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Locoregional Liver-Directed Therapies to Treat Unresectable Colorectal Liver Metastases: A Review

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Abstract

An estimated 70% of patients with colorectal cancer will develop liver metastases during the course of their disease. While the first-line treatment for hepatic metastases is resection, most patients with colorectal liver-only or liver-dominant metastases (CRLM) present with unresectable disease and are not surgical candidates. In the past decade, locoregional liver-directed therapies have demonstrated safety and efficacy in the treatment of patients with unresectable CRLM and chemotherapy-refractory disease. These treatments can be used to attempt conversion to surgical resectability, can control local disease progression, and have the potential to prolong survival. However, they have not yet become the standard of care in many practices. Each treatment has unique risks, and the clinical data are heterogeneous and thus difficult to interpret. In this article, we will review the most recent, high-impact literature on 3 common locoregional therapies used in the treatment of patients with unresectable CRLM: hepatic artery infusion pump chemotherapy, stereotactic body radiation therapy, and selective internal radiation therapy with yttrium-90 embolization. Ultimately, for this patient population, clinical decision-making requires a multidisciplinary discussion which should take into account individual patient characteristics and clinical expertise available at the treatment facility.

Keywords

Colorectal cancer; liver metastases; unresectable; regional therapy; yttrium 90; stereotactic body radiation therapy; hepatic artery infusion pump chemotherapy

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Introduction

Colorectal cancer is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths globally, with an incidence that is projected to increase by 60% by the year 2030.[1] For those with colorectal cancer, the liver is the most common site of metastatic disease. Approximately 25% of patients initially present with synchronous liver metastases, while an estimated 70% of patients will develop liver metastases during the course of their disease.[1,2]

The first-line treatment for patients with colorectal liver-only or liver dominant metastases (CRLM) is resection, yet 70% to 80% of patients present with unresectable disease.[2,3] The 5-year survival rate for patients with unresectable CRLM remains poor, at approximately 5%.[4,5] For these patients, the National Comprehensive Cancer Network (NCCN) guidelines recommend systemic chemotherapy with consideration of additional biologic therapies.[6] However, systemic therapies are frequently difficult for patients to tolerate, with approximately 30% of patients discontinuing treatment before completing the full number of cycles.[7,8] Moreover, despite receiving adequate chemotherapy, many patients develop progressive disease.[9]

Over the past decade, locoregional liver-directed therapies have demonstrated safety and efficacy in the treatment of patients with unresectable CRLM with chemotherapy-refractory disease. However, these therapies have not yet become the standard of care in many practices.[2] Additionally, establishing a consistent and effective management approach is challenging, due to differing practice patterns among institutions as well as a paucity of comparative studies within the literature.[9,10] To address this knowledge gap, this article reviews 3 common locoregional therapies used in the treatment of patients with unresectable CRLM: hepatic artery infusion pump chemotherapy (HAIP), stereotactic body radiation therapy (SBRT), and selective internal radiation therapy with yttrium-90 embolization (Y90). Herein, we will examine recent high-impact literature that reports how these locoregional treatments influence overall survival (OS), progression-free survival (PFS), and conversion to resection, along with their commonly associated adverse events (AEs).

Methods

We performed a comprehensive systematic literature review to identify recent publications discussing the role of HAIP, SBRT, or Y90 in the treatment of unresectable CRLM. We reviewed only literature that focused on a molecularly unselected patient population, which is an important distinction since select tumor mutations in unresectable CRLM may demonstrate durable responses to specific systematic or liver-directed therapies.[11] Specific outcomes of interest included OS; PFS, or local control if PFS data were not reported; conversion to resection; and AEs. AEs were graded using either the Common Toxicity Criteria Adverse Events version 3.0, with specific focus on AEs of grade 3 (serious) or higher, or the Clavien-Dindo classification of surgical complications.[12,13] We included studies published after 2010 and included phase 1, phase 2, and phase 3 trials; systematic reviews; meta-analyses; case-control studies; and prospective or retrospective cohort studies

(Figure). Consensus guidelines, single-case reports, and meeting abstracts were excluded from this review. A total of 26 papers met inclusion criteria and were analyzed.

Hepatic Artery Infusion Pump Chemotherapy

Since its inception in the 1950s, HAIP has been refined as a safe and effective strategy to control disease progression or expand resectability in patients with unresectable CRLM.[14,15] This locoregional therapy capitalizes on the unique blood supply of the liver, as the hepatic artery predominantly supplies liver metastases, while the portal vein perfuses normal hepatocytes. Infusion of chemotherapy directly into the hepatic artery allows selective drug delivery of maximal cytotoxic concentrations to metastatic lesions with relative sparing of the normal liver parenchyma and minimization of systemic AEs. HAIP is typically administered via the gastroduodenal artery by a surgically implanted pump or a percutaneously placed catheter connected to an external pump.[15,16] Furthermore, HAIP allows for high first-pass hepatic extraction and concomitant administration of systemic therapy. The NCCN recommends that HAIP be considered for selected patients with unresectable CRLM; however, it should be implemented only at institutions with surgical and medical oncology expertise in HAIP administration (category 2B recommendation).[6]

We examined 8 peer-reviewed studies focusing on the role of HAIP in the treatment of unresectable CRLM (Table 1). This literature review includes 3 prospective phase 2 trials, 2 retrospective multicenter reviews, 2 retrospective single-institution reviews, and 1 meta-analysis. The included studies examined patients who may have received prior chemotherapy but were not previously treated with resection/ablation or HAIP. The publication years ranged from 2015 to 2021 and the number of patients included in each study ranged from 59 to 3000.

The three phase 2 trials examined survival and resection outcomes among patients with unresectable CRLM who received HAIP in addition to systemic chemotherapy.[17–19] Each of these studies, which included 49, 64, and 64 patients respectively, demonstrated relatively similar median OS (25.5–38 months) and PFS (9.3–13 months). More importantly, up to 52% of patients demonstrated conversion to resectability, therefore offering these patients a chance for cure. In the phase 2 study conducted by D'Angelica et al,[17] all patients received HAIP in addition to systemic chemotherapy. However, most patients (65%) were receiving HAIP and chemotherapy as their second- or third-line therapy for unresectable CRLM. Overall, 47% of patients achieved conversion to resection over a median timeframe of 6 months, and conversion was the only factor associated with prolonged OS and PFS in multivariate analyses.

Four retrospective analyses were reviewed, demonstrating promising trends in median OS and conversion to resection when utilizing HAIP for unresectable CRLM. Dhir et al[20] performed a single-institution retrospective case-control study examining 86 patients who received either HAIP plus chemotherapy or chemotherapy alone. OS was statistically longer for patients who received HAIP plus chemotherapy (32.8 months) compared to those who did not receive HAIP (15.3 months; 95% CI, 0.21–0.72). There was no difference in conversion to resection rates between treatment groups. Lim et al[21] performed a multicenter retrospective comparison of 61 patients who either received HAIP plus

chemotherapy as first- or second-line treatment for unresectable CRLM vs third- or fourth-line treatment. The authors reported an improvement in median PFS in patients receiving HAIP plus chemotherapy as an earlier treatment - 9 vs 6 months (95% CI, 0.18–0.66), but the improvement in median OS was not statistically significant. Among all patients, the conversion to resection rate was 16.4%. Two additional retrospective cohort studies including 89 to 154 patients in each study receiving HAIP plus chemotherapy were reviewed.[22,23] Median OS and the rate of conversion to resection was 19.5 months and 7.8%, respectively, in one study, and 20 months and 27%, respectively, in the other.

A recent meta-analysis pooled data from 90 studies that examined 3,000 patients who underwent hepatic artery–directed therapies; it found a median OS for HAIP as first-line treatment of 21.4 months (95% CI, 19.4–23.3) vs 13.2 months (95% CI, 12.2–14.2) as a second-line or later therapy.[24] Overall, the conversion to resection rate was highest among patients receiving HAIP (15%) compared with other hepatic artery therapies such as transcatheter arterial chemoembolization (4%) or radioembolization (2%).

The main drawbacks of HAIP are the requirements for technical expertise, an experienced team of oncologists, and the potential for biliary toxicity, which may necessitate dose adjustment, coadministration with dexamethasone, or stent placement.[14] In the studies examined, the rate of grade ≥ 3 AEs ranged from 8.4% to 79%, with the most common complications including diarrhea (29%), transaminitis (16%), pump-related complications (14.3%), abdominal pain (12%), biliary sclerosis (8.4%), vomiting (6%), and neutropenia (2%). [17,23] Another possible disadvantage when considering HAIP is that its use may restrict future use of additional locoregional therapies, such as Y90 or transarterial chemoembolization.

In conclusion, in studies of patients who had received prior chemotherapy for unresectable CRLM, the addition of HAIP may improve survival and rates of conversion to resection. However, providers must weigh the potential benefits of HAIP against its risks of toxicity and the need for referral to institutions with HAIP infrastructure and expertise.

Stereotactic Body Radiation Therapy

SBRT aims to precisely deliver large, hypofractionated doses of radiation to target lesions while minimizing its delivery to adjacent normal tissues.[25,26] Through image guidance, this noninvasive locoregional modality induces cell death and coagulation necrosis of the targeted tissue, causing a gradual reduction in tumor size and/or complete replacement by fibrosis.[27,28] Multiple hepatic lesions can be treated simultaneously; however, practitioners must ensure that adequate liver volume is spared from unintended radiation spread.[29] The NCCN states that SBRT is a reasonable treatment option for patients with CRLM who are not candidates for resection, ablation, or participation in a clinical trial.[6]

We analyzed 9 peer-reviewed studies that investigated the clinical outcomes of patients treated with SBRT for unresectable CRLM (Table 2). This literature review included 5 retrospective cohort studies, 1 systematic review, and 3 prospective studies. The publication years ranged from 2010 to 2021, and the number of patients examined ranged from 11 to 656 per study. The patient populations across studies varied markedly with respect to

previous lines of chemotherapy, prior hepatic interventions, and the presence or absence of extrahepatic metastases. Additionally, we observed substantial variation in the main outcome reported, which included a mixture of median OS, percent survival over time, median PFS, and percent local control. This heterogeneity contributed to the complexity in interpretation of these studies.

We examined 5 retrospective cohort analyses reporting outcomes among patients with unresectable CRLM treated with SBRT; the study populations ranged from 11 to 67 patients.[30–34] Median OS ranged from 16.1 to 53 months. Only 1 study reported median PFS, which was 6.6 months (SD ±0.93),[32] whereas other studies reported a 1-year local control rate between 73% and 91.9%.[30,34] A final systematic review that pooled data from 18 studies was assessed.[35] Of 656 patients receiving SBRT for unresectable CRLM, Petrelli et al[35] reported a median OS of 31.5 months and a median PFS of 11.5 months. Three prospective single-arm analyses including between 20 and 60 patients in each study who received SBRT were also reviewed.[36–38] In these studies, median OS ranged from 16 to 34 months and median PFS from 10.8 to 12 months.

Overall, SBRT is well tolerated as it is a noninvasive modality with short treatment sessions typically lasting less than an hour each.[29] In the studies examined, the rate of grade ≥ 3 AEs ranged from 3% to 10%, with the most common complications including nausea (5%), gastrointestinal ulcers (5%), thrombocytopenia (2%), and transient transaminitis (2%).[31,33,38] Another possible disadvantage when considering this locoregional therapy is that tumor response can be limited by histologic subtype and prior use of chemotherapy, both of which have been linked to increased rates of local failure.[29]

In conclusion, SBRT may be an attractive option for patients with chemotherapy-refractory, unresectable CRLM in whom more invasive locoregional therapies that require a percutaneous approach are contraindicated. It is also an appealing option for patients who require the treatment of multiple hepatic tumors if an adequate liver volume can be spared from unintentional radiation spread. Unfortunately, due to a paucity of high-impact studies, interpretation of the clinical data is limited. For this reason, further research is warranted regarding the use of SBRT among patients with unresectable CRLM who are unable to receive more invasive liver-directed therapies.

Selective Internal Radiation Therapy With Yttrium 90 Embolization

Treatment with Y90 involves selectively injecting radioactive yttrium-90 microparticles via a catheter into the hepatic artery branch that feeds a tumor.[39,40] These microparticles then become permanently lodged in the tumor vasculature, consequently delivering high-dose beta radiation to the surrounding tissue to induce tumor necrosis.[38–41] The NCCN states that Y90 radioembolization can be considered in select patients with unresectable CRLM who have chemotherapy-resistant or refractory disease and predominant hepatic metastases.[6]

We examined 9 peer-reviewed studies that focused on the role of Y90 radioembolization in the treatment of unresectable CRLM (Table 3). This included 1 systematic review, 1 prospective and 3 retrospective cohort studies, 1 prospective case series, and 3 reports that

collectively discussed a total of 3 prospective randomized control studies. The papers were published between 2014 and 2019 and included between 52 and 1103 patients in each study.

SIRFLOX, FOXFIRE, and FOXFIRE-Global were all multicenter phase 3 randomized control trials showing that Y90 radioembolization in addition to FOLFOX-based chemotherapy does not improve OS or PFS when compared with chemotherapy alone as first-line treatment for unresectable CRLM.[42,43] A subsequent subgroup analysis of the SIRFLOX and FOXFIRE-Global trials by Gibbs et al[44] showed a 4.9-month increase in median OS (P=0.008) in only those patients with right-sided primary tumors.[44]

Failure of the aforementioned phase 3 trials to show definitive superiority of Y90 radioembolization as a first-line treatment has shifted focus away from this locoregional therapy as an option for patients with unresectable CRLM who have failed 1 or more lines of chemotherapy. While several single-arm studies have been published specifically on this topic, the patient populations across studies are markedly variable with respect to previous lines of chemotherapy, prior hepatic resection or ablation, and the presence of extrahepatic metastases. Patients in these studies were generally high-functioning, with 94% to 100% of patients having an ECOG status of 0 or 1 among single-arm studies reporting the statistic.[45–48] In studies regarding the use of salvage Y90 radioembolization for unresectable CRLM, median OS ranged from 7.6 to 11.6 months.[44–49] Only 1 study reported median PFS for salvage Y90 radioembolization, which was 3 months (95% CI, 2.8–3.1).[2] These outcomes are clearly inferior to those obtained with HAIP and SBRT, and thus we infer that Y90 radioembolization should be reserved for salvage therapy only in patients with unresectable CRLM.

Overall, Y90 radioembolization is safe and well tolerated. However, the delivery of Y90 microparticles to tissues other than the tumor can lead to complications.[40] Fortunately, the beta radiation is quite precise, penetrating on average only 2.5 mm from its source and thereby limiting its effects to the intended delivery site.[40] Serious complications can include gastrointestinal ulcers, radiation pneumonitis, and radioembolization-induced liver disease, which includes portal hypertension or damage to the biliary tree.[40] More common postprocedural complaints include nausea, abdominal pain, and generalized fatigue.[47] An analysis of three phase 3 trials reported that less than 6% of patients developed grade ≥ 3 AEs associated with Y90 radioembolization. Another analysis examining the use of Y90 radioembolization in patients who failed previous lines of chemotherapy reported that between 0% and 13% of participants developed grade ≥ 3 AEs.[2,45–48]

In conclusion, Y90 radioembolization is not recommended as a first-line treatment option for patients with unresectable CRLM. However, it is a potentially safe therapy in the salvage setting. While Y90 radioembolization is generally well tolerated, interpretation of the clinical data reported is limited due to the heterogeneous patient populations and lack of comparison groups. Nonetheless, in a patient population with few remaining treatment options, this therapy has the potential to improve OS (within the right-sided metastases population) with a relatively low incidence of serious AEs. Future areas of research may focus on studying Y90 radioembolization as a first-line therapy for unresectable CRLM in patients with right-sided primary tumors and conducting phase 3 trials comparing it

to other locoregional treatments or supportive care for patients with unresectable CRLM refractory to chemotherapy. Additionally, other uses of Y90 radioembolization reported in the literature deserve further large-scale scientific inquiry, including its use to downsize CRLM for resection and to induce contralateral liver hypertrophy.[50–51]

Conclusions

Locoregional liver-directed therapies are an attractive option for patients with unresectable CRLM. In general, these therapies are well tolerated and AE profiles are minimal. Unfortunately, the lack of large-scale, prospective phase 3 trials complicates the interpretation of available data. HAIP is considered a safe and effective strategy to control disease progression or expand resectability. However, providers must weigh these potential benefits with risks of toxicity and the need for referral to institutions with HAIP infrastructure and expertise. SBRT may be an attractive option for patients with unresectable CRLM for whom locoregional therapies that require a percutaneous approach are contraindicated. Lastly, although Y90 radioembolization was not shown to be effective as first-line treatment for patients with unresectable CRLM, it has shown some potential in patients with chemotherapy-refractory disease and in those with right-sided primary tumors. Ultimately, for patients with unresectable CRLM, clinical decisions require multidisciplinary discussions that carefully consider the patient's disease process, comorbidities, and functional status in addition to the available clinical expertise at the treating facility.

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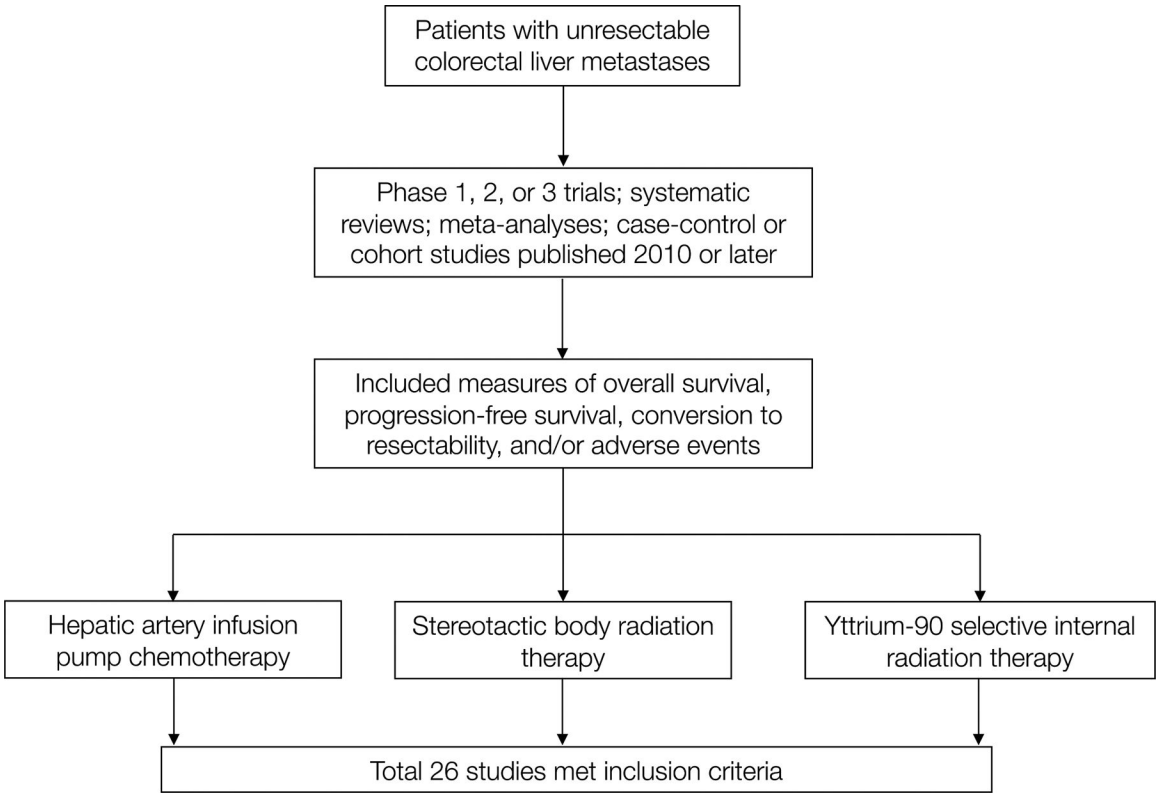

Figure.
Schema of Literature Review Process

Table 1.

Hepatic Artery Infusion Pump Chemotherapy for Treatment of Unresectable CRLM

Study	Design	Treatment	N	Prior treatments	Median OS, months (95% CI)	Median PFS, months (95% CI)	Conversion to resection/ ablation	Adverse events
D'Angelica et al (2015)[17]	Prospective, phase 2	HAIP + chemotherapy	49	Chemotherapy	38 (28 to not reached)	13 (7–16)	47%	41% grade ≥3
Zacharias et al (2015)[24]	Meta-analysis	HAIP	3000	None or chemotherapy	First-line: 21.4 (19.4–23.4) Second-line or later: 13.2 (12.2–14.2)	NR	15%	55% grade ≥3
Lévi et al (2016)[18]	Prospective, phase 2	HAIP + chemotherapy	64	Chemotherapy	25.5 (18.8–32.1)	9.3 (7.8–10.9)	29.7%	77% grade ≥3
Dhir et al (2017)[20]	Retrospective, single-center	HAIP + chemotherapy vs chemotherapy alone	86	Chemotherapy	32.8 vs 15.3 (0.21–0.72)	NR	No group difference	Not reported
Lim et al (2017)[21]	Retrospective, multicenter	HAIP + chemotherapy: first/second- vs third/ fourth-line	61	Chemotherapy	13.5 vs 8.3 (0.4–1.1)	9 vs 6 (0.2–0.7)	16.4%	16% grade ≥3
Pak et al (2018)[19]	Prospective, phase 2	HAIP + chemotherapy	64	Chemotherapy	38 (28.8–53.7)	13 (9–16)	52%	≥20% grade ≥3
Boilève et al (2020)[22]	Retrospective, single-center	HAIP + chemotherapy	89	Chemotherapy	20 (15–24)	9 (8–11)	27%	79% grade ≥3
Muaddi et al (2021)[23]	Retrospective, multicenter	HAIP + chemotherapy	154	Chemotherapy	19.5 (IQR, 10.5–31)	3-year PFS, 4.1%*	7.8%	8.4% biliary sclerosis 4.6% Clavien-Dindo ≥3b during hospitalization

CRLM, colorectal liver-only or liver-dominant metastases; HAIP, hepatic artery infusion pump chemotherapy; OS, overall survival; PFS, progression-free survival; IQR, interquartile range; NR, not reported.

*95% CI and/or *P* value not reported

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Table 2.

Stereotactic Body Radiation Therapy for Treatment of Unresectable CRLM

Study	Design	Treatment	N	Prior treatments	Median OS (±SD[#]), months (95% CI)	Median PFS, months (95% CI)	Adverse events
van der Pool et al (2010)[37]	Prospective, single-center cohort	SBRT	20	Any	34[*]	11[*]	2 cases ≥ grade 3
Kress et al (2012)[30]	Retrospective, single-center cohort	SBRT	11	Any	16.1[*]	1-year LC: 72%	1 case ≥ grade 3
Scorsetti et al (2015)[36]	Prospective, phase 2	SBRT	42	Any	29.0 ±3.7 (21.8–36.2)	12 ±4.2 (3.8–20.2)	None ≥ grade 3
McPartlin et al (2017)[38]	Prospective, phase 1 and 2	SBRT	60	Any	16.0 (11.9–20.5)	10.8[*]	1 case ≥ grade 3
Doi et al (2017)[31]	Retrospective, single-center cohort	SBRT	24	Any	45[*]	NR	Not reported
Petrelli et al (2018)[35]	Systematic review	SBRT	656	Any	31.5[*]	11.5[*]	8.7% ≥ grade 3
Vernaleone et al (2019)[32]	Retrospective, single-center cohort	SBRT	38	Any	20.1 (±2.0)	6.6 (±0.9)	None ≥ grade 3
Flamerique et al (2020)[33]	Retrospective, single-center cohort	SBRT	22	Any	24[*]	NR	1 case ≥ grade 3
Py et al (2021)[34]	Retrospective, single-center cohort	SBRT	67	Any	53 (38–66)	1-year LC: 81.9% (70.2%-89.2%) 5-year LC: 13.1% (6.0%-23.0%)	3% ≥ grade 3

CRLM, colorectal liver-only or liver-dominant metastases; SBRT, stereotactic body radiation therapy; OS, overall survival; PFS, progression-free survival; LC, local control; NR, not reported.

[*]95% CI and/or *P* value not reported.

[#]Where available.

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Table 3.

Yttrium-90 Selective Internal Radiation Therapy for Treatment of Unresectable CRLM

Study	Design	Treatment	N	Prior treatments	Median OS, months (95% CI)	Median PFS, months	Adverse events
Saxena et al (2014)[49]	Systematic review	Y90	979 (20 studies)	Chemo ± hepatic intervention	12 (range, 8.3–36.0)	9 (range, 6–16)	Not reported
Saxena et al (2015)[45]	Retrospective, single-center cohort	Y90	302	Chemo ± hepatic intervention	10.5*	NR	None ≥ grade 3
Hickey et al (2015)[46]	Retrospective, multicenter cohort	Y90	531	Any	10.6 (8.8–12.4)	NR	13% ≥ grade 3
Abbott et al (2015)[47]	Retrospective, single-center cohort	Y90	68	Chemo ± hepatic intervention	11.6*	NR	7.3% ≥ grade 3
Golfieri et al (2015)[48]	Prospective, single-center case series	Y90	52	Chemo ± hepatic intervention	11.0 (8.0–14.0)	NR	6% ≥ grade 3
Van Hazel et al (2016)[43]	Prospective, multicenter RCT	Chemo vs chemo + Y90	530	None	NR	10.2 (chemo) vs 10.7 (chemo + Y90); *P*=0.4	74.4% (chemo) vs 85.4% (chemo + Y90) grade ≥ 3; *P*=0.5
Wasan et al (2017)[42]	3 multicenter RCTs (combined analysis)	Chemo vs chemo + Y90	1103	None	23.3 (chemo) vs 22.6 (chemo + Y90); *P*=0.6	10.3 (chemo) vs 11.0 (chemo + Y90); *P*=0.1	Y90 group greater odds of grade ≥ 3
Gibbs et al (2018)[44]	2 multicenter RCTs (combined analysis)	Chemo vs chemo + Y90, stratified by primary tumor side	739	None	RSP: 22.0 (chemo + Y90) vs 17.1 (chemo); *P*=0.01 LSP: 24.6 (chemo + Y90) vs 26.6 (chemo); *P*=0.3	RSP: 10.8 (chemo + Y90) vs 8.7 (chemo); *P*=0.06 LSP: 11.4 (chemo + Y90) vs 10.8 (chemo); *P*=0.4	RSP: No difference in grade ≥ 3 LSP: Y90 group greater odds of grade ≥ 3
White et al (2019)[2]	Prospective, multicenter cohort	None	399	Chemo ± hepatic intervention	7.6 (6.9–8.3)	3.0 (2.8–3.1)	143 (36%) experienced an AE; 8% were ≥ grade 3

CRLM, colorectal liver-only or liver-dominant metastases; RCT, randomized controlled trial; Y90, yttrium-90 selective internal radiation therapy; chemo, chemotherapy; OS, overall survival; PFS, progression-free survival; RSP, right-sided primary tumor; LSP, left-sided primary tumor; NR, not reported; AE, adverse event.

*95% CI and/or *P* value not reported.