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Surgical referral for colorectal liver metastases: A population-based survey

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Abstract

BACKGROUND—Surgical resection is underutilized for patients with colorectal liver metastases (CLM). Though causes of underutilization are poorly understood, provider attitudes towards surgical referral may be contributory. We sought to understand medical oncologists' perspectives on referral for CLM.

METHODS—We surveyed medical oncologists who treat colorectal cancer in the state of Michigan. We characterized respondents' attitudes regarding clinical and tumor-related contraindications to liver resection for CLM, as well as referral and treatment preferences using case-based scenarios. We then evaluated practice characteristics and treatment preferences between physicians.

RESULTS—We received 112 eligible responses (46% response rate). Nearly 40% of respondents reported having no liver surgeons in their practice area. Commonly perceived contraindications to liver resection included extra-hepatic disease (80.3%), poor performance status (77.7%), the presence of >4 metastases (62.5%), bilobar metastases (43.8%) and metastasis size >5 cm (40.2%). Compared to High-Referring physicians, Low-Referring physicians were as likely to refer a patient with very low recurrence risk (89.3% vs. 98.3%, $p=0.099$), but much less likely to refer a patient with moderate risk (0 vs. 82.8%, $p<0.001$). High-Referring physicians were more likely to consider resection for scenarios consistent with higher recurrence risk (31.0% vs. 10.7%, $p=0.05$).

CONCLUSIONS—We found wide variation in surgical referral patterns for CLM. Many felt that bilobar disease and tumor size to be contraindications to liver-directed therapy, despite a lack of supporting data. These findings suggest an urgent need to increase dissemination of evidence and guidance regarding management for CLM, perhaps through increased specialist participation in tumor boards.

Keywords

colorectal cancer; metastasis; metastasectomy; surgery; surgical resection

INTRODUCTION

Colorectal cancer is the third leading cause of cancer death in the United States, and most deaths are related to metastatic disease.[1, 2] Surgical resection remains an efficacious treatment for colorectal liver metastases (CLM). In selected patients, CLM resection substantially lengthens survival, and in certain cases, can cure patients.[3–5] Recently, there has been an expansion in the number and utilization of other highly effective treatments, including multi-agent chemotherapy, biologic agents and a growing complement of liver-directed interventions, such as radiofrequency and microwave ablation.[6–9] As a result, the definition of resectable metastatic disease continues to evolve, and patients are increasingly being considered eligible for therapy.[7, 10–12]

Surgical treatment for metastatic colorectal cancer, however, remains underutilized.[13–16] It is possible that low surgery rates for CLM reflect lack of referral rather than untreatable disease.[15, 17, 18] Medical oncologists provide care for the vast majority of patients with metastatic disease and drive most treatment decisions, including referral for surgical resection. Thus, medical oncologists are the “gate-keepers” of treatment and referrals for patients with CLM. As treatment decisions become more complex, it is important to understand the motivating factors that underlie a surgical referral. Yet, there are limited data detailing this complex decision-making process.

A deeper understanding of attitudes and practices within the medical oncology community may promote multidisciplinary collaboration and potentially improve care for CLM. In this context, we performed a population-based assessment of medical oncologists’ attitudes towards surgical referral for CLM. Using a novel survey created from previously published instruments,[17, 18] we surveyed oncologists who treat colorectal cancer across the state of Michigan. The objective of the study was to characterize statewide variation in attitudes towards CLM. In addition, we also assessed physician characteristics and attitudes associated with surgical referral of patients with CLM.

METHODS

We performed a postal survey of medical oncologists in the state of Michigan. Our objectives were to characterize practices and factors influencing surgical referral decision-making. Recipients were identified from statewide registries representing over 95% of practicing oncologists in Michigan. Recipient addresses and practice locations were verified by telephone as needed. We excluded retired physicians, trainees (fellows), and physicians who did not treat colorectal cancer from our analysis.

Survey development and implementation

Survey questions (Appendix 1) were developed using input from surgeons and medical oncologists with expertise in colorectal cancer, as well as previously published surveys on

this topic matter. [17, 18] Survey domains included provider experience and practice setting, staging/follow-up practices, access to advanced liver-directed therapies, multidisciplinary cancer conference/tumor board participation, factors considered when referring patients, and treatment preferences for case scenarios (surgery, systemic therapy, liver-directed therapy, palliative treatment) based on a validated CLM recurrence risk score (CLM score). [19, 20] Responses for patient factors and treatment preferences were assessed using 4- or 5-item Likert questions. The survey instrument was pilot tested among liver surgeons and medical oncologists and iteratively refined. To maximize response rate, we used a modified Dillman technique for survey implementation, which included a cash incentive for participation (\$20).[18, 21, 22] Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Michigan.[23] A random 40% sample was used to evaluate for and resolve data entry errors. Re-entry verified a high (>99%) concordance rate between coders.

Statistical analysis

The primary goal was to determine oncologists' attitudes towards referral and treatment for CLM. A secondary goal was to determine whether referral practices were associated with particular practice characteristics. To do this, we characterized respondents *a priori* into 2 categories ("Low"- and "High-Referring") based on their approach to patient scenarios. The "Low-Referring" group was characterized by responding "rarely" or "never" to questions regarding the referral of patients with lower recurrence risk (CLM scores ≤ 3). The "High-Referring" group responded they would "often" or "always" refer patients with higher recurrence risk (CLM scores ≥ 3). Physicians that overlapped categories (n=12) were excluded from analysis. Descriptive characteristics and scenario-based responses were compared between groups using Fisher's exact test, Pearson chi-squared tests or rank-sum tests as appropriate.

To assess the robustness of our findings, we performed sensitivity analyses. In one, we reclassified physicians into low- and high-referring groups using more exclusive criteria. Low-Referring physicians were defined as those who would never/rarely refer patients with CLM scores 0–2 and High-Referring physicians were defined as those would often/always refer patients with CLM scores 4 and higher. In another, we stratified respondents according to whether they reported having liver surgeons in their practice area, to see if treatment preferences differed based on availability of local expertise.

We performed statistical analyses using STATA Release 12 (StataCorp, College Station, TX). Reported p-values are 2-sided with statistical significance established at $P < 0.05$. The University of Michigan Institutional Review Board approved the survey instrument and study protocol.

RESULTS

The initial mailing included 297 recipients. 47 respondents did not treat CRC, and 6 were not medical oncologists, leaving 244 eligible surveys. A total of 112 eligible, complete responses were received for a response rate of 46%. Respondents were geographically diverse. Table 1 shows the practice characteristics of responding oncologists. The median

time of practice duration was 20 years (interquartile range 7–28 years). The majority of respondents practiced in a community-based setting with or without residents (67, 59.8%), evaluated 11–50 patients/year (66, 58.9%), and practiced in large (population > 100,000) or medium-sized (>25,000) cities or suburbs (98, 87.5%). Forty-one (36.6%) respondents reported having no liver surgeons in their practice area, and 14 (12.5%) reported having neither liver surgeons nor liver-specialized interventional radiology services in their practice area. The majority (103, 92%) attended multidisciplinary tumor boards; of those, most (78, 75.7%) attended on a weekly basis.

Attitudes and beliefs regarding contraindications to liver resection are shown in Table 2. Few (10, 8.9%) respondents felt age was often or always a contraindication to liver resection. Of the 12 characteristics surveyed, the most commonly perceived contraindications were extra-hepatic disease (90, 80.3%), poor performance status (87, 77.7%) and the presence of >4 metastases (70, 62.5%). Other commonly perceived contraindications to liver resection were prior liver resection (31, 27.7%), bilobar metastases (49, 43.8%) and metastasis size >5 cm (45, 40.2%).

Figure 1 shows changes in respondent attitudes towards referral as CLM recurrence risk increased in patient scenarios. In general, as recurrence risk increased, the proportion of physicians who would often or always refer decreased steadily. A higher proportion of respondents would rarely or never refer patients with bilobar (vs. unilobar) disease and a recurrence risk score of 3. At the extremes, 3 (2.7%) respondents would rarely/never refer patients with CLM score 0, while 7 (6.2%) would often or always refer patients with high CLM recurrence risk (CLM score 4) and evidence of extra-hepatic disease.

In our assessment of scenario-based referral and treatment attitudes, 28 physicians would rarely or never refer patients with low CLM recurrence risk (CLM score 3, hereafter referred to as “Low-Referring”) and 58 physicians would often or always refer patients with high recurrence risk (CLM score 3, hereafter referred to as “High-Referring”). Practice differences and attitudes regarding liver resection contraindications between groups are shown in Table 3. Though practice characteristics were largely similar, there were differences between Low-Referring and High-Referring physicians in their attitudes regarding liver resection contraindications. In particular, Low-Referring physicians were more likely to consider metastasis size >5cm (60.7% vs. 30.0%, $p=0.011$) and high CEA level (25.0% vs. 6.9%, $p=0.034$) as contraindications to liver resection.

Table 4 shows attitudes regarding CLM resectability and treatment decisions between Low-Referring and High-Referring physicians. As expected, with increasing CLM recurrence risk the likelihood of surgical referral decreased dramatically among Low-Referring, but not High-Referring physicians. For example, compared to High-Referring physicians, Low-Referring physicians were as likely to refer a patient with very low recurrence risk (CLM 0) (89.3% vs. 98.3%, $p=0.099$), but much less likely to refer a patient with moderate (CLM score 3) recurrence risk (0 vs. 82.8%, $p<0.001$).

Treatment choices varied across groups as well. While both groups were likely to use chemotherapy in all situations, a higher proportion of High-Referring physicians considered

liver resection as a treatment option, especially at higher risk levels (CLM scores 3 and 4, Table 4). For most scenarios, Low-Referring physicians were more likely to consider a combination of chemotherapy and liver-directed nonsurgical interventions than High-Referring physicians. For a patient with potentially unresectable disease (CLM score 4 with extrahepatic disease), treatment choices were similar between groups, but High-Referring physicians were still more likely to refer such patients for evaluation by a surgeon.

In the sensitivity analysis, fewer respondents were so-called Low-Referring (N=16) or High-Referring (N=48) physicians. Practice characteristic differences and perceptions regarding liver contraindications were similar to the primary analysis, with Low-Referring physicians considering metastasis size >5cm a liver resection contraindication more frequently than High-Referring physicians. There were similar trends in first treatment choices as well, with High-Referring physicians consistently more likely to consider liver resection across various recurrence risk scores. When stratified by availability of liver surgeons, the two groups were largely similar with regard to practice characteristics, liver resection contraindications, referral likelihood and treatment choices.

DISCUSSION

In this statewide survey of medical oncologists, we found broad variation in attitudes regarding CLM management. A significant proportion of respondents practiced in areas without surgeons with liver expertise. Many considered metastasis size (40.2%) or bilaterality (43.8%) to be contraindications for resection. Between Low- and High-Referring physicians, there were strikingly different management preferences for similar patients. Together, these results imply a lack of knowledge diffusion of modern CLM resectability criteria [10], and that important treatment decisions for such patients may not include input from liver-directed treatment specialists.

Though the medical literature is replete with studies showing improved cancer outcomes for patients who undergo liver resection for CLM, [3–5] surgery remains underutilized.[14–16] The current study adds to our understanding of the reasons many CLM patients are not referred for surgical consideration. A few other studies have suggested physician practice characteristics and attitudes towards CLM resection vary.[17, 18] The present study goes further by highlighting regional variation in CLM management using a statewide sample of oncologists with diverse practice settings. Importantly, we have identified potential barriers to optimal care, including variability in provider knowledge of resectability criteria.

Many respondents considered bilaterality and metastasis size to be contraindications to liver resection. Moreover, attitudes regarding metastasis size as a resection contraindication differed between Low- and High-Referring physicians. This suggests an over-reliance on prognostic tools such as the CLM clinical risk score[20] to drive surgical referral decision-making, which may translate into under-treatment in certain cases. For example, Jones and colleagues [24] demonstrated up to 30% of patients considered unresectable and managed with palliative chemotherapy actually had potentially resectable disease. These findings are concerning in light of recent evidence demonstrating improved survival after multimodality treatment and complete disease resection, even for patients with poor prognostic scores. For

example, Tomlinson *et al* [5] demonstrated even patients with very high recurrence risk scores could be cured if their metastatic disease was completely resected. Similarly, Nathan *et al* [25] demonstrated high conditional survival rates for patients with surgically resected disease, including those with poor predicted prognoses. Consequently, the present study may imply the need for greater specialist input.

The need for multidisciplinary collaboration in CLM management has never been higher. Liver resection eligibility criteria have expanded.[10] At the same time, the effectiveness of non-surgical treatment options has improved.[26] For example, modern chemotherapy regimens have permitted longer life expectancy and a greater chance for converting CLM to resectable lesions.[27–29] Despite this, there remains a lack of strong consensus on optimal treatment patterns, which increases the likelihood of variable care.[30]

Variation in referral practices was not associated with different practice settings. As shown in the present study, the practice settings, locations and patient volume between Low- and High-Referring physicians were nearly identical. Rather, the decision to refer seems heavily dependent on provider attitudes towards CLM in general. Supporting this premise are the observed variation in respondent referral thresholds for patients of similar recurrence risk, variation in treatment preferences associated with different referral preferences, and a lack of influence of nearby liver specialists.

These observed differences in treatment preferences are especially interesting given respondents' high rates of attendance and patient presentation at tumor boards. One explanation of these findings is that surgeons may not always attend tumor boards. As a result, respondents may be less likely to consider surgical resection.[31] On the other hand, these findings could represent a failure on the surgeon's part to increase awareness of resection criteria and surgical outcomes, as it is unknown to what extent these guidelines and data are known in the general community. In either case, there is a clear need to improve communication to facilitate familiarity with and/or access to knowledge of resection eligibility. A key step toward improving access to extirpative treatment in Michigan will be ensuring the dissemination of newer evidence and guideline-supported treatment decisions at multi-disciplinary case conferences.

There are important limitations to this study. First, we could not determine the degree to which a provider's reported attitudes and treatment preferences were associated with their actual practice and why such referral patterns exist. However, the focus of the study was to identify potential barriers to surgical referral, not actual referral rates. Second, survey responses are influenced by individual recall and may be biased towards ideal practice. However, a strength of our study is its broad representation of statewide oncologists and reasonable survey response rate (46%) though generalizability of the findings to national care patterns may be limited, especially if the availability of liver specialists differs. Similarly, the results of the present study suggest a high degree of variation in decision making and are congruent with other work.[17, 18, 32] Results also were not substantially changed in sensitivity analyses. Differences in referral patterns are multifactorial and related to beliefs about indications for resection as well as availability of systemic treatment options. Third, we could not assess the degree to which reported tumor board practices

represented institutions' true practices. Further research regarding tumor board composition, attendance, and content will be essential to further understanding and improving barriers to knowledge dissemination.

In conclusion, a survey of medical oncologists in Michigan uncovered broad variation in referral practices and management preferences for CLM. Moreover, it revealed that many oncologists hold certain tumor characteristics to be contraindications to resection, even though such factors are no longer necessarily considered contraindications by surgeons. Given the high self-reported attendance rates at multidisciplinary tumor boards, these findings imply an urgent need to increase dissemination of evidence and guidance regarding liver-directed management for CLM. To accomplish this, it will be imperative to share these results and identify causes for variation in referral patterns. First steps may include broader surgical participation in tumor boards.[31] Decision-support tools, which have been shown to be effective in other populations, may also play a role in this setting.[33] Increasing dialogue in geographically remote areas may require different strategies such as use of telemedicine for tumor board.[34] These findings suggest a need to increase awareness of CLM management options and effective dialogue across all specialists who care for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Respondent likelihood of surgical referral based on CLM risk score [19, 20]

Table 1

Survey respondent characteristics

	N (%) of respondents Total = 112 physicians
Years in practice (med, IQR)	20 (7–28)
Practice setting	
Private practice	39 (34.8)
Community-based, no residents	14 (12.5)
Community based, with residents	53 (47.3)
Academic/Research	16 (14.3)
Other	5 (4.5)
Population setting	
Large city	61 (54.5)
Medium city or suburb	37 (33)
Small city/town	13 (11.6)
Rural	1 (0.9)
Patient volume (unique patients/yr)	
0 – 10	22 (19.6)
11–50	66 (58.9)
51 – 100	17 (15.2)
>100	4 (3.6)
Manages stage I/II follow-up	97 (86.6)
Area resources	
Liver surgeons	71 (63.4)
Interventional radiology with liver expertise	96 (85.7)
None	14 (12.5)
Guidelines used	
AHPBA	5 (4.5)
ASCO	60 (53.6)
NCCN	105 (93.8)
Other	2 (1.8)
Multiple	58 (51.8)
Participates in tumor board	103 (92)
Tumor board frequency	
Weekly	78 (75.7)
Twice a month	18 (17.5)
Once a month	6 (5.8)
Other	1 (1)
Proportion of patients presented at tumor board	
< 25%	34 (33)

	N (%) of respondents Total = 112 physicians
26 – 75%	37 (35.9)
>75%	26 (25.2)
Personally reviews liver images	89 (79.5)

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Table 2

Respondent perceptions about contraindications to liver resection

CHARACTERISTIC	N (%) of respondents*				
	Never	Rarely	Sometimes	Often	Always
<i>Patient characteristics</i>					
Patient age	8 (7.1)	33 (29.5)	57 (50.9)	9 (8.0)	1 (0.9)
Medical comorbidities	1 (0.9)	3 (2.7)	41 (36.6)	41 (36.6)	21 (18.8)
ECOG > 2	0	3 (2.7)	20 (17.9)	49 (43.8)	38 (33.9)
Impaired liver function	1 (0.9)	10 (8.9)	45 (40.2)	42 (37.5)	11 (9.8)
Prior liver resection	5 (4.5)	23 (20.5)	50 (44.6)	20 (17.9)	11 (9.8)
<i>Liver metastasis-specific characteristics</i>					
Synchronous metastases	22 (19.6)	38 (33.9)	32 (28.6)	10 (8.9)	8 (7.1)
>4 metastases	3 (2.7)	9 (8.0)	26 (23.2)	41 (36.6)	29 (25.9)
Metastasis size >5 cm	4 (3.6)	17 (15.2)	44 (39.3)	28 (25)	17 (15.2)
Bilateral/bi-lobar disease	2 (1.8)	10 (8.9)	47 (42.0)	29 (25.9)	20 (17.9)
<i>Systemic disease-related characteristics</i>					
Extra-hepatic metastases	0	0	19 (17.0)	38 (33.9)	52 (46.4)
CEA > 200 ng/mL	26 (23.2)	38 (33.9)	34 (30.4)	8 (7.1)	4 (3.6)
Disease-free interval <12 mo	18 (16.1)	33 (29.5)	43 (38.4)	11 (9.8)	2 (1.8)

* Based on the question: "How often do you consider the following to be contraindications to liver resection for CRC metastases?"

Table 3

Practice characteristic and perceptions about liver resection contraindication differences between High and Low referring physicians

	Low-referring N=28 physicians	High-referring N=58 physicians
Years in practice (med, IQR)	18 (5–30)	18 (7–26)
Practice setting		
Private practice	6 (21.4)	13 (22.4)
Community-based	20 (71.4)	30 (51.7)
Academic/Research	2 (7.1)	11 (19.0)
Other	0 (0)	4 (6.9)
Population setting		
Large city	15 (53.6)	32 (55.2)
Medium city or suburb	9 (32.1)	19 (32.8)
Small city/town	3 (10.7)	7 (12.1)
Rural	1 (3.6)	0 (0)
Practice volume (unique patients/yr)		
0 – 10	7 (25.0)	8 (13.8)
11–50	17 (60.7)	36 (62.1)
51 – 100	2 (7.1)	10 (17.2)
more than 100	2 (7.1)	2 (3.4)
Skipped	0 (0)	2 (3.4)
Manages stage I/II follow-up	27 (96.4)	51 (87.9)
Participates in tumor board	26 (92.9)	53 (91.4)
>75% patient presentation in tumor board	6 (21.4)	13 (22.8)
Area resources		
Liver surgeons	18 (64.3)	36 (62.1)
IR with liver expertise	24 (85.7)	47 (81.0)
None	4 (14.3)	9 (15.5)
Personally reviews liver imaging	22 (78.6)	47 (81.0)
Often or always a liver resection contraindication		
Patient age	3 (10.7)	5 (8.6)
Medical comorbidities	18 (64.3)	29 (50.0)
ECOG > 2	23 (82.1)	44 (75.9)
Impaired liver function	16 (57.1)	25 (43.1)
Prior liver resection for CLM	9 (32.1)	15 (25.9)
Other metastases	24 (85.7)	46 (79.3)
Metastasis size >5 cm ^d	17 (60.7)	18 (31.0)
Bilateral/Bilobar disease	16 (57.1)	27 (46.6)

	Low-referring N=28 physicians	High-referring N=58 physicians
>4 metastases	20 (71.4)	36 (62.1)
CEA > 200 ng/mL ^a	7 (25.0)	4 (6.9)
Synchronous metastases	7 (25.0)	7 (12.1)
Disease-free interval <12 mo	5 (17.9)	6 (10.3)

^a: P-value (from rank-sum test, pearson chi-squared or fisher's exact test) <0.05

Table 4

Scenario-based responses between Low-referring (N=28) and High-referring (N=58) physicians

CLM RECURRENCE RISK SCORE	N (%) of physicians					
	CLM 0		CLM 2 (TN)		CLM 3 (TND-unilat)	
	Low-referring	High-referring	Low-referring	High-referring	Low-referring	High-referring
<i>Scenario-based attitudes</i>						
Probably or clearly resectable	27 (96.4)	54 (93.1)	16 (57.1)	52 (89.7) ^a	5 (17.9)	44 (75.9) ^a
Would often/always refer	25 (89.3)	57 (98.3)	10 (35.7)	53 (91.4) ^a	0 (0)	48 (82.8) ^a
<i>First treatment choice</i>						
Chemotherapy	16 (57.1)	25 (43.1)	22 (78.6)	43 (74.1)	26 (92.9)	45 (77.6)
Liver resection	16 (57.1)	40 (69)	9 (32.1)	30 (51.7)	1 (3.6)	22 (37.9) ^a
Liver-directed intervention	6 (21.4)	7 (12.1)	6 (21.4)	7 (12.1)	6 (21.4)	10 (17.2)
Chemo + liver directed intervention	3 (10.7)	3 (5.2)	8 (28.6)	7 (12.1)	7 (25.0)	3 (5.2) ^a
CLM RECURRENCE RISK SCORE	N (%) of physicians					
	CLM 3 (TND-bilat)		CLM 4 (TNSD)		CLM 4 (TSDC) + extra-hepatic	
	Low-referring	High-referring	Low-referring	High-referring	Low-referring	High-referring
<i>Scenario-based attitudes</i>						
Probably/clearly resectable	1 (3.6)	31 (53.4) ^a	2 (7.1)	29 (50.0) ^a	0 (0)	6 (10.3)
Would often/always refer	0 (0)	31 (53.4) ^a	0 (0)	38 (65.5) ^a	0 (0)	8 (13.8) ^a
<i>First treatment choice</i>						
Chemotherapy	26 (92.9)	47 (81.0)	26 (92.9)	50 (86.2)	28 (100)	57 (98.3)
Liver resection	1 (3.6)	16 (27.6) ^a	3 (10.7)	18 (31.0) ^a	0 (0)	4 (6.9)
Liver-directed intervention	7 (25.0)	14 (24.1)	6 (21.4)	13 (22.4)	2 (7.1)	7 (12.1)
Chemo + liver directed intervention	9 (32.1)	7 (12.1) ^a	4 (14.3)	8 (13.8) ^a	3 (10.7)	6 (10.3)

^a: p-value (Pearson chi-squared or Fisher's exact test) <0.05

Note: T: Metastasis number>1 N: Node-positive primary S: Metastasis size > 5 cm, D: Disease free interval < 12m; C: CEA > 200 ng/mL