

# Choices of Therapeutic Strategies for Colorectal Liver Metastases Among Expert Liver Surgeons A Throw of the Dice?

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**Objective:** To test the degree of agreement in selecting therapeutic options for patients suffering from colorectal liver metastasis (CRLM) among surgical experts around the globe.

**Summary/Background:** Only few areas in medicine have seen so many novel therapeutic options over the past decades as for liver tumors. Significant variations may therefore exist regarding the choices of treatment, even among experts, which may confuse both the medical community and patients.

**Methods:** Ten cases of CRLM with different levels of complexity were presented to 43 expert liver surgeons from 23 countries and 4 continents. Experts were defined as experienced surgeons with academic contributions to the field of liver tumors. Experts provided information on their medical education and current practice in liver surgery and transplantation. Using an online platform, they chose their strategy in treating each case from defined multiple choices with added comments. Inter-rater agreement among experts and cases was calculated using *free-marginal multirater kappa* methodology.

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A similar, but adjusted survey was presented to 60 general surgeons from Asia, Europe, and North America to test their attitude in treating or referring complex patients to expert centers.

**Results:** Thirty-eight (88%) experts completed the evaluation. Most of them are in leading positions (92%) with a median clinical experience of 25 years. Agreement on therapeutic strategies among them was none to minimal in more than half of the cases with *kappa* varying from 0.00 to 0.39. Many general surgeons may not refer the complex cases to expert centers, including in Europe, where they also engage in complex liver surgeries.

**Conclusions:** Considerable inconsistencies of decision-making exist among expert surgeons when choosing a therapeutic strategy for CRLM. This might confuse both patients and referring physicians and indicate that an international high-level consensus statements and widely accepted guidelines are needed.

**Keywords:** colorectal liver metastasis, expert liver surgeons, surgery, variability of treatment strategies

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Surgery is considered the mainstay approach included in most effective oncological strategies to cure patients with liver metastases from colorectal origin (CRLM). This is well illustrated in the setting of multiple bi-lobar metastases by combining extended liver surgery with novel systemic drug combinations, yielding a 5-year survival rate of about 50%.<sup>1–3</sup>

Notably, the selection criteria for liver surgery have evolved dramatically over the past 2 decades. The current focus is no longer related to the size and the number of lesions, but the ability to achieve a complete (R0) resection along with a sufficient remnant liver to prevent postoperative liver failure.<sup>2,4,5</sup> The introduction of multi-stage, volume-manipulating hepatectomies, and liver-tissue-sparing techniques have therefore increased tumor resectability, and consequently improved long-term survival.<sup>3</sup> In addition, a variety of ablative therapies, such as thermal ablation, irreversible electroporation, regional hepatic intra-arterial chemotherapy, chemo- or radio-embolization, and stereotactic radiotherapy have been added to the armamentarium of effective complementary therapies to surgical resection.<sup>6</sup> Finally, liver transplantation (LT) is also increasingly accepted for selected cases of metastatic tumors.<sup>7</sup> Although numerous surgical options are available for CRLM, choosing the best ones or the best combinations, however, represents a novel challenge of consistent decision-making, particularly in view of the paucity of conclusive high-level evidence publications.<sup>8</sup> Therefore, significant variations may exist among surgeons regarding their choices of treatment. This may confuse both patients and associated health care providers, who are logically looking for consistency in the choice of best available care and comparison of treatment outcomes might be difficult to interpret. The disagreement in choosing treatment modalities in patients with liver tumors starts already with the evaluation of resectability,<sup>9</sup> which sets the goal for a curative versus palliative approach.<sup>10</sup> We postulated that the educational background of individual surgeons, including exposure to LT, country-related surgical culture, and experience in different surgical strategies might affect the choices of surgical strategies among experts.

Currently, no data is available assessing the magnitude of such postulated discrepancies among worldwide experts. The aim of this study was to evaluate surgical approaches in the presence of CRLM among expert liver surgeons around the globe. The evaluation was based on a clinical vignette study of 10 cases with different complexity. Inasmuch as general surgeons initially see many of these patients, we also presented these cases to this group and assessed their attitude in treating or referring complex cases to expert centers.

## PATIENTS AND METHODS

### Study Design

The design is based on a clinical case study of 10 cases with CRLM sometimes associated with lung metastases. All cases were treated at the coordinating center (University Hospital Zurich) and were carefully selected to cover a broad spectrum of tumor scenarios in the liver. The extent of the disease ranged from single metastasis to diffuse bi-lobar lesions (Fig. 1). We grouped the complexity of the cases in 2 categories defined as (a) low complexity cases including oligometastatic disease in the liver, not involving larger vessels and limited to one hemi-liver (cases 1–4) and (b) high complexity cases with multiple bi-lobar metastases, and/or involving major liver vessels (cases 5–10). In 6 cases, the primary colorectal tumor had already been removed.

We selected only noncirrhotic patients without major comorbidities to focus the decision-making on the oncologic approaches and particularly the surgical strategies. An interactive online platform (SurveyMonkey) was used to present each respective case including the relevant medical history of the patient, as well as scrollable magnetic resonance imaging scans with arterial and venous phases as well as axial and coronal views (Fig. 1).

Cases were presented in detail to 43 expert liver surgeons from 23 countries in four continents. Experts were identified on the basis of their academic contributions to the field of liver surgery, that is, with publications in high impact factor journals, and performing major liver resections for at least 10 years. Some of them were or had been also involved in a LT program. Invitation was sent personally by the senior author (PAC) via email to each selected expert including a description of the study aims and methodology. Reminders were sent in absence of response exceeding 2 weeks. The survey was completed anonymously, and importantly participants agreed to perform the evaluation of each respective case exclusively by themselves, and in no circumstances to delegate this task to junior colleagues.

Experts were asked for their demographic data, detailed previous medical education, involvement in LT, and the focus of their surgical practice covering hepato-biliary surgery only or also LT, or other fields of surgery. These questions were followed by the detailed presentations of the 10 cases along with respective questions on different therapeutic strategies (Supplementary material 1, <http://links.lww.com/SLA/C446>). To fully complete the survey, each participant was asked to answer 137 questions in total.

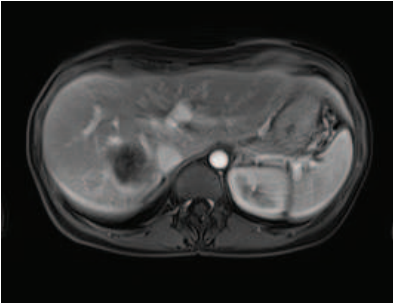
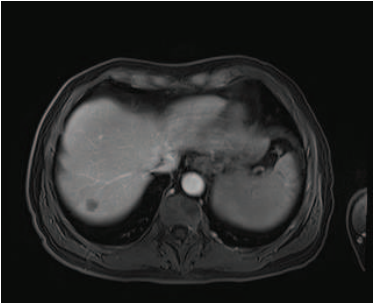
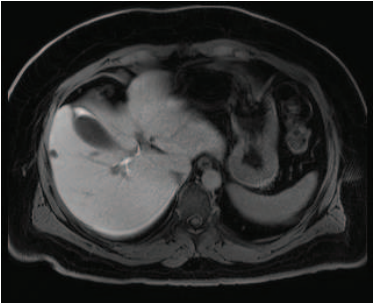
Along with the degree of agreement among experts for each respective case, a subgroup analysis was performed assessing potential factors influencing the decision-making of surgical approaches.

To test how general surgeons treat patients with CRLM and whether they refer to expert centers, we sent a slightly adjusted survey to 60 general surgeons located in Switzerland, South Korea, Japan, and USA. Criteria for general surgeons included the lack of focus on liver diseases working at nonacademic centers. This group of surgeons was identified by the respective local coauthors of the study.

### Statistical Analysis

We used median and interquartile range (IQR) to describe continuous data, and numbers and proportions to describe categorical data. Fisher exact test was used to test for associations between categorical variables.

To test the interrater agreement among expert liver surgeons, we used the free-marginal multirater kappa test which is a chance-adjusted index of agreement for multirater categorization of nominal variables for each case.<sup>11</sup> Agreement levels range from 0 to 1, with 0 describing absolutely no agreement among participants and 1

<p><b>Case 1*</b></p>	<p>48-year-old female patient with synchronous rectal cancer liver metastasis. The primary tumor is asymptomatic. The patient did not receive any treatment so far</p>	 <p>Hypointense lesion in Segment VII</p>
<p><b>Case 2*</b></p>	<p>65-year-old male patient with metachronous sigmoid cancer liver metastasis. Left hemicolectomy performed one year ago. No adjuvant chemotherapy was given</p>	 <p>Lesion with central fibrotic component in segment VII</p>
<p><b>Case 3*</b></p>	<p>46-year-old male patient with synchronous hepatic metastasized right colon tumor. After 4 cycles of systemic therapy with FOLFOXIRI and Bevacizumab restaging showed a regression of the liver metastases as well as the primary</p>	 <p>Lesions in segment V/VI, V and VI</p>

**FIGURE 1.** Description of the cases. \*Low complexity cases.

indicating a 100% agreement. Agreement levels were defined as follows:  $\kappa$  level 0.00–0.20 none, 0.21–0.39 minimal, 0.40–0.59 weak, 0.60–0.79 moderate, and 0.80–0.90 strong, above 0.90 almost perfect.<sup>12</sup> Calculations were done in SPSS 24.0 for Mac (SPSS Inc, Chicago, USA) and in online Kappa Calculator.<sup>13</sup>

## RESULTS

### General Characteristics of Expert Liver Surgeons

Thirty-eight (86%) of the 43 invited expert liver surgeons completed the full evaluation of the ten cases, 16 surgeons (42%) were from Europe, 11 (29%) from the USA, 6 (16%) were from Asia,

and 5 (13%) from South America. The median time to complete the survey was 126 minutes (IQR: 34–175 minutes).

Thirty-five participants (92%) held a leading position as Department or Section chiefs with a median clinical experience of 25 years (range: 14–39 years) in liver surgery. Most of them ( $n = 30$ , 79%) were working in specialized centers performing more than 100 cases of liver surgery per year. Their practices focus on hepato-pancreato-biliary (HPB) surgery with 25 (68%) of them additionally performing LT. More than half of participants ( $n = 23$ , 61%) had completed a formal fellowship training in HPB or LT surgery and most ( $n = 31$ , 82%) do currently run a fellowship program at their department.

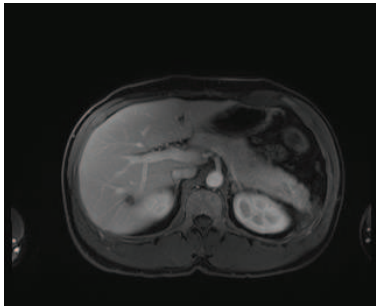
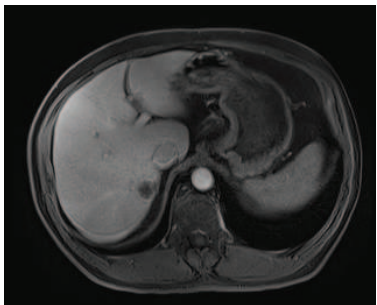
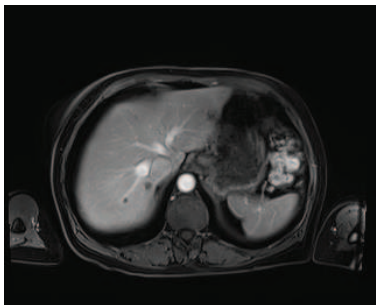
<p><b>Case 4*</b></p>	<p>41-year-old male patient with synchronous hepatic metastasized rectum cancer. As the primary was already symptomatic rectum resection was performed by an open approach without any neoadjuvant systemic therapy. After rectum surgery 6 cycles of systemic therapy with FOLFOXIRI and Bevacizumab were given</p>	 <p>Lesions in Segment VI/VII</p>
<p><b>Case 5</b></p>	<p>61-year-old male patient with synchronous rectal cancer liver metastases. After short time protocol radio/chemotherapy robotic rectum resection was performed 6 month ago followed by 7 cycles of chemotherapy with FOLFOX. Steatotic liver parenchyma (Total 40%; macrovesicular steatosis 20%)</p>	 <p>Lesions in segment II, IVb, V, VI and VII</p>
<p><b>Case 6</b></p>	<p>72-year-old male patient with synchronous hepatic metastasized right colon tumor. As the colon tumor was symptomatic laparoscopic right hemicolectomy was performed 4 month ago (TNM: pT4 pN1b (3/21) cM1 V1 R0) followed by 4 cycles adjuvant chemotherapy with FOLFIRI and Cetuximab</p>	 <p>Lesions in segment II, V (2), V/VI, V/VIII, VII and VIII</p>

FIGURE 1. (Continued)

Regarding manipulation of the liver volume, all 38 experts have portal vein embolization (PVE) available at their center and one third (n = 13, 34%) have used hepatic vein embolization on occasions. Most (n = 36, 95%) experts were familiar with techniques of 2-stage hepatectomies with 2 thirds of them (n = 27, 71%) having performed Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS). Moreover, one third (n = 13, 34%) have performed LT in selected cases of CRLM. Concerning the oncologic approach most, but surprisingly not all, experts (n = 30, 79%), routinely discuss their patients at interdisciplinary tumor boards in their institutions.

### Variability in Selecting Therapeutic Strategies Among Experts

Inter-rater agreement among experts regarding therapeutic decision was overall none to minimal. This observation was particularly significant in high complexity cases. Some almost perfect agreement was, however, observed such as the evaluation of resectability in low complexity cases (median  $\kappa = 1.00$ ), which dropped to a  $\kappa$  of 0.71 (IQR 0.35–0.82) in high complexity cases. For example, the most complex case (number 10) was considered to be resectable by only two third (n = 24) of experts. The percentages of experts

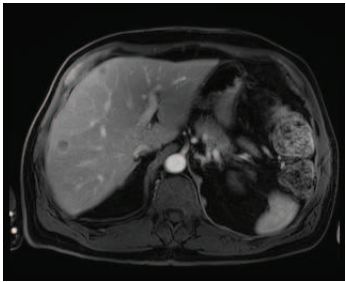
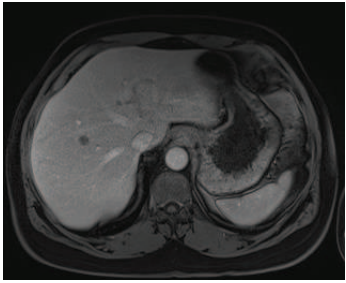
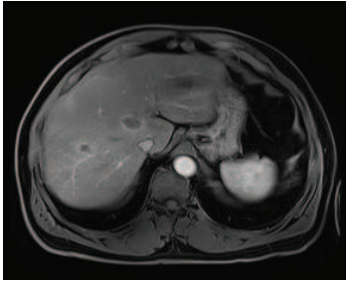
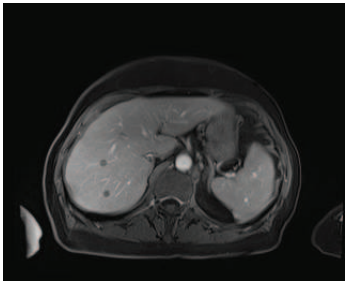
<p><b>Case 7</b></p>	<p>60-year-old male patient with metachronous rectal cancer liver metastases. After short time of radio-/chemotherapy, a laparoscopic rectum resection was performed 6 month ago, followed by 3-month adjuvant chemotherapy with FOLFOX</p>	 <p>Lesions in segment IVa (3 lesions), VI/VII and VIII</p>
<p><b>Case 8</b></p>	<p>61-year-old male patient with synchronous bilobar hepatic and pulmonary metastasized rectum cancer. After 6 cycles of systemic chemotherapy with FOLFIRINOX and Bevacizumab all liver metastases show a good response. Rectum first approach was chosen, and rectum resection was performed several weeks ago</p>	 <p>Multiple bilobar liver lesions (&gt;9)</p>
<p><b>Case 9</b></p>	<p>57-year-old male patient with synchronous hepatic metastasized left sided colon tumor. Neoadjuvant therapy with 6 cycles of FOLFIRI and Cetuximab did show a good response of the liver metastases. The primary is asymptomatic</p>	 <p>Lesions in segment IVa, V, VI, VII and VIII (2). Two suspected lesions in segment II</p>
<p><b>Case 10</b></p>	<p>65-year-old female patient with synchronous hepatic and pulmonal metastasized right sided colon cancer. Neoadjuvant chemotherapy with 6 cycles of FOLFOXIRI and Bevacizumab show a remission of the tumors in the liver as well as lung. The pulmonary nodules are 5 and in resectable locations</p>	 <p>Multiple metastasis in segment II, III, V, VI, VII, VIII</p>

FIGURE 1. (Continued).

**TABLE 1. Agreement (Percentage) Among Experts for Each Clinical Case**

	1*	2*	3*	4*	5	6	7	8	9	10	All (IRQ)
Resectability (Yes/No)	100	100	100	100	95	95	97	84	89	63	96 (88–100)
Initial treatment (surgery, chemotherapy)	53	84	97	97	82	86	58	83	86	68	84 (66–89)
Approach (open, minimally invasive)	71	63	58	46	92	89	95	94	100	96	91 (62–95)
Portal vein embolization (Yes/No)	92	100	79	100	89	68	95	75	57	52	84 (65–96)
Preoperative volumetry (Yes/No)	71	97	66	95	79	57	84	56	81	67	75 (64–87)
Type of surgery (2-stage, 1-stage)	100	100	95	100	89	62	92	62	44	44	91 (58–100)
Type of resection (anatomical, parenchyma sparing)	47	82	47	61	81	49	51	56	79	60	58 (49–80)
Ablation in combination with resection (Yes/No)	97	97	76	92	50	62	55	51	65	56	64 (54–93)

\*Low complexity cases.

**TABLE 2. Inter-rater Agreement Among Experts for Each Clinical Case**

	1*	2*	3*	4*	5	6	7	8	9	10	All (IRQ)
Resectability (Yes/No)	1.00	1.00	1.00	1.00	0.80	0.80	0.89	0.45	0.61	0.04	0.85 (0.57–1.00)
Initial treatment (surgery, chemotherapy)	0.11	0.45	0.89	0.89	0.38	0.52	0.00	0.43	0.51	0.10	0.44 (0.11–0.61)
Approach (open, minimally invasive)	0.16	0.11	0.00	0.02	0.69	0.52	0.80	0.77	1.00	0.84	0.61 (0.09–0.81)
Portal vein embolization (Yes/No)	0.70	1.00	0.32	1.00	0.60	0.10	0.80	0.23	0.01	0.04	0.46 (0.09–0.85)
Preoperative volumetry (Yes/No)	0.16	0.89	0.08	0.79	0.32	0.01	0.45	0.02	0.36	0.08	0.24 (0.07–0.54)
Type of surgery (2-stage, 1-stage)	1.00	1.00	0.80	1.00	0.59	0.03	0.69	0.03	0.06	0.00	0.64 (0.03–1.00)
Type of resection (anatomical, parenchyma sparing)	0.45	0.38	0.02	0.02	0.36	0.01	0.03	0.02	0.40	0.09	0.06 (0.02–0.39)
Ablation in combination with resection (Yes/No)	0.89	0.89	0.26	0.69	0.03	0.03	0.02	0.03	0.06	0.03	0.05 (0.03–0.74)

\*Low complexity cases. Agreement levels (*kappa*): 0.00–0.20 none, 0.21–0.39 minimal, 0.40–0.59 weak, 0.60–0.79 moderate, 0.80–0.90 strong, above 0.90 almost perfect.

choosing the same strategy for each clinical case are shown in Table 1.

The inter-rater agreement in choosing the surgical access, open versus minimally invasive, varied from moderate (median  $\kappa = 0.79$ , IQR 0.65–0.88) in high complexity cases, with 91% (n = 32) of the experts opting for an open approach, to none (median  $\kappa = 0.07$ , IQR 0.01–0.15) in low complexity cases.

A minimal to weak agreement was also observed regarding the use of PVE, and preoperative measurement of future liver remnant before proceeding to surgery (PVE median  $\kappa = 0.46$ , IQR 0.09–0.85, volumetry median  $\kappa = 0.24$ , IQR 0.07–0.54). Surprisingly, even in high complexity cases, no agreement was found in the use of PVE or preoperative assessment of the future liver remnant (PVE median  $\kappa = 0.17$ , IQR 0.03–0.65, volumetry median  $\kappa = 0.20$ , IQR 0.02–0.38).

When analyzing expert’s strategy to perform 1- versus a 2-stage hepatectomy, perfect agreement was expectedly documented in low complexity cases with all experts opting for a 1-stage approach. No agreement could be, however, documented in complex cases with a median of only 35% (n = 12) of participants selecting a 2-stage procedure.

Other surgical therapeutic strategies such as the type of resection (anatomical vs parenchyma sparing), and the combination of ablative strategies during surgery also did not show any agreement among expert liver surgeons (Tables 2 and 3).

**Factors Influencing Treatment Decisions**

In low complexity cases, inter-rater agreement was moderate to almost perfect in most of the groups, except surgical approach (open vs minimally invasive), type of resection (anatomical vs parenchyma sparing) and preoperative assessment of the future remnant liver. Therefore, we restricted the subgroup analysis to the 6 high complexity cases. We investigated factors, which could have influenced therapeutic choice of each expert, such as demographic origin, formal fellowship training, focus of surgical practice (HPB alone vs HPB + LT), or hosting official fellowship training at the respective centers.

Experts from Europe and South America evaluated liver metastases in high complexity cases as resectable in almost all cases, whereas several experts from Asia and North America upfront denied surgical curative options. The choice for resection of the presented cases was rated equally by experts, irrespective of the completion a previous formal fellowship.

Experts with surgical focus on HPB and LT chose PVE and 2-stage hepatectomies more frequently than experts limiting their practice to HPB surgery (PVE 30%, IQR 10–62 vs 20%, IQR 6–39, 2-stage hepatectomy 41%, IQR 13–70 vs 27% IQR 0–44).

**Characteristics and Attitudes of General Surgeons**

A modified survey aimed at addressing referral practices was completed by 60 general surgeons, whose practices does not focus on hepatic surgery. This included 20 surgeons from Asia (Japan and Korea), 16 from Europe (Switzerland) and 24 from North America

**TABLE 3. Inter-rater Agreement Among Experts in Low and High Complexity Cases [Median (IQR)]**

	Low Complexity	High Complexity
Resectability (Yes/No)	1.00 (1.00–1.00)	0.71 (0.35–0.82)
Initial treatment (surgery, chemotherapy)	0.67 (0.20–0.89)	0.41 (0.08–0.51)
Approach (open, minimally invasive)	0.07 (0.01–0.15)	0.79 (0.65–0.88)
Portal vein embolization (Yes/No)	0.85 (0.42–1.00)	0.17 (0.03–0.65)
Preoperative volumetry (Yes/No)	0.48 (0.10–0.87)	0.20 (0.02–0.38)
Type of surgery (2-stage, 1-stage)	1.00 (0.85–1.00)	0.05 (0.02–0.62)
Type of resection (anatomical, parenchyma sparing)	0.20 (0.02–0.43)	0.06 (0.02–0.37)
Ablation in combination with resection (Yes/No)	0.79 (0.37–0.89)	0.03 (0.03–0.04)

Agreement levels (*kappa*): 0.00–0.20 none, 0.21–0.39 minimal, 0.40–0.59 weak, 0.60–0.79 moderate, 0.80–0.90 strong, above 0.90 almost perfect.



(USA). The median clinical surgical experience of this group was 15 years (range: 1–36 years). Interestingly, 3 quarters of surgeons ( $n = 12$ ) from Switzerland regularly perform liver surgery, and even indicated past experience in assisting or performing 2-stage hepatectomies at academic centers. In contrast only 3 surgeons (15%) in Asia and 4 surgeons (17%) in North America are involved in liver resections. About 90% of general surgeons (14/16) in Switzerland responded that they refer on occasion complex cases to expert centers, whereas this figure dropped to 71% in North America and 60% in Asia.

## DISCUSSION

This study investigated how expert liver surgeons with strong academic background offer therapeutic strategies for various degree of involvement of CRLM, the most frequent type of liver metastases worldwide. Although we suspected some discrepancies, we observed unexpected major disagreements ranging from the choice of minimal invasive liver resections, to combination of liver resection with PVE, or the use 2-stage hepatectomies. The reasons affecting the choice of highly varying therapeutic strategies remain largely unclear, but possibly involve both the type of training of the respective surgeons and loco-regional institutional considerations. This data is important demonstrating that established surgical experts have obviously different interpretations of existing recommendations or guidelines. This may be also caused by a current lack of high evidence studies, which was well discussed at the last European Surgical Association meeting.<sup>8</sup>

Several features seem highly relevant in the interpretation of this analysis. First, our survey achieved a participation of 86%, which we consider as exceptional based on a lower response rates observed on most online studies in the medical field, ranging between 20% and 40%.<sup>14,15</sup> This high compliance seems particularly remarkable considering that completion of the evaluations of the 10 cases required 2 hours or more for each expert. Secondly, our interrater analysis relied on the kappa test that presents one of the most commonly used statistical tools to assess the degree of agreement among raters. We selected on purpose cases of CRLM, the fourth most deadly cancer worldwide, also representing a well-studied condition for a long time with countless publications in many disciplines, and the availability of many guidelines.<sup>16,17</sup> In addition, the case restriction to CRLM increased the homogeneity of the studied field in contrast to a mix with other liver tumors such as Hepatocellular carcinoma with potential underlying liver disease and portal hypertension. We were, therefore, surprised to find so many low levels of agreement among established experts in the field. Third, the disagreement on therapeutic strategies was not only observed in high complexity cases involving multi-modality approaches, but also in low complexity cases, for example regarding the choice of open versus minimal invasive approaches. Finally, we tested whether general surgeons do refer CRLM patients, particularly the complex cases, to expert centers. We found that many patients with complex CRLM are never offered appropriate referrals to dedicated expert centers, a practice which runs counter to the collective literature that has established that patients with CRLM treated by specialized HPB teams are more likely to undergo curative resection and enjoy long-term survival.<sup>18</sup>

It remains unclear which factors most affect the reported choices for the treatment. In a subgroup analysis of all 38 participating experts, we identified a trend of geographic factors with more “aggressive” surgeons from Europe and South America in deciding to embark in complex resection strategies, such as ALPPS than their colleagues from Asia or USA. Those surgeons were also more often involved in a parallel liver transplant program. In this respect, exposure to a formal fellowship training may additionally impact on practice of experts.<sup>19</sup> In other areas, it has been shown for example, that formal HPB fellowships are associated with significant

difference in the approach of postoperative complications including fistula after pancreatico-duodenectomies.<sup>20</sup> In the current study, it is more difficult to detect differences because we targeted senior experts with more than 10 years of experience in liver surgery, which may buffer the impact of a formal training at this stage of their career.

Other studies have also underlined inconsistencies of decision-making in the treatment of CRLM.<sup>10,21</sup> For example, a recent study assessing resectability of CRLM on computed tomography scans reported substantial disagreement among Dutch experienced liver surgeons.<sup>10</sup> Similar observations have been reported by a national survey across Canadian HPB surgeons focusing on surgical practice patterns with high variations regarding the choice of the technique for liver transection, the use of Pringle maneuver, blood conservation strategies and postoperative pain management.<sup>21</sup> In the current study, we extended this observation to the use of different tools to treat a variety of CRLM. For example, we failed to show any agreement on the use of PVE before surgery, the assessment of preoperative volumetry to predict the size of the future liver remnant, and the type of resection (parenchymal sparing vs anatomical resection). There was also a high variability in proceeding with combined primary and secondary tumor ablation for synchronous metastases or selecting ablation techniques to treat CRLM.

In a second part, we tested how general surgeons are involved with liver surgery and whether they would refer complex cases of CRLM to expert centers. This topic is of high relevance, because many patients may not be offered adequate therapies or a curative surgery, and misleadingly presented at local multidisciplinary tumor boards (MTB) for palliative approaches only. Such risk is perhaps even higher in health care system lacking centralization policies.<sup>22,23</sup> It is obviously difficult to gather sufficient and validated data on this highly sensitive topic. We therefore selected a snapshot approach in 2 high-level medicine countries in Asia, in the USA and Switzerland. In none of these countries, centralization is reinforced by law. Interestingly, two third of the participating general surgeons in Switzerland reported regular involvement with liver surgery, even with past or current exposures with 2-stage hepatectomies, although this figure dropped to less than 20% in both Asiatic countries and the USA, where they admit low level of expertise with liver tumors. As counter-intuitive to these different local practices, most Swiss surgeons mentioned that they regularly refer their complex cases to expert centers, whereas only two third of the responders from Asia and the USA supported referral to experts. We are tempted to interpret this data as precarious because either general surgeons engage in complex liver surgery, rather than referral to the local experts, or despite low interest in resecting livers they might not refer their liver tumor patients to centers. This suggests that many patients with complex CRLM may never be offered proper expertise from expert multidisciplinary centers. This needs clearly larger scale studies to better assess the magnitude of the issue and how this may relate to the various health care systems

This study contains inherent limitations. First, only academic liver surgeons with publications in the field were invited, opening the possibility of biases from their own contributions. Other experts at nonacademic centers may have responded differently. Second, the participation of 38 senior experts may not allow detecting all factors affecting choices of therapy because the subgroup analysis was not adequately powered. Inevitably, opinions of experts are influenced by personal experience and local expertise from other disciplines. Importantly, the study focused on the surgical aspects of complex oncologic scenarios ignoring the contribution of other participants to MTB. The real world of decision-making in oncologic conditions includes oncologists, gastroenterologists, interventional radiologists etc. We would argue, however, that surgeons set the therapeutic goals

of targeting a cure or a palliative approach. Thus, it might be of interest to test the high discrepancies observed in this study in multidisciplinary decisions. Surprisingly, however, a fifth of participating experts do not discuss their patients at tumor boards. Although there is no doubt that MTBs have a key role in decision-making of interdisciplinary tumor treatment, the study was designed for the scenario of how surgeons would choose their surgical strategy of tumor eradication when MTB would recommend surgery.

Finally, the analysis of the attitude of general surgeons could have been biased by the selection of the participants by the experts, but here we would expect even more deficit of referral from unknown general surgeons. We also suspect that some patients with colorectal liver metastasis are seen by general practitioners or oncologist first and may be directly referred to expert centers without being seen by the general surgeons. How this could affect the referral pattern remains unclear.

In conclusion, choices of therapeutic strategies among expert liver surgeons actually look like “a throw of the dice.” This alarming data should trigger major efforts in establishing guidelines of standard of care, and recommendations to protocol any deviation from standard care. In this setting, registries are important to prospectively collect data, and enable international analysis contributing to constructive consensus conferences and the design of widely accepted guidelines.

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