therapy, timing of treatment, use of appropriate treatment modality, and management of the primary tumor. The definition of oligometastatic disease is evolving, and, in turn, also is the criteria for identifying appropriate candidates for local therapy. While initially only patients with liver metastases were considered candidates for local therapy, treatments have evolved to provide local ablative therapy options for nearly all body sites. Consensus definitions for oligometastatic disease have been developed.[50,51] However, with an already established history of local therapy and a paucity of prospective studies to demonstrate efficacy, it is unclear if these blanket definitions also apply to patients with mCRC. Regarding timing of local therapy, most favor upfront systemic therapy both to serve as a biological test of the disease and to permit response in some patients who are considered borderline candidates for resection. For patients with resectable/ablatable metastatic disease, the primary tumor should also be removed as part of curative intent therapy. For patients with an asymptomatic primary tumor and synchronous metastatic disease that is not amenable to complete resection/ablation, removal of the primary tumor is not indicated as no benefit has been shown with primary tumor resection compared to continued systemic therapy alone.[52]

The selection of treatment modality for patients with mCRC is dependent on multiple factors, and necessitates the need for multidisciplinary input as discrepancies exist in feasibility of hepatic resection between surgeons and non-surgeons.[53] While surgical resection is considered the standard of care for eligible patients with lung and/or liver disease based on decades of experience, evidence is mounting on the use of alternative therapies for patients not eligible for surgery or who have disease that is not amenable to complete surgical resection. However, a well-designed prospective randomized trial evaluating the utility of local therapy in patients with non-liver limited oligometastatic CRC is crucial for defining the benefit of this potentially toxic therapy.

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Summary

For patients with mCRC confined to the liver or lungs, patients eligible for curative-intent resection experience prolonged disease control and OS. For patients with more advanced disease, including those with both hepatic and pulmonary disease, and those with extrahepatic and extrapulmonary disease, the role of local therapy is less clear, but emerging data has shown potential benefits of local therapy in this select group of patients and additional studies to further define this benefit are urgently needed. Additional questions remain regarding identifying appropriate candidates for treatment and determining the ideal timing and modality of treatment for these patients and should be the subject of future clinical trials.

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Key Points:

- In eligible patients, curative intent surgical resection of hepatic and pulmonary metastases results in improved disease control and prolonged overall survival with the potential for cure based on largely retrospective data.
- For patients with liver-limited disease not amenable to complete surgical resection, multimodality ablative therapy can be considered and may result in improved outcomes compared to continued systemic therapy alone.
- For patients with both intra- and extrahepatic disease, preliminary data has demonstrated feasibility of treatment to all sites and the potential for prolonged survival following multi-modality treatment.
- For patients with a limited number of metastatic sites not necessarily confined to the liver or lungs, preliminary data demonstrates prolonged overall survival following ablative radiation therapy compared to standard of care therapy, although further studies are needed to verify these findings in a metastatic colorectal cancer patient population.
- Management of patients with advanced colorectal cancer requires multidisciplinary management to identify candidates where local therapy can be considered as well as determining the appropriate timing and treatment modality.

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Synopsis

Curative intent surgical resection of colorectal metastases to the liver and lungs in eligible patients results in improved disease control and prolonged overall survival with the potential for cure in a subset of patients. Additional ablative and local therapies for use in the liver, lungs, and other body sites have been developed with emerging data on the utility and toxicity of these treatments. Future studies should focus on identification of appropriate candidates for treatment and determining the optimal modality and timing of treatment accounting for both patient and disease factors.

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Clinics Care Points

- Multidisciplinary management is key to determine local therapy candidacy for patients with advanced colorectal cancer.
- Patients with hepatic and pulmonary metastases, who are eligible, should be considered for curative intent surgical resection.
- For patients with liver-limited disease that is not amenable to complete surgical resection, multimodality ablative therapy should be considered.
- For patients with more advanced disease including those with both hepatic and pulmonary disease not amenable to complete surgical resection, the use of local therapy including ablative radiation therapy can be considered for eligible patients.

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Table 1:

Select studies evaluating the role of local therapy for colorectal liver metastases

Author	Treatment modality	Study design	Number of patients	Lesion size	Local control or complete response rate	Acute mild/grade 1–2 toxicities	Acute severe/ grade 3+ toxicities
Choti et al[54]	Surgery	Retrospective	226	Median 3.9 cm	5-yr disease-free survival 20%	NR	2 peri-operative deaths
Petrelli et al[55]	SABR	Systematic review	656	Median 2–3.5 cm (0.6 – 11.6)	60 – 96%	31%	9%
Van Amerongen et al[56]	RFA vs surgical resection	Meta-analysis	751 RFA 1,276 surgery	NR	32–82% RFA 77–98% surgery	Total complication rate reported: 12% RFA, 2 grade 5 25% surgery, 8 grade 5	
Kron et al[57]	RFA vs surgical resection	Systematic review	779 RFA 1359 surgery	NR	24–85% RFA 60–98 % surgery	NR	NR
Gavriildis et al[58]	MWA vs RFA vs surgery	Meta-analysis	350 MWA 1253 RFA 1798 Surgery	NR	42–74% MWA 63–71% RFA 43–94% Surgery	NR	NR
Correa-Gallego et al[59]	Open RFA or MWA	Retrospective	127	Median 1.0 cm (1.0–2.0)	80% for RFA at 2.5 years, 94% for MWA at 18 months	24% vs 27%	Not reported
Wasan et al[10]	FOLFOX +/− TARE	Combined analysis of 3 phase III trials	1,103	NR	At best response, CR rate 4.5% for TARE+FOLFOX vs 1.6% for FOLFOX alone	74% TARE+FOLFOX 67% FOLFOX alone	16.4% from TARE, 8 were grade 5
Van Hazel et al[60]	TARE + FOLFOX vs FOLFOX + Bevacizumab	Phase III randomized trial	263 mFOLFOX6 267 TARE + mFOLFOX6	NR	At best response, CR rate 6% mFOLFOX6 + TARE 1.9% mFOLFOX6	58% with TARE + mFOLFOX6 46% with mFOLFOX6 + Bevacizumab	85.4% with TARE, 9 were grade 5 73% with FOLFOX + Bev, 5 were grade 5
Kemeny et Al[17]	5-FU +/− HAI	Phase III randomized trial	74 5-FU/ leucovorin 82 5-FU/ leucovorin + HAI	NR	2-yr survival free of hepatic recurrence 60% 5-FU/ leucovorin 90% 5-FU/ leucovorin + HAI	NR	7% 5-FU/ leucovorin 6% 5-FU/ leucovorin + HAI

Abbreviations: CR, complete response; HAI, hepatic artery infusion; MWA, microwave ablation; NR, not reported; OS, overall survival; RFA, radiofrequency ablation; SABR, stereotactic ablative radiotherapy; TARE, transarterial radioembolization

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Table 2:

Select studies evaluating the role of local therapy for colorectal lung metastases

Author	Treatment modality	Study design	Number of patients	Mean follow-up	Local control	Progression-free survival	Overall survival	Comments
Davini et al[20]	Surgery	Retrospective	210	56 months	7.14% resection margin recurrence	NR	1-year: 95% 3-year: 74% 5-year: 54%	76% with single lung metastasis
Fournel et al[21]	Surgery	Retrospective	306	3.06 years	NR	3-year: 38.9% 5-year: 28.3% 7-year: 22.7%	3-year: 77.8% 5-year: 59.0% 7-year: 56.9%	64% with unilateral disease
Okumura et al[22]	Surgery	Retrospective	785	65 months (median)	NR	5-year: 37.1%	5-year: 68.1%	74% with single lung metastasis
Renaud et al[23]	Surgery	Retrospective	574	62 months (median)	21% 5-year pulmonary recurrence-free survival	NR	5-year: 58%	50% with single lung metastasis
Lencioni et al[29]	Radiofrequency ablation	Phase II, single arm	106, colorectal in 53	15 months	88%	NR	1-year: 89% 2-year: 66%	Pneumothorax in 20% of procedures
De Baère et al[30]	Radiofrequency ablation	Prospective database	566, colorectal in 293	35.5 months (median)	Local tumor progression per patient: 1-year: 10.4% 2-year: 15.5% 3-year: 17.5% 4-year: 18.1%	1-year: 40.2% 2-year: 23.3% 3-year: 16.4% 4-year: 13.1%	1-year: 92.4% 2-year: 79.4% 3-year: 67.7% 4-year: 58.9% 5-year: 51.5%	For CRC patients, size >2 cm and ≥3 lesions associated with worse OS; Pneumothorax in 67% of procedures requiring chest tube in 58%
Jung et al[32]	SABR	Retrospective	50	42.8 months (median)	1-year: 88.7% 3-year: 70.6%	3-year: 24.0%	3-year: 64.0%	No grade 3+ Toxicity reported
Jingu et al[31]	SABR	Retrospective	93	28 months (median)	3-year: 65.2% 5-year: 56.2%	NR	3-year: 55.9% 5-year: 42.7%	2 patients with grade 3+ toxicity
Kinj et al[33]	SABR	Retrospective	53	33 months (median)	1-year: 79.8% 2-year: 78.2%	1-year: 29.2% 2-year: 14.6%	1-year: 83.8% 2-year: 69.3% 5-year: 58.3%	No grade 3+ Toxicity reported

Abbreviations: CRC, colorectal cancer; NR, not reported; OS, overall survival; SABR, stereotactic ablative radiotherapy