Original Study

Consideration of Metastasis-Directed Therapy for Patients With Metastatic Colorectal Cancer: Expert Survey and Systematic Review

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Abstract

The role of metastasis-directed therapy (MDT) in patients with metastatic colorectal cancer (mCRC) with disease involving more than just the liver remains controversial and is marked by a paucity of prospective evidence. A survey of multidisciplinary experts in the management of mCRC identified wide variability based on provider specialty in the distribution and extent of metastatic disease for which MDT would be recommended.

Background: A survey of medical oncologists (MOs), radiation oncologists (ROs), and surgical oncologists (SOs) who are experts in the management of patients with metastatic colorectal cancer (mCRC) was conducted to identify factors used to consider metastasis-directed therapy (MDT). **Materials and Methods:** An online survey to assess clinical factors when weighing MDT in patients with mCRC was developed based on systematic review of the literature and integrated with clinical vignettes. Supporting evidence from the systematic review was included to aid in answering questions. **Results:** Among 75 experts on mCRC invited, 47 (response rate 62.7%) chose to participate including 16 MOs, 16 ROs, and 15 SOs. Most experts would not consider MDT in patients with 3 lesions in both the liver and lung regardless of distribution or timing of metastatic disease diagnosis (6 vs. 36 months after definitive treatment). Similarly, for patients with retroperitoneal lymph node and lung and liver involvement, most experts would not offer MDT regardless of timing of metastatic disease diagnosis. In general, SOs were willing to consider MDT in patients with more advanced disease, ROs were more willing to offer treatment regardless of metastatic site location, and MOs were the least likely to consider MDT. **Conclusions:** Among experts caring for patients with mCRC, significant variation was noted among MOs, ROs, and SOs in the distribution and volume of metastatic disease for which MDT would be considered. This variability highlights differing opinions on management of these patients and underscores the need for well-designed prospective randomized trials to characterize the risks and potential benefits of MDT.

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Introduction

Colorectal cancer (CRC) is a leading cause of cancer-related death with over 1 million deaths worldwide in 2019.[1] Nearly

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25% of patients present with metastatic disease at diagnosis, while another 20% will develop metastatic disease at some point in their disease course.[2] Over the last several decades, utilization of biomarker testing and advances in systemic therapy have resulted in dramatic improvements in survival for patients with metastatic CRC (mCRC).[3] In addition, increased utilization of surgical resection of liver metastasis has been associated with improvements in survival over this same time period.[3,4] Resection of metastases for individuals with liver-limited disease may provide long disease-free intervals with the potential for cure in some patients. Data to support resection of liver-confined disease is primarily limited to retrospective series with minimal prospective evidence available.[5-8] Similarly, evidence to support resection of lung-confined disease is limited to retrospective series with no prospective data demonstrating a survival benefit for surgical resection in this group of patients.[9-11] Several small prospective series have shown feasibility and favorable preliminary outcomes following metastasectomy for patients with mCRC characterized by both intra- and extrahepatic disease.[12-14] More recent data involving multiple tumor histologies suggest that the addition of stereotactic ablative radiotherapy (SABR) to standard of care systemic therapy improves progression-free and overall survival (OS) over treatment with standard of care systemic therapy alone.[15,16]

Oligometastatic disease is a favorable prognostic factor in patients with mCRC.[17] There is debate, however, about the definition of what constitutes oligometastatic disease relative to different malignancies, including CRC. In turn, broad consensus recommendations have been published to consolidate the definition of oligometastatic disease.[18-20] Despite these attempts, recommendations for metastasis-directed therapy (MDT) in patients with mCRC remains predominantly influenced by provider or institutional preference. To date, there remains a lack of prospective data to guide treatment decision-making in patients with mCRC with a disease distribution outside of what would traditionally be considered for surgical resection. Furthermore, advances in imaging and treatment techniques including surgical resection, ablative radiation therapy, and image-guided thermal ablation have expanded the criteria for which MDT may be considered, making consensus recommendations more challenging. Given the paucity of prospective data proving clear clinical benefit of MDT with potential treatment-related toxicity, there is a need to establish guidelines on which patients should be considered for such an approach. The purpose of the current study was to survey experts who care for patients with CRC on the indications for MDT among patients with mCRC and to assess whether management patterns differ among medical oncologists (MO), radiation oncologists (RO), and surgical oncologists (SO).

Materials and Methods

This study was determined to be IRB exempt. Using the Population, Intervention, Comparator, and Outcome (PICO) framework, the evidence regarding treatment outcomes was assessed using Cochrane methodology.[21] To yield a comprehensive set of relevant articles, peer-reviewed journals indexed in Ovid Medline database were searched covering the timeframe from 1/1/2000 and 2/17/2021. Eligible studies included prospective phase 2 and 3 trials, meta-analyses, and retrospective analyses (Full Search Strategy in Supplementary Material - Appendix A). Two authors (EM & CA) independently screened the comprehensive list of 784 articles, and one assessed the full-text articles to determine the final studies to be included (Table 1). Discrepancies between the reviewers were resolved by consensus. A total of 131 articles were identified using the search strategy that met all inclusion criteria. One additional study[22] was included through backward citation searching as it significantly contributed to the literature. Forward citation searching was performed on the selected documents to determine whether any essential eligible articles published no later than 2/17/21 were inaccessible from the search strategy. One study was identified,[12] resulting in 133 total studies (Supplementary Material - Appendix B). Ultimately, 79 references were used to formulate the questions for the survey based on topics as highlighted in Table 1.[7,8,10,11,13,14,16,22-93] Confirmation of inclusion of all appropriate steps is noted via the PRISMA-S checklist (Supplementary Material - Appendix C).

The survey consisted of 18 questions (Supplementary Material – Appendix D) focused on use of MDT in patients with mCRC. Respondents were asked to enter their names at the start of the survey, but the results were anonymized for analysis. Questions were included to identify practice type and specialty. Additional questions focused on potential reasons for offering MDT, anticipated patient outcomes when considering use of MDT, use of SABR in patients with mCRC, and additional clinical factors that are considered when deciding on treatment. Multiple clinical vignettes were provided inquiring about extent of disease and asking the respondent to determine in which situations they would offer MDT. For all clinical questions, supporting evidence from the systematic review was provided either as pop-up hover over text or following the question stem. The final questions in the survey were free text inquiring about any absolute contraindications to MDT or any additional comments. Of note, all questions were reviewed by a separate expert panel (JC, TP, HM, GC) prior to the final release of the survey.

Selected specialists in MO, RO, and SO who are experts in the care of patients with mCRC were invited to complete the survey by email with a link to the Qualtrics survey. The experts were identified through their participation in one of the National Cancer Institute (NCI) Task Forces or National Clinical Trials Network (NCTN) Cooperative Groups focused on CRC. Survey responses were collected from June 2022 until December 2022.

Survey responses were summarized using descriptive statistics. Comparison of survey responses between specialty groups were summarized using Pearson's chi-squared test, Fisher's exact test, and the Kruskal-Wallis rank sum test. All statistical analysis was conducted using R version 4.2.2.

Results

A total of 75 surveys were sent to 21 MOs, 26 ROs, and 28 SOs who are experts in the management of patients with CRC. The survey response rate was 62.7% with participation by 16 MOs, 16 ROs, and 15 SOs. Of the 47 respondents, 42 completed all questions included in the survey. All respondents practice in an Academic/Research Program, which included NCI-designated comprehensive cancer centers.

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Table 1 Summary of Supportive Evidence From Systematic Review Included in the Survey

Question Topic	Supporting Evidence Provided
Use of stereotactic today radiation therapy as a local therapy for patients with metastatic colorectal cancer.	24-26,29-34,37-43
For liver-only disease, treatment requires combination of surgery and radiofrequency (RFA) or microwave ablation (MWA); patient not a candidate for surgery, but RFA/MWA can treat all disease.	7,8,48,52,55,56,60,66,67,70
Treatment of patients with multiple organ involvement addressable with local therapy.	11,57,71
Treatment of patients with addressable lung-confined disease.	11
Treatment of patients with liver or lung disease considered for resection, but patient not able to tolerate perioperative chemotherapy.	47,59,62,63
Treatment of patients with bulky disease.	54
Treatment of patients with synchronous (≤6 months from initial diagnosis) or metachronous (≥6 months from initial diagnosis) metastatic disease.	10,80,84
Treatment of patients with a favorable response to systemic therapy.	75,76,90
Treatment of patients with a right sided primary tumor location.	23,74,81,83,93
Treatment of patients with KRAS tumor mutation.	73,86,91
Treatment of patients with BRAF tumor mutation.	73,86,91
Treatment of patients age ≥70 years old.	23,79,87,92
Treatment of patients based on distribution of disease (liver, lung, retroperitoneal lymph node involvement) and either 6 or 36 months from completion of curative treatment to metastatic diagnosis.	10,13,14,30,72,82
Limit on number of liver lesions considered for treatment in liver-only disease, also accounting for synchronous versus metachronous disease diagnosis.	49,77,84,89
Limit on number of lung lesions considered for treatment in lung-only disease, also accounting for synchronous versus metachronous disease diagnosis.	10,71,80,88
Limit on number of lesions regardless of organ location except brain or peritoneum	16,25,85
Organ involvement where local therapy should no longer be considered.	10,13,14,30,72,78,82

Rationale for Metastasis-Directed Therapy

The most important reasons for considering MDT in patients with mCRC (Q4) were prolonging OS (60% ranked first), prolonging disease-free survival (DFS) (49% ranked second) and providing a systemic therapy break (40% ranked third). Whereas SOs were more likely to rank improving OS as the most important reason for MDT (80% SO vs. 56% MO and 44% RO, $P = .081$), MOs were more likely to rank a systemic therapy break as the first or second most important reason for MDT (56% MO vs. 31% RO and 13% SO, $P = .13$). A summary of responses are shown in Figure 1.

Anticipated Outcomes Following Metastasis-Directed Therapy

Respondents were asked to provide what 5-year metric is reasonable to warrant consideration of MDT (Q5). Relative to 5-year DFS rate among all specialties, the median was 30% (IQR: 20, 30%), which was similar among providers of different specialties ($P = .9$). For OS, the median response was 30% (IQR: 20, 45%), which was also similar among specialties ($P = .8$). Participants were also asked to provide their opinion on the minimum time of stable disease following treatment to warrant MDT (Q6). The median time was 6 months (IQR: 6, 8 months) for all specialties. SO (43%) responded that time periods of 12 months or longer were more appropriate compared with RO (6%) or MO (19%) who reported shorter intervals ($P = .056$).

Utilization of Stereotactic Ablative Radiotherapy

The utilization of SABR as a primary therapy for patients with mCRC was also queried (Q7). Overall, SABR was felt to be most appropriate when (1) a patient and/or metastasis was not optimal for surgery (84%) (100% MO vs. 85% SO vs. 69% RO, $P = .041$) or (2) in combination with resection to extend indications for treatment of all sites of disease (67%) (Supplemental Figure 1). Using SABR in combination with resection to extend indications for treatment of all sites of disease was supported across all specialties.

Factors in Decision Making for Delivery of Metastasis-Directed Therapy

Multiple survey questions inquired about factors considered when deciding on MDT for patients with mCRC. When considering MDT for patients with liver-only disease requiring a combination of surgery and radiofrequency (RFA) or microwave (MWA) ablation (Q9), respondents overall either generally favored (49%) or strongly favored (44%) treatment (Figure 2). SOs strongly favored treatment (77%) compared with both ROs (44%) and MOs (19%) ($P = .001$). When considering treatment of a patient with liver-only disease who was not a candidate for resection but could be treated with RFA/MWA, most respondents generally favored (53%) (46% SO vs. 62% RO vs. 50% MO, $P = .8$) or strongly favored (40%) (38% SO vs. 38% RO vs. 44% MO) treatment.

Respondents were asked to weigh multiple other factors when deciding on MDT (Q10) with results summarized in Figure 3. In brief, for patients with treatable lung-confined metastasis, most

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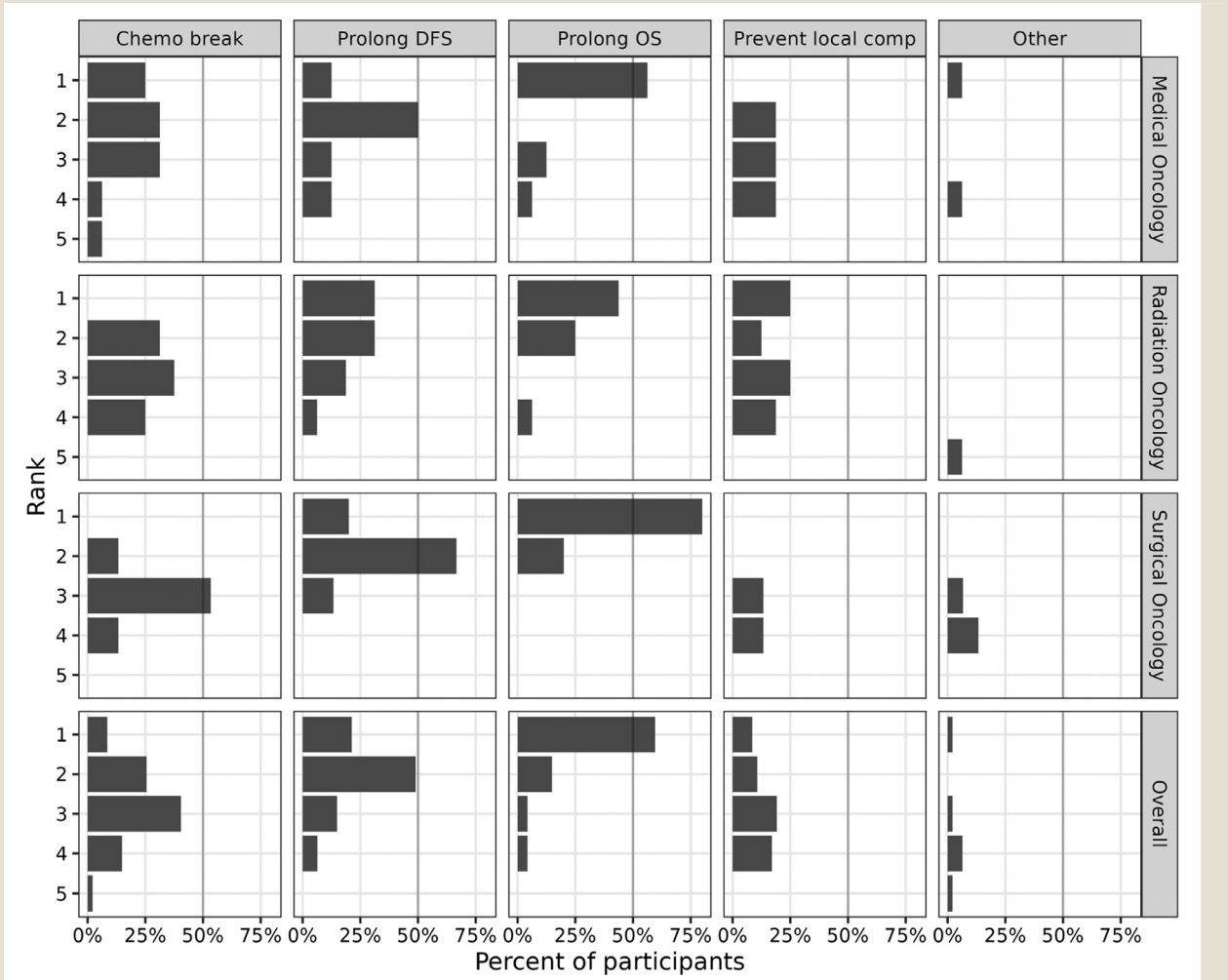
Figure 1 Reasons for offering local therapy (resection or thermal ablation or stereotactic ablative radiation therapy) for patients with metastatic colorectal cancer with associated rank by specialist and among all respondents. Chemo break - Provide systemic therapy break; Prolong DFS - prolong disease-free survival; Prolong OS - prolong overall survival; Prevent local comp - prevent local complications; Other.



generally favored (58%) or strongly favored (36%) treatment which was consistent across specialties. Inability to tolerate perioperative chemotherapy for patients with liver or lung metastasis considered for resection did not seem to deter most respondents from offering MDT with 56% either strongly or generally favoring treatment. For patients with bulky disease, most respondents either were neutral or generally or strongly against treatment (73%) with SOs more willing to offer treatment in these scenarios (39% generally or strongly favoring treatment) compared to 38% of ROs generally (0% strongly) favoring treatment and 0% of MOs, $P < .001$. The timing of metastatic disease diagnosis did seem to impact recommendation for treatment. For patients with metachronous (>6 months from initial diagnosis) metastatic disease there was a strong preference for generally or strongly favoring treatment (84%). However, for patients with synchronous (≤6 months from initial diagnosis) metastatic disease, treatment recommendations were split with nearly an equal distribution between generally favoring treatment (31%), neutral regarding treatment (33%), and generally against treatment (24%) among all respondents. Right sided primary tumor location and presence of a KRAS mutation dampened enthusiasm for treatment overall. Nearly half (49%) of respondents were generally or strongly against treatment for patients with BRAF mutations which was similar across specialties. Finally, when evaluating patients ≥70 years of age, most respondents felt neutral regarding treatment (53%) with the rest generally or strongly favoring treatment (54% SO vs. 44% RO vs. 38% MO, $P = .6$).

Distribution of Disease

To better understand how the distribution of disease impacts the decision to offer MDT to patients, there were two clinical vignettes which included a patient with colon cancer who was treated definitively and now presented with metastatic disease with an increas-

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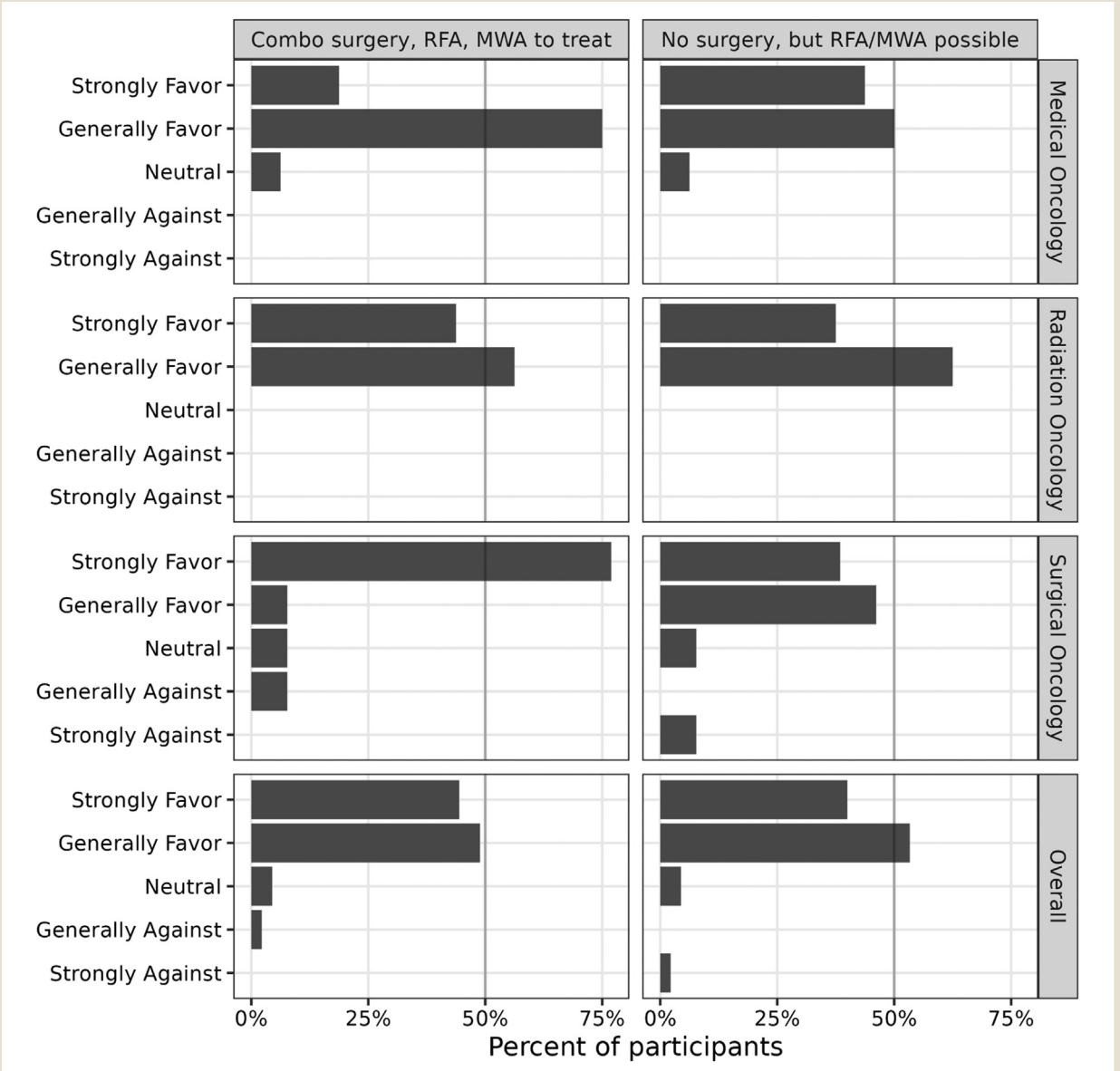
Figure 2 Factors to consider when evaluating a patient with metastatic colorectal cancer confined to the liver for treatment by specialist and among all respondents. Combo surgery, RFA, MWA to treat – treatment would require combination therapy with surgery, radiofrequency ablation or microwave ablation to treat. No surgery, but RFA/MWA possible – patient is not a candidate for liver resection, but could be treated with radiofrequency ablation or microwave ablation.



ingly extensive distribution of disease (Q11, Q12) (Figure 4). The respondents were asked to select all disease distributions where they would routinely offer MDT. In the first question (Q11), 6 months had passed between completion of adjuvant chemotherapy and diagnosis of metastatic disease (upper time range for synchronous presentation). Overall, respondents would offer MDT in patients with 3 liver lesions (100% unilobar, 88% bilobar) or in patients with 3 liver lesions (88% unilobar, 81% bilobar) and a single lung metastasis. Nearly 75% of respondents would also offer MDT for patients with a retroperitoneal lymph node (RP LN), but no other areas of disease. Over 50% of respondents would offer treatment in a patient with 3 lesions in the liver with a unilobar distribution and a RP LN (55%), but only 45% would offer treatment in a patient with 3 bilobar liver metastases and a RP LN. Less than 25% of respondents would offer MDT for patients with more extensive disease.

In general, SOs were willing to offer treatment in patients with more extensive disease than the other specialties including in patients with liver-only disease. For patients with 3 liver lesions with a bilobar distribution and no other lesions, 100% of SOs and ROs would offer treatment compared with only 67% of MOs ($P = .004$). A similar difference was observed for patients with liver and lung disease. For patients with 3 liver lesions (unilobar or bilobar) and

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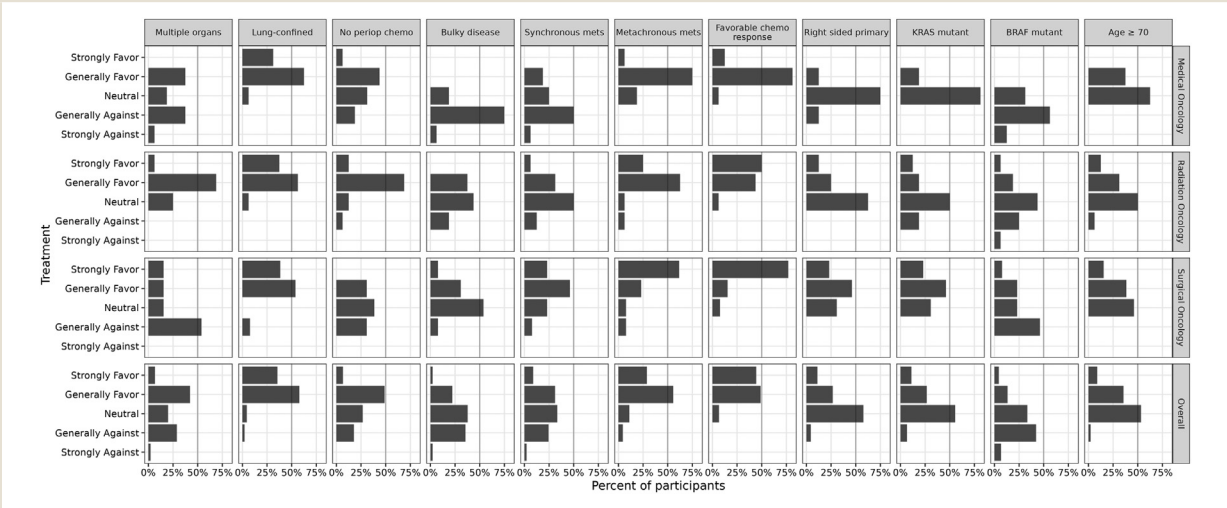
Figure 3 Factors to consider when evaluating a patient with metastatic colorectal cancer to any organ for resection or ablation (thermal ablation or stereotactic ablative radiation therapy) by specialist and among all respondents. Multiple organs – multiple organ involvement that is addressable with local therapy; Lung-confined – presence of treatable lung-confined metastasis; No periop chemo – for patients with liver or lung disease considered for resection, patient not able to tolerate peri-operative chemotherapy; Bulky disease – patient with "bulky" disease; Synchronous mets – synchronous (≤6 months from initial diagnosis) metastatic disease; Metachronous mets – metachronous (≥6 months from initial diagnosis) metastatic disease; Favorable chemo response – favorable response to systemic therapy; Right sided primary – right sided primary tumor location; KRAS mutant; BRAF mutant; Age ≥70 years old.



a single lung metastasis, 100% of SOs and ROs would offer treatment, but only 67% (unilobar), $P = .004$ or 47% (bilobar), $P < .001$ of MOs, respectively, would offer MDT. Similarly for 3 patient scenarios with more advanced disease (3 liver lesions with bilobar distribution and 3 lung metastases with unilateral distribution; 3 liver lesions with unilobar distribution and 3 lung metastases with bilateral distribution; 3 liver lesions with bilobar distribution and 3 lung metastases with bilateral distribution), no MOs would consider treatment compared to 25% and 55% ($P = .004$), 19% and 45% ($P = .010$), and 25% and 45% ($P = .015$) of ROs and SOs, respectively. Only 53% of MOs would consider MDT for a patient with a RP LN and no other lesions compared with 100% of ROs and 64% of SOs ($P = .004$). No MOs would offer treatment in patients with a disease distribution including the liver and lung and RP LNs, compared to a minority of ROs and SOs who would consider MDT.

In the second question regarding disease distribution (Q12), the same scenarios were presented, but with 36 months (metachronous presentation) between completing definitive treatment and the metastatic diagnosis as summarized in Figure 4. Overall, respondents were more likely to offer MDT for patients with more advanced disease. Over 50% would offer MDT in patients with 3 liver lesions (100% unilobar, 98% bilobar), 3 liver lesions (98% unilobar, 86% bilobar) and a single lung metastasis, a RP LN (81%), 3 liver lesions with unilobar distribution and a RP LN (71%), and 3 liver lesions with bilobar distribution and a RP LN (57%). Nearly 50% would offer treatment to patients with 3 liver lesions (48% unilobar, 45% bilobar) and 3 lung metastases with a unilateral distribution. Nearly 1/3 would still offer treatment to patients with 3 liver lesions with a unilobar (33%) distribution or bilobar (29%) distribution and 3 lung metastases with bilateral distribution. Over 1/3 (38%) would offer treatment in a patient with 3 liver lesions with a unilobar distribution with a RP LN and a single lung metastasis.

As before, SOs were more often willing to offer MDT in patients with more advanced disease compared to the other specialties, although in this scenario the differences in managing liver-only disease were not observed. For patients with 3 liver lesions with a unilobar distribution and a single lung metastasis, the specialties agreed with offering MDT. However, with more advanced disease, MOs were less likely to offer MDT. For patients with 3 liver lesions with a bilobar distribution and a single lung metastasis, 100% of SOs and ROs would offer treatment, but only 60%, $P = .001$ of MOs would consider MDT. An increasing number of lung metastases seemed to dampen enthusiasm for MDT. For patients with 3 liver lesions with a unilobar distribution and 3 lung metastases with a unilateral distribution, 64% of SOs, 50% of ROs, and 33% of MOs would offer MDT ($P = .3$). MOs were also less likely to offer MDT in patients with bilateral lung metastases. For patients with 3 liver metastases in a bilobar distribution and 3 lung metastases with a bilateral distribution, 0% of MOs compared to 38% of ROs and 55% of SOs would offer MDT, $P = .003$. The majority of providers would offer MDT in patients with an isolated RP LN, 73% of SOs and MOs, and 94% of ROs, ($P = .3$). However, enthusiasm waned for patients with a RP LN and other areas of disease. For patients with 3 liver lesions with a bilobar distribution and a RP LN, 73% of SOs and 81% of ROs would consider MDT compared to 20% of MOs, $P = .001$. MOs (13%) were willing to consider MDT in patients with 3 liver lesions with a unilobar distribution and a RP LN and a single lung metastasis, but not in patients with more

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Figure 4 Disease distribution in a patient who presented with (A) metastatic disease 6 months following definitive treatment (left column) or (B) metastatic disease 36 months following definitive treatment where metastasis-directed therapy would be considered by specialist and among all respondents (right column). Liver – 3 uni – 3 liver lesions in a unilobar distribution; Liver – 3 bi – 3 liver lesions in a bilobar distribution; Lung – single – single lung metastasis; Lung – 3 uni – 3 lung metastases with a unilateral distribution; Lung – 3 bi – 3 lung metastases with a bilateral distribution; RP LN – retroperitoneal lymph node.

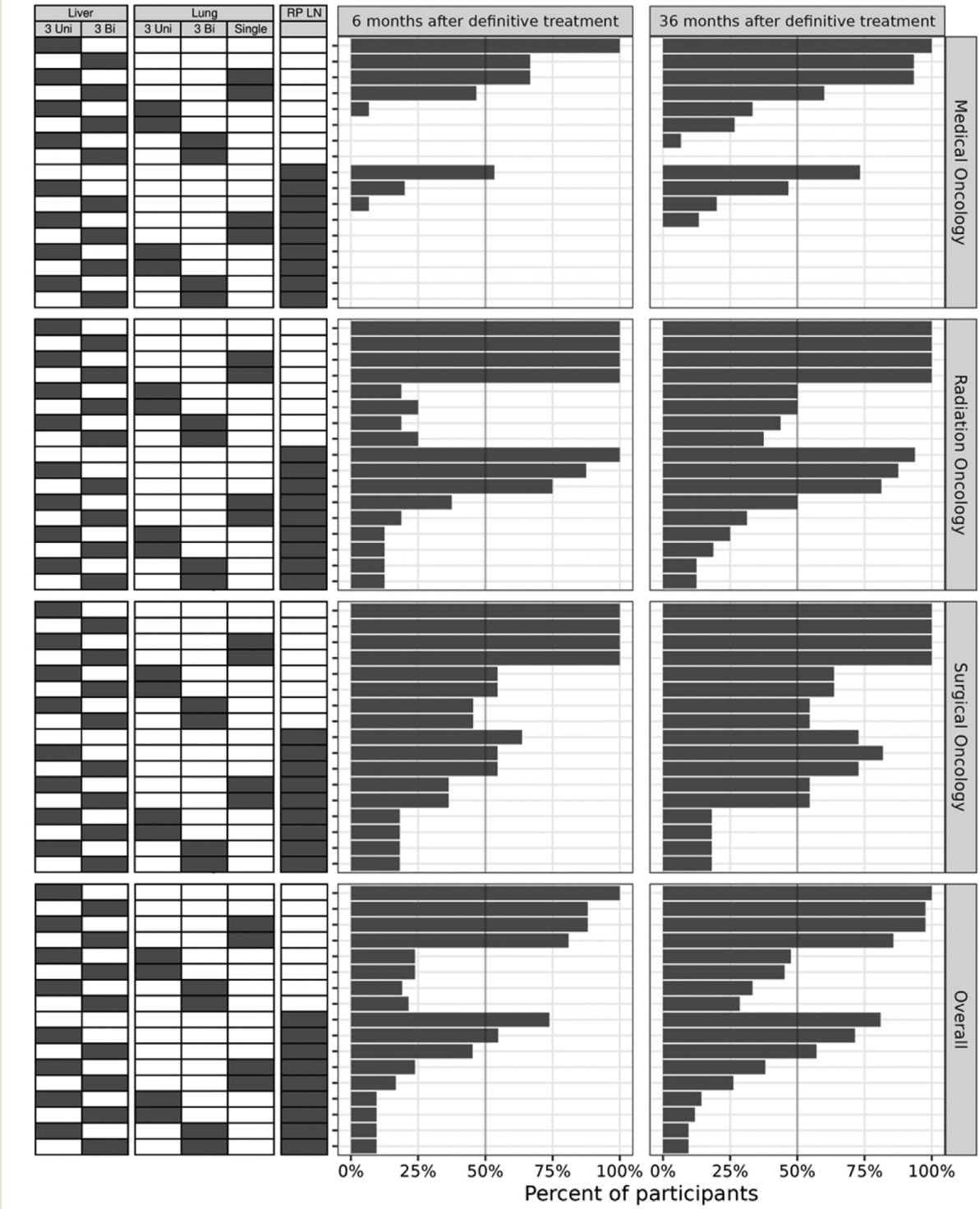

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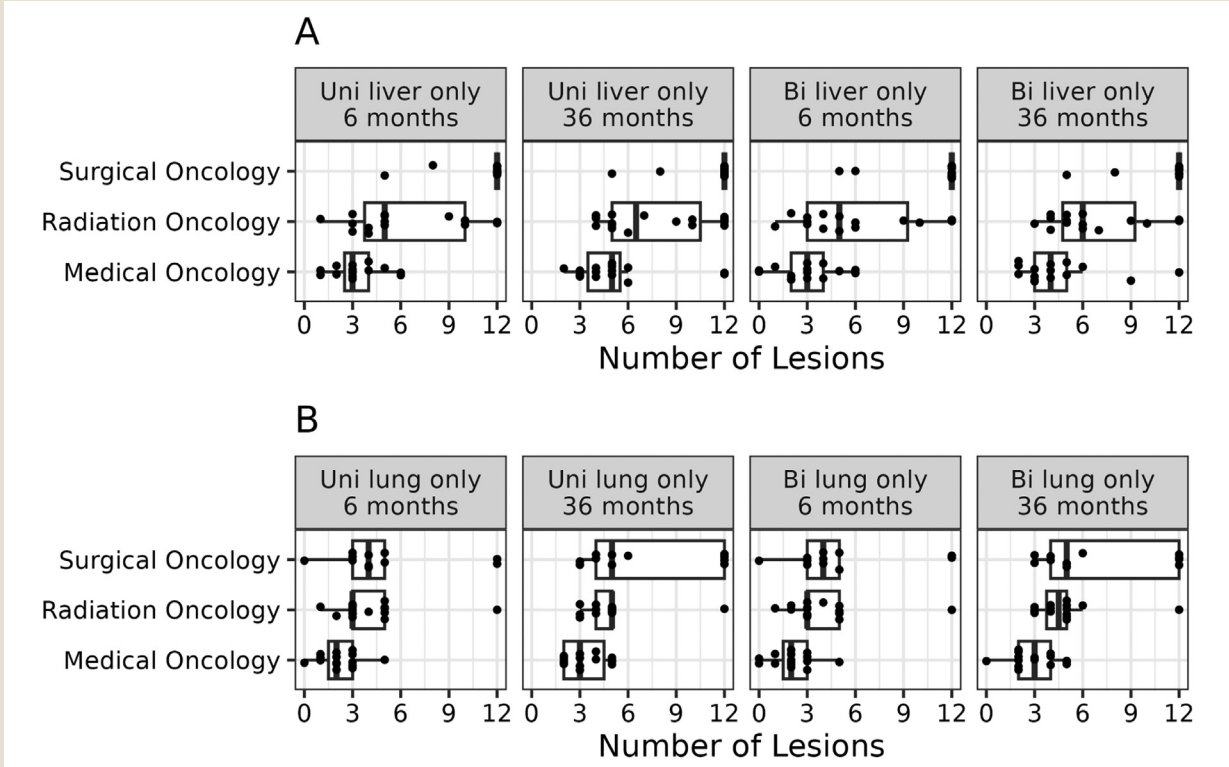
Figure 5 (A) Number of lesions in the liver that would be considered for resection/ablation based on lobar involvement and time from completion of curative therapy to metastatic disease diagnosis. (B) Number of lesions in the lung that would be considered for resection/ablation based on laterality and time from completion of curative therapy to metastatic disease diagnosis. Uni liver only, 6 months – Unilobar liver distribution 6 months to metastatic diagnosis; Uni liver only 36 months - Unilobar liver distribution 36 months to metastatic diagnosis; Bi liver only, 6 months - Bilobar liver distribution 6 months to metastatic diagnosis; Bi liver only, 36 months - Bilobar liver distribution 36 months to metastatic diagnosis. For all cases in (A), patient had liver-only disease. Uni lung only, 6 months – Unilateral lung distribution 6 months to metastatic diagnosis; Uni lung only 36 months – Unilateral lung distribution 36 months to metastatic diagnosis; Bi lung only, 6 months – Bilateral lung distribution 6 months to metastatic diagnosis; Bi lung only, 36 months – Bilateral lung distribution 36 months to metastatic diagnosis. For all cases in (B), patient had lung-only disease.



advanced disease including a similar distribution but bilobar liver metastases or 3 lung metastases.

Number of Lesions

To better understand how the number of metastases in the lung or liver impacts the decision to offer MDT to patients, there were two clinical vignettes which included a patient with colon cancer treated definitively but now with metastatic disease (Q13, Q14). The patient had completed 4-6 months of systemic therapy with stable disease or partial response on interval imaging. The respondents were asked to select an upper limit (scale from 0-12) on the approximate number of lesions which they would resect or ablate if safe and feasible. For liver only disease, there were 4 scenarios based on distribution (unilobar vs. bilobar) and timing from completion of curative intent therapy to metastatic diagnosis (6 or 36 months). In each scenario, SOs were at the upper end of the scale, MOs were at the lower end, and ROs were in the middle as shown in Figure 5A. For unilobar and 6 months to metastatic diagnosis, median (IQR): MO 3 (3, 4), RO 5 (4, 10), SO 12 (12, 12), $P < .001$. For unilobar and 36 months to metastatic diagnosis: MO 5 (4, 6), RO 7 (5, 11), SO 12 (12-12), $P < 0001$. For bilobar and 6 months to metastatic diagnosis, median (IQR): MO 3 (2, 4), RO 5 (3, 9), SO 12 (12, 12), $P < .001$. For bilobar and 36 months to metastatic diagnosis, median (IQR): MO 4 (3, 5), RO 6 (5, 9), SO 12 (12, 12), $P < .001$.

For lung metastases, similar scenarios were presented based on distribution (unilateral vs. bilateral) and timing from completion of curative intent therapy to metastatic diagnosis (6 months or 36 months) with the results shown in Figure 5B. Compared with liver only disease, the responses for lung disease were more similar, although SOs seemed to consider a higher number of lung lesions for resection. For unilateral and 6 months to metastatic diagnosis, median (IQR): MO 2 (2, 3), RO 3 (3, 5), SO 4 (3, 5), $P = .003$. For unilateral and 36 months to metastatic diagnosis: MO 3 (2, 5), RO 5 (4, 5), SO 5 (4, 12), $P = .005$. For bilateral and 6 months to metastatic diagnosis: MO 2 (2, 3), RO 3 (3, 5), SO 4 (3, 5), $P =$

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.003. For bilateral and 36 months to metastatic diagnosis: MO 3 (2, 4), RO 5 (4, 5), SO 5 (4, 12), $P = .003$.

The respondents were also asked to provide a limit on the number of lesions where they would no longer consider surgery or ablative therapy assuming that it is safe and feasible (Q15). In assessing the various specialties, 40% of MOs and 63% of ROs had an upper limit compared with 0% of SOs, $P = .004$. The median number of lesions for this upper limit was 5 for both MO (IQR 3, 5) and RO (IQR 5, 5).

Specific Organ Involvement

To assess the influence of organ site on provider decision making when considering MDT, respondents were asked to select from a list if metastatic disease to a particular organ would prevent consideration of MDT assuming that it was feasible and safe (Q16). Overall, 52% felt that involvement of any single organ was not a contraindication to MDT, with a higher proportion of ROs (75%) compared to MOs (47%) and SOs (27%), $P = .044$ as shown in Figure 6. When assessing individual organs and responses of individual specialties, a higher proportion of SOs felt that extra-abdominal lymph nodes, bone, and brain metastases were organs where MDT should not be considered compared to ROs and MOs.

Absolute Contraindications to Metastasis-Directed Therapy

Respondents were also asked to provide free text on any absolute contraindications to MDT for patients with mCRC in their practice. A summary is provided in Supplemental Table 1. Some of the more common concerns were poor patient performance status, the presence of widespread disease not treatable with MDT, and progression on or shortly after completing curative systemic therapy. Multiple respondents also noted that the presence of peritoneal disease and life expectancy <3 months were absolute contraindications. There were some themes which were also discipline specific including proximity of metastases to luminal gastrointestinal structures and inability to preserve a healthy liver remnant.

Discussion

This study highlights multiple important factors that the experts consider when deciding on MDT for patients with mCRC. The majority of respondents felt that prolonging OS and DFS are the most important reasons for considering MDT, and that 5-year rates of 30% for both OS and DFS and a 6-month interval following treatment without evidence of disease are reasonable expectations. While MO were least likely to offer MDT, the most common reason they favored MDT is the quality-of-life focused outcome of a break from systemic therapy. In addition, there was strong support for the use of multimodality MDT both to extend indications for treatment of all sites of disease and to treat liver-only disease when surgery alone is not feasible. Other considerations included the distribution of disease that the experts would consider for MDT, including the number of organ systems involved and timing of diagnosis of metastatic disease.

While the majority of data are retrospective and predominantly include liver-confined disease, MDT appears to improve OS in select patients with mCRC. A retrospective study from MD Anderson Cancer Center included locally advanced rectal cancer patients treated definitively with neoadjuvant chemoradiation and total mesorectal excision who recurred following treatment.[6] Patients with lung-only and liver-only recurrence who underwent surgical resection had significantly longer 5-year survival than those who did not undergo resection, 51% versus 13%, respectively, with $P < .001$, though it is possible the improved outcomes are at least in part due to patient selection. The use of multimodality therapy as local treatment for patients with unresectable colorectal liver metastases was investigated in the European Organisation for Research and Treatment of Cancer (EORTC) 40004 CLOCC trial.[7,8] In this phase II randomized trial, patients with <10 unresectable liver metastases were randomized to systemic therapy alone with or without the addition of local treatment with RFA ± resection. In the long-term follow-up of this study (median of 9.7 years), there was a statistically significant difference in OS in favor of the multimodality treatment arm (HR = 0.58, 95% CI: 0.38, 0.88, $P = .01$) with 5-year OS of 43.1% in the combined modality therapy arm and 30.3% in the systemic therapy alone arm.[8]

Distribution and volume of disease as well as timing of metastatic disease diagnosis are all important factors to consider when deciding on administering MDT but remain an area of controversy with limited data available. For patients with treatable lung-confined disease, there was fairly strong support for MDT across specialties with 58% generally favoring treatment and 36% strongly favoring treatment. Multiple retrospective series have shown promising long-term survival outcomes following pulmonary metastasectomy.[9,94,95] Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC) was a phase III multicenter non-inferiority trial of patients with resectable CRC lung metastases comparing metastasectomy to observation.[11] The trial was designed to randomize 300 patients, but was closed due to poor accrual after accruing 93 patients. In the metastasectomy arm, 1-6 lung lesions were resected with chemotherapy use similar between the two arms. The median OS after metastasectomy was 3.5 years versus 3.8 years for the control arm with an estimated unadjusted hazard ratio for death within 5 years, 0.93, 95% CI: 0.56-1.56. In our survey, experts were more likely to offer treatment in patients who presented with metachronous disease and were willing to offer MDT in patients with more advanced disease if a longer time period had passed between completion of definitive therapy and metastatic disease diagnosis. Multiple studies including those investigating lung metastasectomy for CRC and Fong's clinical risk score highlight that a shorter disease-free interval between resection of the primary tumor and development of metastatic disease are associated with poor OS.[10,84]

Amongst all respondents, when 6 months had passed after completion of definitive therapy and diagnosis of metastatic disease (upper time limit of synchronous presentation), in patients with liver and lung disease, 3 lesions in both the liver and the lung, regardless of distribution, seemed to be the threshold above which most would not offer MDT. In the presence of a RP LN, when assessing all respondents, most would not offer MDT in the setting of bilobar liver metastases or both liver and lung metastases. If 36 months had passed between completing definitive treatment

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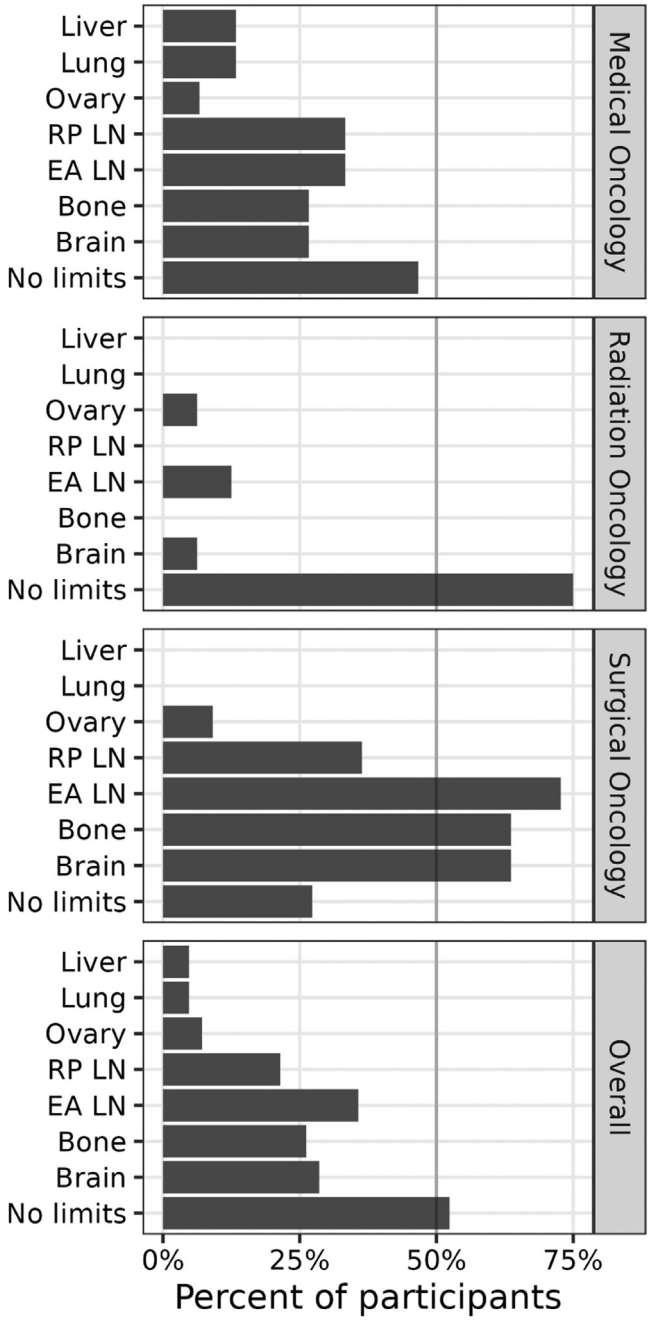
Figure 6 Organ or site involvement where metastasis-directed therapy would no longer be considered with responses by specialist and among all respondents. RP LN – retroperitoneal lymph nodes; EA LN – extra-abdominal lymph nodes; No limits – No organ where surgery/ablative therapy could no longer be considered.



and the metastatic diagnosis (metachronous presentation), more experts would consider MDT in patients with more advanced disease compared to a synchronous presentation, but the majority would still not consider MDT in patients with 3 lesions in both the liver and the lung, regardless of distribution, or in patients with a RP LN and liver and lung metastases. With this extended time between definitive treatment and metastatic diagnosis, more than 50% of SOs would offer MDT to patients with 3 lesions in both the liver and the lung regardless of the distribution and over 50% would offer treatment to a patient with a RP LN metastasis, 3 bilobar liver metastases, and a single lung metastasis.

There was also variation in the threshold volume of disease for MDT eligibility. SOs were at the upper limit for patients with liver-

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only disease, followed by RO and then MOs who were at the lower end. These results were consistent with those reported in a prior survey of MOs assessing perceptions of resectability, chemotherapy sequencing, and referral for surgical consultation of patients with colorectal liver metastases that identified discrepancy between what expert surgeons and MOs considered resectable.[96] While the present study did not incorporate radiographic images or specific location of liver metastases to provide additional insight into potential surgical resectability, MOs were consistently less willing to offer MDT to patients with more advanced disease. The results of our study further highlight the need to discuss patients with mCRC in a multidisciplinary tumor board with appropriate representation by MO, colorectal surgery, liver and thoracic surgery, RO, and diagnostic and interventional radiology. Caring for these patients is complex and deciding who may be a candidate for MDT requires careful discussion and shared decision making from a multidisciplinary team as highlighted in the recent American Society of Clinical Oncology[97] and American Radium Society Guidelines.[98]

Most respondents did not identify any single organ as an absolute contraindication for MDT, although this was largely driven by the response of ROs. Site involvement where MDT was felt to be inappropriate included extra-abdominal lymph nodes (36%), brain (29%), and bone (26%). The response to this question is likely tied to the respective literature that is published in each of the disciplines. The data in the SO literature largely focuses on resection primarily in the liver, with data suggesting that patients with extrahepatic disease have inferior outcomes compared to those with liver-confined disease.[82] However, recent RO literature supports use of SABR at multiple sites throughout the body. The SABR-COMET trial was a tumor agnostic phase II trial for which patients with 1 to 5 metastases were eligible for randomization to either palliative standard of care treatment or SABR to all metastatic sites followed by standard of care treatment.[16,85] Sites treated in this study include the adrenal glands, bone, liver, lung, brain, and lymph nodes. In the long term follow-up of SABR-COMET, the 8-year OS was 27.2% in the SABR arm versus 13.6% in the control arm (HR = 0.50, 95% CI: 0.30, 0.84, $P = .008$) with rates of grade ≥ 2 acute or late toxic effect 30.3% versus 9.1% ($P = .019$) with no new grade 3 to 5 toxic effects.[15]

When questioned about absolute contraindications to MDT, several common and expected themes emerged including poor performance status, progression on systemic therapy, the presence of widespread disease not amenable to MDT, and short life expectancy (Supplemental Table 1). However, there was also the troubling theme that insurance coverage may dictate delivery of therapy. An analysis of the National Cancer Database (NCDB) previously reported on utilization of metastasectomy for patients with mCRC with liver and/or lung involvement.[99] The uninsured/Medicaid group had a higher proportion of Black patients (25.9% vs. 13.4%, $P < .001$) and patients with Spanish/Hispanic ethnicity (13.4% vs. 4.8%, $P < .001$), but fewer comorbidities as indicated by the Charlson-Deyo score (score of zero in 80.8% vs. 74.3%, $P < .001$). After controlling for patient factors, uninsured/Medicaid patients were 43% less likely to undergo metastasectomy than patients with private insurance/Medicare (OR = 0.57, 95% CI: 0.51, 0.64). In a separate study of the NCDB, Mitsakos et al. evaluated the impact of health insurance and race on treatment and OS in patients with mCRC.[100] The authors found that Black patients and patients who were either under-insured or uninsured were less likely to receive systemic therapy for mCRC and had increased mortality.

In general, there is a need for more prospective data to guide management of patients with mCRC, particularly for patients with liver-confined disease beyond what is considered surgically resectable. The recently opened A022101—a Pragmatic Randomized Phase III Trial Evaluating Total Ablative Therapy for Patients with Limited Metastatic Colorectal Cancer: Evaluating Radiation, Ablation, and Surgery (ERASur) trial (NCT05673148) is a phase III study being conducted through the NCI's NCTN. It includes patients with limited mCRC with up to 4 sites of disease based on organ where patients receive 4-6 months of induction first-line systemic therapy and are then randomized to either total ablative therapy to all lesions using a combination of SABR with or without surgical resection and/or MWA versus continued systemic therapy alone. In this study, individual sites of disease include each hemiliver, each lobe of the lungs, each adrenal gland, lymph nodes amenable to a single resection or treatment in a single SABR field, and bone metastases amenable to treatment in a single SABR field without a limit on the number of individual metastases per site. The primary endpoint of the study is OS. The Randomized Phase II Trial to Evaluate the Strategy of Integrating Local Ablative Therapy with First-Line Systemic Treatment for Unresectable Oligometastatic Colorectal Cancer (RESOLUTE) (ACTRN12621001198819) is evaluating the addition of local ablative treatment to systemic therapy in patients with mCRC with 3-10 lesions. The primary endpoint for this study is PFS at 12 months from randomization. Both studies will help to further elucidate the role of MDT in patients with more advanced disease beyond what is traditionally considered for MDT as shown in the results of this survey study.

Limitations of our study include a relatively low response rate of SOs compared to MOs and ROs, and not including thoracic surgeons in the survey. Second, this was a survey of experts, and may not necessarily reflect practice patterns in the broader oncologic community. While the goal of the systematic review was to provide evidence to aid in answering the survey questions, multiple questions were limited by lower-level evidence, again highlighting the need for more prospective studies addressing how to best use MDT for these patients. Further, there may have been differences in how thoroughly the respondents read the provided evidence, leading to heterogeneity of responses. In addition, questions regarding tumor board discussion of patients with mCRC including frequency of patient presentation based on physician specialty were not included in the survey. Finally, the goal of this survey study was to identify broad themes and general scenarios where expert physicians might consider MDT for patients with mCRC. Of course, many clinical situations exist outside of the scenarios presented in this survey where MDT could be considered, and a survey to inquire about all such potential scenarios was not feasible.

Conclusions

In conclusion, among experts caring for patients with mCRC, prolonging OS ranked as the most important and prolonging DFS

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as the second most important reasons for offering MDT. The 5-year DFS and OS to warrant consideration of MDT were both 30% while the minimum time of stable disease following treatment to justify consideration of MDT was 6 months. Given the importance noted of a break from systemic therapy by the MO, increased attention should be given to this quality-of-life focused metric when designing MDT trials. Regarding location of disease, most experts would not consider MDT in patients with 3 lesions in both the liver and the lung regardless of distribution or timing of metastatic disease diagnosis (6 vs. 36 months after definitive treatment). Similarly, in patients with RP LN and lung and liver involvement, most experts would not offer MDT regardless of timing of metastatic disease diagnosis. Overall, most experts did not feel that involvement of any particular organ site precluded consideration of MDT although this varied widely by physician specialty. We found significant variation amongst MOs, ROs, and SOs in the distribution and volume of disease where MDT would be considered. In general, SOs were willing to consider MDT in patients with more advanced disease and ROs were more willing to offer treatment regardless of metastatic site location. MOs were the least likely to consider MDT, an important consideration given they are typically the referring providers and can be the potential gatekeepers to MDT. The variability of results in this survey based on specialty highlights the spectrum of expert opinions of those who routinely manage patients with mCRC. However, it also underscores the need for consistent multi-disciplinary discussions in addition to well-designed prospective randomized trials to further characterize the risks and potential benefits of MDT for patients diagnosed with mCRC.

Clinical Practice Points

- The management of patients with metastatic colorectal cancer (mCRC) with liver only disease has been well established based on largely retrospective data. However, for patients with metastatic disease outside of the liver, the role of metastasis-directed therapy (MDT) is less clear.
- In our survey of the experts, we found significant variation amongst medical, radiation, and surgical oncologists in the distribution and volume of metastatic disease where MDT would be considered.
- Overall, the threshold where most would no longer consider MDT was in a patient with 3 lesions in both the liver and lung regardless of distribution and independent of timing of metastasis diagnosis (synchronous vs metachronous).
- Our results emphasize the need for well-designed prospective trials to clarify the role of MDT in patients with mCRC and the need for consistent multi-disciplinary evaluation and discussion when considering treatment options for these patients.

Disclosure

Eric D. Miller, Kathryn E. Hitchcock, Paul B. Romesser, Sepideh Gholami are part of the study team for A022101, the ERASur trial. No other authors have interests to declare that are relevant to this work.

CRediT authorship contribution statement

Eric D. Miller: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Brett G. Klamer:** Methodology, Formal analysis, Data curation, Writing – review & editing, Visualization. **Jordan M. Cloyd:** Conceptualization, Methodology, Validation, Writing – review & editing. **Timothy M. Pawlik:** Conceptualization, Methodology, Validation, Writing – review & editing. **Terence M. Williams:** Conceptualization, Validation, Writing – review & editing. **Kathryn E. Hitchcock:** Conceptualization, Validation, Writing – review & editing. **Paul B. Romesser:** Conceptualization, Validation, Writing – review & editing. **Harvey J. Mamon:** Conceptualization, Methodology, Validation, Writing – review & editing. **Kimmie Ng:** Conceptualization, Validation, Writing – review & editing. **Sepideh Gholami:** Conceptualization, Methodology, Validation, Writing – review & editing. **George J. Chang:** Conceptualization, Methodology, Validation, Writing – review & editing. **Christopher J. Anker:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2024.01.004.

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