

ORIGINAL ARTICLE

Assessing the management of hepatic colorectal cancer metastases: is treatment consistent in Ontario?

Lakshbir Sandhu¹, Adrian Fox¹, Cindy Nhan², Heidi Barnett², Robin S. McLeod¹, Steven Gallinger¹ & Carol-Anne Moulton¹

¹Department of Surgery, Division of General Surgery, University of Toronto and ²Cancer Care Ontario, Toronto, ON, Canada

Abstract

Objectives: Advances in surgical techniques and chemotherapeutic options have expanded indications for surgery in patients with metastatic colorectal cancer. This study aimed to examine how hepatopancreatobiliary (HPB) surgeons approach the management of patients with hepatic colorectal cancer metastases (HCCM).

Methods: A web-based survey utilizing 10 clinical scenarios was distributed by e-mail to 37 HPB surgeons in Ontario, Canada. The study region has a population of approximately 13 million people and a universal, single-payer health care system. Descriptive analyses were used to tabulate results.

Results: Twenty-two (59%) surgeons responded to the survey. The majority (19/22, 86%) of respondents favoured neoadjuvant chemotherapy for patients with multiple synchronous and unilobar metastases; only nine of 22 (41%) respondents favoured neoadjuvant chemotherapy for patients with a single synchronous metastasis. In the setting of residual resectable disease following downstaging chemotherapy, 77% (17/22) of surgeons advocated hepatic resection with either radiofrequency ablation (RFA) or wedge resection of the 'ghost' lesions. Over 80% of surgeons would perform a liver and pulmonary resection in a patient with hepatic and multiple unilobar lung metastases. None would offer liver resection to patients with multiple retroperitoneal node involvement, although 55% (12/22) would do so if a single retroperitoneal node was involved. Preoperative portal vein embolization was favoured over RFA in patients with a small metastasis and inadequate functional hepatic volume.

Conclusions: Notable heterogeneity was observed among Ontario's HPB surgeons in approaches to HCCM.

Keywords

liver, colorectal neoplasms, metastases, neoplasm, survey, hepatopancreatobiliary surgery

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Correspondence

Lakshbir Sandhu, Division of General Surgery, Toronto General Hospital, University Health Network, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada. Tel: +1 416 340 4800 (ext. 6054). Fax: +1 416 340 4814. E-mail: lakho.sandhu@utoronto.ca

Introduction

Colorectal cancer is the third leading cause of cancer-related mortality in men and women worldwide. Every year, 120 000 new cases of colorectal cancer and 600 000 deaths are reported.¹

This study was presented in part at the Canadian Association of General Surgeons' Annual Surgical Forum, 10–13 September 2009, Victoria, BC.

Approximately one quarter of colorectal cancer patients present with metastases at diagnosis and an additional 30–40% will develop hepatic metastases during the course of the disease.² Surgical resection is the only definitive curative modality for hepatic colorectal cancer metastases (HCCM).^{3–6} Complete resection of metastatic disease results in 5-year survival rates of 36–58%.^{4,7–12}

Over the last decade, advances in surgical techniques and chemotherapeutic and biologic agents have considerably

broadened surgical indications for patients with metastatic colorectal cancer. With such rapid and substantive expansion of resection criteria, there is potential for variation in surgical practice. Morris *et al.* found considerable variation in liver resection rates across cancer networks and hospitals in England between January 1998 and June 2004.¹² Notably, significant variation persisted across both hospitals and cancer networks, despite adjustments for case mix; in a number of networks and hospitals identified as outliers, patients were significantly more likely to undergo resection for hepatic metastases. It is unclear whether this heterogeneity is attributable to variation in referral practices, differences in subsequent access to hepatopancreatobiliary (HPB) specialists or to surgeons' varying thresholds for resectability. This paper reports the findings of a web-based survey conducted to explore whether the latter may influence approaches to both 'simple' and complex clinical cases of HCCM among HPB surgeons in Ontario, Canada.

Materials and methods

In April 2008, an online survey was distributed to 37 surgeons who perform HPB surgical procedures in Ontario, Canada. The study region has a population of approximately 13 million people and a universal, single-payer health care system. Surgeons were identified via their membership in the Cancer Care Ontario HPB Community of Practice. Cancer Care Ontario, which is governed by the Cancer Act of Ontario, is a provincial agency that directs and oversees public health care expenditures for cancer services and oncologic quality improvement initiatives. Study subjects were contacted by e-mail and invited to participate in this anonymous survey. They received two reminders by e-mail at 4 weeks and 2 weeks prior to the response deadline. Those who failed to meet the deadline received an additional telephone call reminder.

This web-based survey comprised 10 items, each probing one or two of the following management issues for patients with HCCM: (i) the role of perioperative chemotherapy; (ii) the role of downstaging chemotherapy and surgical approach thereafter; (iii) the role of liver resection in the presence of extrahepatic disease, and (iv) the use of radiofrequency ablation (RFA) as a preferred or adjunctive component to surgery. Prior to distribution, the survey was piloted by five individuals with content expertise in HPB surgical oncology and survey methods. The clinical scenarios were subsequently revised to eliminate ambiguity. Descriptive analyses were used to tabulate results.

Results

Of the 37 surgeons who were e-mailed an invitation to participate, 22 (59%) responded to the survey. Nine respondents (40%) practised at centres that met Cancer Care Ontario's HPB Surgical Oncology Standards at the time (i.e. at least 50 HPB surgical procedures were performed yearly and a minimum of 20 of these operations were pancreatic resections). Over 95% of respondents ($n = 21$) answered all questions.

Table 1 Responses to items on treatment proposals for two patients with right-sided colon cancer and HCCM ($n = 22$ respondents)

(a) The patient is aged 67 years and has a right-sided colon cancer (T3N1) resected at an outside hospital 2 weeks ago. HCCM is noted intraoperatively. CT of the abdomen demonstrates a single lesion in the middle of the right lobe	
Answer option	n (%)
Neoadjuvant chemotherapy	9 (40.9%)
Upfront surgery	
• Right hepatic lobectomy followed by pseudoadjuvant chemotherapy	13 (59.1%)
(b) The patient is aged 67 years and has a right-sided colon cancer (T3N1) resected at an outside hospital 2 weeks ago. HCCM is noted intraoperatively. CT of the abdomen demonstrates six lesions in the right lobe	
Answer option	n (%)
Neoadjuvant chemotherapy	19 (86.4%)
Upfront surgery	
• Right hepatic lobectomy followed by adjuvant chemotherapy	3 (13.6%)

HCCM, hepatic colorectal cancer metastasis; CT, computed tomography.

'Upfront' surgery vs. neoadjuvant chemotherapy

Participants were presented with two scenarios featuring synchronous disease. In the first case, a single metastasis is discovered intraoperatively during resection of a primary colon cancer. The HPB surgeon is consulted postoperatively for his or her opinion regarding subsequent management. Respondents were slightly more in favour of 'upfront' surgery followed by 'pseudoadjuvant' chemotherapy (chemotherapy delivered after liver resection) (13/22, 59%), rather than neoadjuvant chemotherapy (9/22, 41%) (Table 1a). In the second case, the patient presents with multiple synchronous liver metastases limited to one lobe. Considerably more respondents in this instance suggested neoadjuvant chemotherapy (19/22, 86%) and only three (14%) advocated upfront surgery and subsequent chemotherapy (Table 1b).

In another scenario, a young patient presents with multiple HCCM in the right lobe and a single metastasis in the left lateral segment, 3 years after colon resection for stage III cancer. She has undergone appropriate adjuvant chemotherapy in the interim. Eleven (50%) of the 22 respondents favoured upfront surgery and nine (41%) favoured neoadjuvant chemotherapy (Table 2). Two (9%) participants chose palliative chemotherapy alone.

When the same pattern of liver disease was presented synchronously with the primary colon cancer, the majority of surgeons opted for immediate neoadjuvant chemotherapy and restaging ($n = 18$, 82%); opinion among the remaining respondents was divided between upfront surgery ($n = 2$, 9%) and palliative chemotherapy ($n = 2$, 9%) (Table 3). There was no support for an immediate staged resection.

Participants were asked about their approach to a patient with an asymptomatic rectal cancer (T3N1, 9 cm from the anal verge)

Table 2 Responses to an item on treatment proposals for a 55-year-old patient with eight metastases in the right lobe and a 2.5-cm metastasis in segment III, 3 years after resection of a primary stage III colon cancer and adjuvant chemotherapy ($n = 22$ respondents)

Answer option	n (%)
Referral to medical oncology for neoadjuvant chemotherapy followed by restaging and possible surgery	9 (40.9%)
Upfront surgery	
• Right portal vein embolization followed by right hepatic lobectomy and left lateral segmentectomy	3 (13.6%)
• Right hepatic lobectomy and radiofrequency ablation of left lateral segment metastasis	2 (9.1%)
• Staged resection:	
• Left lateral wedge resection of segment III lesion and ligation of the right portal vein followed by right hepatic lobectomy if adequate regeneration	4 (18.2%)
• Right hepatic lobectomy followed by left lateral segmentectomy if adequate regeneration of left lobe	2 (9.1%)
Referral to medical oncology for palliative chemotherapy	2 (9.1%)

Table 3 Responses to an item on treatment proposals for a 55-year-old patient with a primary stage III colon cancer and eight metastases in the right lobe and a 2.5-cm metastasis in segment III ($n = 22$ respondents)

Answer option	n (%)
Referral to medical oncology for neoadjuvant chemotherapy followed by restaging and possible surgery	18 (81.8%)
Upfront surgery	
• Right portal vein embolization followed by right hepatic lobectomy and left lateral segmentectomy	1 (4.5%)
• Right hepatic lobectomy and radiofrequency ablation of left lateral segment metastasis	1 (4.5%)
• Left lateral wedge resection of segment III lesion, ligation of the right portal vein followed by right hepatic lobectomy if adequate regeneration	0
• Staged resection	0
Referral to medical oncology for palliative chemotherapy	2 (9.1%)

in the setting of liver metastases. Sixteen (73%) respondents chose neoadjuvant chemoradiotherapy as the initial treatment for the rectal cancer, followed by surgery, whereas four (18%) recommended a low anterior resection without neoadjuvant chemoradiotherapy. One surgeon chose chemotherapy alone, suggesting a palliative approach to this patient. No participant chose simultaneous low anterior resection and right hepatic lobectomy as initial therapy.

Downstaging chemotherapy

Participants were presented with a scenario involving a 62-year-old man, 2 years after resection of stage II colon cancer. This patient has liver metastases that are considered unresectable, with

one lesion in each of segments II, III, IVa, IVb and VII. After 8 months of chemotherapy, the left-sided lesions are smaller and the segment VII lesion is no longer visible (i.e. it has become a 'ghost' lesion). Two (9%) surgeons deemed this pattern of disease incurable and recommended continued chemotherapy. The remaining surgeons chose a more aggressive approach. Eighteen (82%) surgeons chose treatment regimens specifically designed to achieve loco-regional control of the ghost lesion with a left hepatic lobectomy and either a wedge resection ($n = 17$) or RFA ($n = 1$). One respondent considered the ghost lesion to be biologically inactive and selected left hepatic lobectomy alone, and another preferred to stop chemotherapy and assess for interval disease progression before pursuing a left hepatic lobectomy if the ghost lesion failed to reappear.

An additional scenario probed the surgeons' willingness to consider high-risk operations involving hepatic vein reconstruction. In this instance, a 58-year-old patient presents with two metastases straddling all three hepatic veins, 3 years after resection of a stage II cecal adenocarcinoma. The scenario specifies that a right trisegmentectomy and re-implantation of the left hepatic vein will be required to achieve an R0 resection. There was significant heterogeneity among the 21 participants who responded to this item. Three (14%) surgeons chose palliative chemotherapy, whereas six (29%) suggested that such a patient should be referred to another centre. Eight (38%) respondents suggested initial downstaging chemotherapy and four (19%) favoured upfront surgery. In this instance, upfront surgery was defined as a right trisegmentectomy and re-implantation of the left hepatic vein. Of note, the four surgeons who chose upfront surgery practised at a transplant centre.

Extrahepatic disease

When challenged by patients with both lung and liver metastases, the majority of the 22 respondents offered surgery in the setting of unilobar lung involvement, and 10 (45%) offered surgery to those patients with bilobar lung disease. Fewer surgeons were in favour of combining hepatic resection with portal lymphadenectomy; six (27%) suggested a hilar lymphadenectomy and six (27%) recommended a 'node picking' procedure (Table 4). No respondent offered liver surgery when metastatic disease was present in multiple retroperitoneal nodes, although 12 (55%) favoured surgery if only a single retroperitoneal node was involved. Seventeen (77%) respondents suggested liver resection in conjunction with the removal of a single persistent node in the mesentery of a previously resected colon cancer, but only three (14%) suggested this surgery in the setting of multiple mesenteric nodal metastases.

Radiofrequency ablation vs. surgery

Finally, the surgeons were presented with a patient with a single 2-cm metachronous metastasis in the middle of the right lobe of the liver. In this patient, the left lobe is prohibitively small, constituting 20% of total liver volume. Five (23%) of the 22 surgeons

Table 4 Responses to the item: In which of the following scenarios would you perform a hepatic resection in combination with resection of extrahepatic disease at the same time or at a subsequent operation (assume a disease-free interval of >12 months from the primary operation and an asymptomatic patient) (*n* = 22 respondents)

Answer option	<i>n</i> (%)
Lung metastases	
• Single lung metastasis	21 (95.5%)
• Multiple lung metastases involving a single lobe	18 (81.8%)
• Multiple lung metastases involving two lobes	10 (45.5%)
Portal lymph node metastases	
• Node picking	6 (27.3%)
• Hilar lymphadenectomy	6 (27.3%)
Retroperitoneal metastases	
• Solitary retroperitoneal lymph node	12 (54.5%)
• Multiple retroperitoneal lymph nodes	0
Mesenteric metastases	
• Solitary metastasis within mesentery of resected colonic primary	17 (77.3%)
• Multiple nodal metastases within mesentery of resected colonic primary	3 (13.6%)

suggested RFA of the liver lesion in lieu of surgical management and the remaining 17 (77%) favoured portal vein embolization (PVE) followed by surgery.

Discussion

The aim of this survey was to assess the approaches of Ontario HPB surgeons in hypothetical scenarios concerning issues currently under debate in HPB surgery, in an era prior to the development of provincial consensus guidelines (April 2008). Variations in practice were apparent in responses to many of the clinical scenarios presented in the 10-item survey.

The only contemporary trial to address the question of perioperative chemotherapy for HCCM found a statistical trend towards increased survival with the use of neoadjuvant ('sandwich') chemotherapy; however, patients in the comparator arm received surgical resection alone without any chemotherapy.¹³ Respondents were clearly divided between the administration of pseudoadjuvant and neoadjuvant chemotherapy (Table 1) for the patient with a single synchronous HCCM in the right lobe. To date, there is insufficient evidence in support of one approach vs. the other and until data from randomized trials become available, varied practice patterns are likely to continue. Currently, multi-centre trials are underway to assess the benefits of preoperative vs. postoperative chemotherapy in this setting.¹⁴

Liver surgery for patients with HCCM and extrahepatic metastases remains controversial.³ Portal lymph node involvement has been investigated by a number of studies that have reported few or no survivors at 5 years among HCCM patients who underwent therapeutic portal lymphadenectomy for

involved nodes, especially distal field or celiac nodes.^{15–19} A significant proportion of surgeons surveyed in the present study said they would consider resection of extrahepatic disease including portal (6/22, 27%), retroperitoneal (12/22, 55%) and mesenteric (3–17/22, 14–77%) lymph nodes, which suggests they have incorporated recent Level II evidence into their practice.²⁰ Based on a number of retrospective studies,^{21–23} complete resection of lung and liver metastases is generally accepted as the standard of care; these studies have demonstrated that the survival of patients who undergo pulmonary and liver metastasectomy is comparable with that of patients with isolated liver metastases. Not surprisingly then, the majority of respondents to the present survey (21/22, 95%) did not consider an isolated, single pulmonary colorectal cancer metastasis a contraindication to hepatectomy. However, the number of surgeons in favour of hepatectomy fell when the patient exhibited multiple metastatic lesions isolated to a single pulmonary lobe. Because the literature published on this topic is limited, the extent of pulmonary disease burden that should be considered amenable to surgery is still debatable.

The utility of PVE for increasing the size of the future liver remnant (FLR) prior to a major liver resection is well established. The majority (17/22, 77%) of participants in the present survey chose PVE for a patient requiring a right hepatic lobectomy with an anticipated FLR of <20%. However, five (23%) surgeons chose instead to achieve loco-regional control of the single right-sided metastasis with an ablative technique rather than PVE and surgery. To date, there is no Level I evidence to suggest that RFA is equivalent to surgery in its likelihood of achieving a cure in HCCM.

This survey used an anonymous, online, electronic, multiple-choice questionnaire and is subject to the shortcomings of such instruments.²⁴ Nonetheless, its findings demonstrate variation in approaches to patients with HCCM, despite active efforts around the time of the survey to regionalize HPB surgical oncology care in Ontario. Although complete uniformity in surgical management is unrealistic and unnecessary, further efforts in developing and implementing surgical guidelines should lead to the provision of more consistent care for these complex patients.

Conclusions

The present study demonstrates heterogeneity in the approach to HCCM among Ontario HPB surgeons. Given the relatively low volume and high acuity of HPB surgical oncology patients, it seems feasible that greater consistency in care is possible for these patients, assuming they have relatively equal access to specialized centres. Recent efforts to resolve some of the more important clinical questions in the specialty with prospective, randomized trials should also reduce controversy and heterogeneity of care in a specialty fraught by a paucity of Level I evidence.

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Conflicts of interest

None declared.

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