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ORIGINAL ARTICLE

Pan-European survey on current treatment strategies in patients with upfront resectable colorectal liver metastases

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Abstract

Background: There is a lack of consensus on the definition of upfront resectability and use of perioperative systemic therapy for colorectal liver metastases (CRLM). This survey aimed to summarize the current treatment strategies for upfront resectable CRLM throughout Europe.

Methods: A survey was sent to all members of the European-African Hepato-Pancreato-Biliary Association to gain insight into the current views on resectability and the use of systemic therapy for upfront resectable CRLM.

Results: The survey was completed by 87 surgeons from 24 countries. The resectability of CRLM is mostly based on the volume of the future liver remnant, while considering tumor biology. Thermal ablation was considered as an acceptable adjunct to resection in parenchymal-sparing CRLM surgery by 77 % of the respondents. A total of 40.2 % of the respondents preferred standard perioperative systemic therapy and 24.1 % preferred standard upfront local treatment.

Conclusion: Among the participating European hepato-pancreato-biliary surgeons, there is a high degree of consensus on the definition of CRLM resectability. However, there is much variety in the use of adjunctive thermal ablation. Major variations persist in the use of perioperative systemic therapy in cases of upfront resectable CRLM, stressing the need for further evidence and a consensus.

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Introduction

Approximately 50 % of patients with colorectal carcinoma have metastatic disease confined to the liver (CRLM).[1] Long remission has been reported for resectable CRLM, supporting the curative intent of local treatment.[2,3] However, the definition of resectability is not standardized and may vary depending on the experience of the multidisciplinary team.[4,5] The definition of R0-resectability depends on technical-anatomical aspects, but over the years, biological aspects have also been taken into account.[4,5]

Different treatment modalities are used to treat upfront resectable CRLM.[2,6,7] In most studies, surgery appeared to be the most popular option for long-term survival. However, over the past decades, minimally invasive image-guided techniques, such as thermal ablation, have been increasingly used as alternatives to surgical resection in cases of difficult anatomical localization for resection. This avoids extensive resections and consequently helps to maintain a sufficient remnant liver.[6,7]

Unfortunately, the majority of patients still develop a recurrence of CRLM after the first local treatment.[8,9] To decrease recurrence rates, the use of (neo-) adjuvant or postoperative systemic therapy is recommended by international cancer networks and the European Cancer Society (ESMO) in patients with unfavorable oncological criteria.[10,11] Peri-operative systemic therapy aims to eradicate micrometastatic disease, decrease the recurrence rate, and improve survival outcomes.[12,13] Different systemic therapy regimens, mainly extrapolated from adjuvant experience, have shown conflicting results with improvements in disease-free but not overall survival.[14–16] With a lack of definitive evidence on superiority, a deficit of international consensus on the optimal treatment of upfront resectable CRLM remains.

This survey aims to provide insights into the current views on the treatment of upfront resectable CRLM among surgeons and their tumorboards across Europe. These data could support strategies to analyse and further improve clinical research on treatment strategies for CRLM.

Materials and methods

Target group

The survey was sent by email to all members (approximately 1200 members) of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA) using SurveyMonkey ((https://MonkeySurvey.com)). Two reminders were sent to non-responders.

Survey

The survey was conducted between March 2022 and July 2022 and consisted of 42 questions. The survey started with general information on the demographics of the respondents and their experience of liver surgery. It continues with the role of different local treatment strategies (ablation, resection, and stereotactic body radiation therapy (SBRT)), the definition of the future liver remnant, definitions of technical anatomical resectability, parameters for resectability, patient-related characteristics, tumor biology (metachronous, mutation status, number and size of metastases), use of systemic therapy, treatment strategies for synchronous CRLM, use of multidisciplinary team meetings, and interests in future research. The survey was overseen by the E-AHPBA Innovation and Development Committee in collaboration with the authors. The E-AHPBA supports educational and scientific activities from its members and therefore introduced the 'educational pyramid' (i.e., platinum, gold, silver, and blue seal activities) to categorize and provide the most suitable support for a course, meeting, or clinically relevant study project. The complete survey can be found in Supplemental 1.

Definitions

The term 'upfront resectable' is used throughout the manuscript as a description of a CRLM eligible for local treatment strategies such as surgical resection and/or thermal ablation and/or SBRT without prior systemic therapy.

Statistical methods

Data were analyzed using IBM SPSS Statistics for Windows version 28.0 (IBM Corp., Armonk, NY, USA). Normally distributed continuous data are presented as mean and standard deviation (SDs). Non-normally distributed continuous data were presented as medians and interquartile ranges or 95% confidence intervals (CIs). Categorical (binary, nominal, and ordinal) data are presented as frequencies and percentages. Statistical significance was defined as a two-tailed P-value <0.05.

Results

Respondents' characteristics

A total of 105 surgeons from 24 countries participated in the survey, and 87 respondents completed the survey. Table 1 shows respondents' characteristics. The median age of the responding surgeons was 45.2 years (SD, 8.5), with varying years of experience as attending surgeons. Overall, 66 (62.9 %) surgeons were employed at university medical centers, 35 (33.3 %) at teaching hospitals, and four (3.8 %) at community or independent centers.

Definition of resectability of CRLM

Table 2 demonstrates a summary of the outcomes of the questions about the definition of resectability. First, the technical and anatomical criteria for resectability were investigated. A summary of the questions is demonstrated in Table 2. When asked about the maximum number of CRLM to be considered resectable, the vast majority of respondents (99 %) stated that they had abandoned the traditional definition for resectability of <4 metastases.[17–19] Only 29 % of respondents gave a maximum number that they would consider resectable, namely median 12 CRLM (range, 5–25). The remaining 71 % of respondents stated that there was no place for the maximum number. The

Table 1 Respondents' characteristics

Characteristics	N = 105
What is your age?	45.2 (SD 8.5)
How many years have you been working as an attending surgeon? (Post-surgical training/fellowships included)	
<5 years	21 (20. %)
5–10 years	31 (29.5 %)
11–15 years	18 (17.1 %)
16–20 years	11 (10.5 %)
>20 years	23 (21.9 %)
In what type of medical center are you working?	
University	66 (62.9 %)
Teaching hospital	35 (33. %)
Community/independent	4 (3.8 %)
How many liver resection do you perform per year?	
0	3 (3.2 %)
<20	22 (21 %)
20–40	30 (28.6 %)
41–60	23 (21.9 %)
61–100	10 (9.5 %)
>100	9 (8.6 %)
In which country do you work?	
Austria	6
Belgium	6
France	3
Finland	1
Greece	9
Germany	9
Hungary	1
Ireland	2
Italy	9
the Netherlands	11
Norway	3
Portugal	3
Poland	3
Russian Federation	2
Spain	14
Sweden	6
Swiss	3
Turkey	2
United Kingdom	4
Other	8

respondents were asked how to define technical-anatomical resectability; 48.6 % of the respondents stated that the definition should consist of complete macroscopic resection and maintaining ≥30 % future liver remnants. A total of 17.1 % of respondents stated that upfront R0/R1 resection of all hepatic lesions covered the definition of technical-anatomical resectability. Only 6.7 % of the respondents defined technical-anatomical resectability as only preservation ≥30 % of the future liver remnant.

The mean minimum standardized future liver remnant (sFLR) used in different hospitals for resectability in the case of a healthy livers was 28.7 % (SD, 4.7). The sFLR in cases of preoperative chemotherapy and a cirrhotic/cholesteric liver, were respectively 35.9 % (SD, 5.8) and 45.2 % (SD, 7.9).

Tumor biology was considered in the decision-making process for upfront resectability by 91.6 % (76/83) of the respondents. Thereafter, respondents were asked which parameters they used to define potential negative tumor biology, and answers were as follows: 60.9 % synchronous onset of the disease, 72.4 % resectable extrahepatic disease, 39.1 % uni- vs. bilobar disease, 54.0 % RAS mutation, 51.7 % BRAF mutation, 37.9 % Mismatch Repair (MMR) status, 34.5 % sidedness of the primary tumor, and 21.8 % risk scores. Parameters that were added by the respondents themselves were the response to preoperative therapy (3.4 %), oncological markers (1.1 %), and timing of occurrence of the metastasis (2.3 %).

A total of 55.2 % stated that technical-anatomical resectability and tumor biological criteria, as mentioned above, are considered as the two most important parameters for upfront resectability. The other respondents chose only technical-anatomical resectability (15.2 %) as the most important parameter and the remaining tumor-biological criteria alone (5.7 %).

The contributions of patient characteristics were presented to the respondents. A total of 93.1 % (81/87) of the respondents specified that patient characteristics were used in the decision regarding local resectability. Parameters used in the case of patient characteristics were as follows: age (65.5 %), performance status (ECOG/WHO) (75.9 %), ASA classification (54.0 %), underlying liver disease (79.3 %), Charlson comorbidity index (35.6 %), patient's wishes (2.3 %), and nutritional status (3.4 %).

Role of thermal ablation

The availability and application rates of different local treatment strategies are shown in Table 3. Surgical resection and thermal ablation were available for most respondents. However, SBRT is not readily available.

The use of thermal ablation varied considerably among the respondents. In 7.2 % of respondents, thermal ablation was only used when lesions were ineligible for surgical resection. Of the respondents, 77 % considered thermal ablation suitable as an adjunct to resection as a parenchymal-sparing treatment strategy in cases of deeper lesions. Only 2.4 % of the respondents stated that thermal ablation and surgical resection were equally suitable, independent of the location of the lesion. If thermal ablation was used in the respondent's hospital, the mean maximum size of the CRLM eligible for thermal ablation was 3.35 cm (SD, 0.9).

Table 2 Results of the definition of resectability among the respondents'

Definition of resectabiliy	
In the past resectability was defined by up to 4 metastases. Is this definition still used for the majority of cases in your center?	Missing 21
Yes	(99 %)
No	(1 %)
If yes, what number do you consider appropriate?	Missing 24
…(Median, (range))	12 (5–25)
No absolute number, volume of remnant function liver is more important	71 % of the respondents'
How do you define technical anatomical resectability	Missing 21
Upfront R0/R1 resection of all hepatic lesions is possible	18 (17.1 %)
≥30 % estimated future liver remnant of healthy liver tissue (non-cirrhotic, non-steatotic)	7 (6.7 %)
Complete macroscopic resection is feasible, while maintaining at least a ≥30 % future liver remnant	51 (48.6 %)
Tumor distribution (scattered or clustered, mono- or bilobar)	2 (1.9 %)
Other definition, …	6
Does your MDT include tumor-biology in decision making on resectability/ablatability?	Missing 22
No	7 (8.4 %)
Yes	76 (91.6 %)
What is the most important parameter for local treatment (resectable/ablatable)?	Missing 22
Technical-anatomical resectability/ablatability	16 (15.2 %)
Oncological criteria (number of lesions, presence or suspicion of extra hepatic disease, FONGscore)	6 (5.7 %)
Both	58 (55.2 %)
Other	3
Does your MDT take patient-related characteristics into account for resectability/ablatability?	Missing 22
No	6 (6.9 %)
Yes	81 (93.1 %)

Role of systemic therapy in upfront resectable CRLM

Treatment of upfront resectable CRLM

When investigating the role of systemic therapy in upfront resectable CRLM, 40.2 % (35/87) of the respondents stated that they treated patients with perioperative systemic therapy and local treatment, 24.1 % (21/87) of the respondents treated patients with upfront local treatment without any systemic therapy, 13.8 % (12/87) of them treated the patients with local treatment and adjuvant systemic therapy, and 4.6 % (4/87) of them stated that they treated the patients with neoadjuvant systemic therapy and local treatment. A total of 6.9 % (6/87) of the respondents stated that they used all the aforementioned in daily practice, and their choice of treatment depended on the biological characteristics of the tumor. Fig. 1 shows the distribution of different treatment strategies across Europe; notably, different treatment strategies are applied in different countries.

The choice of systemic therapy regimen differed among the respondents and was as follows: 31.0 % (27/87) chose double/triplet chemotherapy with anti-vascular endothelial growth factor (VEGF) therapy, 19.5 % (17/87) chose doublet chemotherapy, 11.5 % (10/87) chose triplet chemotherapy, and 14.9 % (13/87) chose doublet/triplet chemotherapy with anti-epidermal growth factor receptor (EGFR) therapy. A total of 11.5 % (10/87) of respondents stated that the choice of chemotherapy depended on the mutational status. Similarly, the duration of neoadjuvant systemic therapy differed among responders: 39.1 % (34/87) treated the patients for three months prior to surgery, 33.3 % (29/87) for two months, and 12.6 % (11/87) for best response. Of the respondents, 4.6 % (4/87) mentioned that they received 4–6 cycles of neoadjuvant treatment.

When asked if immunotherapy is a treatment option for MMR-deficient tumors, 44.8 % stated that it is only used in specific cases, 17.1 % stated that it is used as the standard of care for metastatic disease, and 17.1 % stated that they did not use immunotherapy.

The waiting period after cessation of systemic therapy until liver resection depended on the regimen used but was within 5 weeks in the majority of the centers.

A multidisciplinary team meeting (MDT) is the standard of care to evaluate the treatment strategy, with three-quarters of the respondents having at least one participating radiologist, oncologist, and liver surgeon, half of whom also had a colorectal surgeon, radiation oncologist, and an interventional radiologist present during their discussions.

Table 3 Local treatment strategies availability and usage for the respondent

Is resection for resectable colorectal liver metastases performed in your hospital?	Missing 6
Yes	97 (92.4 %)
No	2 (1.9 %)
What percentage of all local treatment for colorectal liver metastases is performed by resection?	Missing 6
<20 %	9 (8.6 %)
21–40 %	5 (4.8 %)
41–60 %	22 (21 %)
61–80 %	31 (29.5 %)
81–100 %	31 (29.5 %)
Is ablation a strategy of local treatment for resectable colorectal liver metastases performed in your center?	Missing 17
Yes	58 (55.2 %)
Yes, but only in case of technical difficulty for surgical resection	26 (24.8 %)
No	4 (3.8 %)
What percentage of local treatment for colorectal liver metastases is performed by ablation alone?	Missing 19
<20 %	63 (60 %)
21–40 %	17 (16.2 %)
41–60 %	3 (2.9 %)
61–80 %	2 (1.9 %)
81–100 %	1 (1 %)
What is the role of ablation as adjunct to CRLM resection	Missing 22
No role, ablation is only applied if lesions are technically non-resectable	6 (5.7 %)
In combination with resection for lesions <1 cm when deeper seeded as part of parenchymal sparing surgery	5 (4.8 %)
In combination with resection for lesions <2 cm when deeper seeded as part of parenchymal sparing surgery	25 (23.8 %)
In combination with resections for lesions <3 cm when deeper seeded as part of parenchymal sparing surgery	45 (42.9 %)
As equal to resection in lesions <3 cm irrespective of their localization in the liver	2 (1.9 %)
Other, …	10
What percentage of local treatment for colorectal liver metastases is performed by a combined ablation/resection strategy?	Missing 18
<20 %	54 (51.4 %)
21–40 %	26 (24.8 %)
41–60 %	3 (2.9 %)
61–80 %	4 (3.8)
81–100 %	0
Is SBRT a strategy of local treatment for colorectal liver metastases performed in your center?	Missing 19
Yes	41 (39 %)
No	45 (42.9 %)

Considerations in case of synchronous CRLM

Treatment strategies for synchronous CRLM with colon cancer have also been investigated. 16.1 % (14/87) of the respondents stated that they used a liver-first strategy, 55.2 % (48/87) performed a simultaneous resection of CRLM and the primary colon tumor, and 3.4 % (3/87) performed a colon-first strategy (besides emergency casuistry of symptomatic severe anemia, obstruction, etc.). Looking at the use of systemic therapy, 25.3 % (22/87) of the respondents used neoadjuvant/perioperative systemic therapy as a treatment strategy for synchronous CRLM. A total of 17.2 % (15/87) respondents stated that the choice of treatment strategy was based on patient and biological characteristics, and these were neoadjuvant/perioperative treatment and alternate synchronous resection, liver-first resection, or resection of primary colon tumor first. The favored treatment strategies for synchronous metastasized colon cancer are listed in Table 4.

The same question was asked for patients with synchronous rectal tumors. A total of 34.5 % (30/87) of the respondents stated that liver-first was the main treatment strategy, 3.4 % (3/87) treated the primary rectal tumor first (besides emergency presentation), 32.2 % (28/87) favored a synchronous resection. Neoadjuvant/perioperative systemic therapy in the treatment

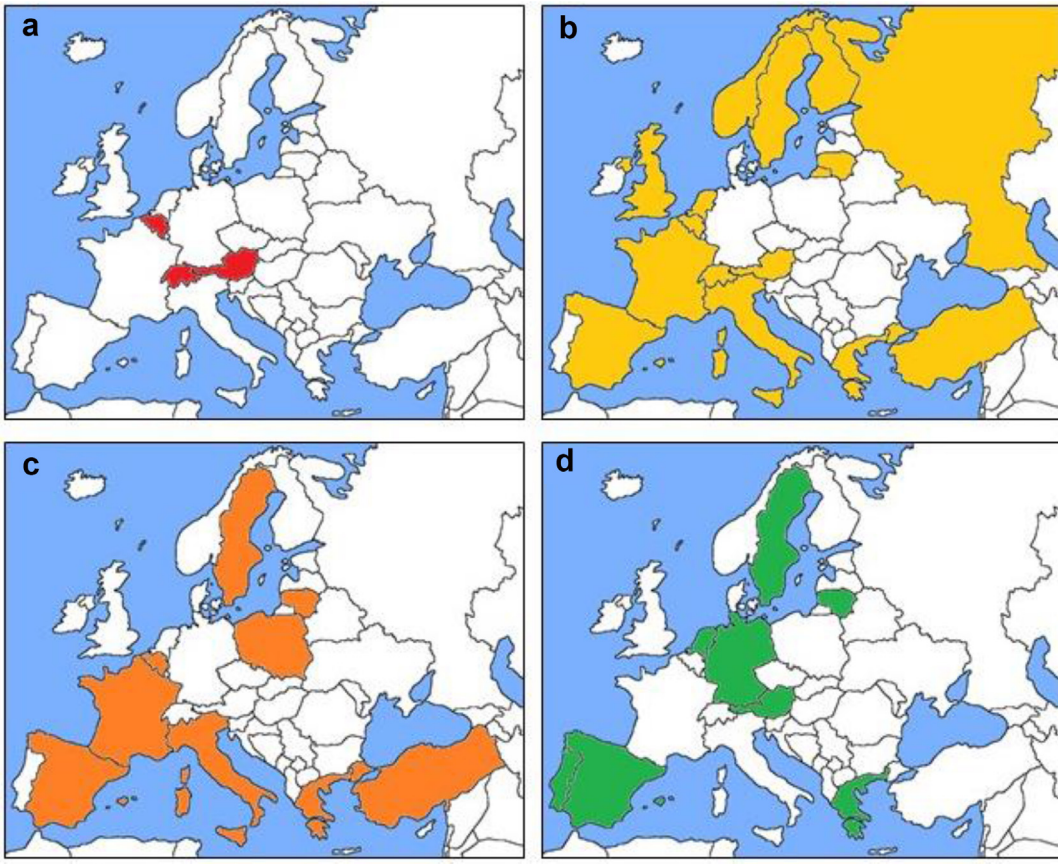

Figure 1 Overview of different treatment strategies stratified by country. (a) Neoadjuvant chemotherapy and local treatment; (b) Perioperative chemotherapy and local treatment; (c) Adjuvant chemotherapy and local treatment; (d) Local treatment without chemotherapy

strategy was used by 20.7 % of the respondents. The favored treatment strategies for synchronous metastasized rectal cancer are shown in Table 5.

Discussion

This survey demonstrated the variability of practices in patients with upfront resectable CRLM across Europe. There is a consensus in the assessment of whether CRLM is upfront resectable; both technical, anatomical, and oncological criteria are considered. However, wide variability exists in the indications for thermal ablation and the use of systemic treatment for upfront resectable CRLM.

Similar to the survey respondents, the ESMO guidelines define resectability based on technical and oncological criteria. The oncological criteria are described in the ESMO guidelines in terms of the number of lesions, presence of extrahepatic disease, and the Fong score. In contrast, survey respondents often did not

Table 4 Different treatment strategies for synchronous metastasized colon cancer

Treatment strategy for synchronous colon cancer	Missing 30
Liver first	16.1 % (14/87)
Neoadjuvant/perioperative systemic therapy followed by synchronous resection in case of a minor liver resection	18.4 % (16/87)
Neoadjuvant/perioperative systemic therapy followed by synchronous resection in case of a major liver resection	6.9 % (6/87)
Primary colon tumour first	3.4 % (3/87)
Synchronous resection in case of minor liver resection	17.2 % (15/87)
Synchronous resection in case of major liver resection	8.0 % (7/87)
Treatment strategy based on patient and biological characteristics	17.2 % (15/87)

Table 5 Different treatment strategies for synchronous metastasized rectal cancer

Treatment strategy for synchronous rectal cancer	Missing 29
Liver first	25.3 % (22/87)
Neoadjuvant/perioperative systemic therapy followed by synchronous resection in case of a minor liver resection	16.1 % (14/87)
Neoadjuvant/perioperative systemic therapy followed by synchronous resection in case of a major liver resection	5.7 % (5/87)
Primary colon tumour first	3.4 % (3/87)
No synchronous resection in case of rectal cancer	6.9 % (6/87)
Short-course radiotherapy followed by synchronous resection in selected cases of minor liver resection	9.2 % (8/87)
Short-course radiotherapy followed by synchronous resection in selected cases of major liver resection	2.3 % (2/87)
(Chemo) radiotherapy and liver first strategy in the waiting time for the rectal rumour.	9.2 % (8/87)
Treatment strategy based on patient and biological characteristics	8.0 % (7/87)

find the number of lesions to be an absolute limit. The presence of extrahepatic metastasis and high-Fong score variables were deemed relevant.

According to the ESMO guidelines, the treatment strategy should be directed towards complete resection; however, the guidelines do not provide a firm consensus on the use of systemic treatment strategies. This can be the result of multiple published studies on multimodal treatment strategies for resectable CRLM; however, none of them demonstrated an overall survival benefit. Systematic reviews and meta-analyses[13,20–23] have attempted to clarify the benefits of perioperative systemic therapy for resectable CRLM; however, due to the need for adequately powered studies, it is difficult to make conclusive statements. The most widely cited randomised trial is the EORTC 40983 trial by Nordlinger *et al.*, which found no statistically significant difference in overall survival with the addition of perioperative chemotherapy (FOLFOX4) compared to surgery alone for patients with resectable CRLM; median overall survival 61.3 months [CI, 51.0–8.34] for the perioperative systemic therapy group vs. 54.3 months [CI, 41.9–79.4] for the surgery-only group. Although the trial was a priori not powered to detect an overall survival benefit[15] it demonstrated a progression-free survival (PFS) benefit for eligible patients median PFS, 20.9 months [CI, 17.1–28.9] for the perioperative chemotherapy group vs. 12.5 months [CI, 9.7–18.2] for the surgery-only group ($P = 0.035$), which was the primary endpoint after 3 years. The JCOG0603 trial by Kanemitsu *et al.* demonstrated a significant 2.6 year-absolute improvement in DFS (4.3 vs. 1.7 years) with adjuvant mFOLFOX6; however, there was a numerical trend towards a worsening 5-year OS of 71.2 % in the adjuvant group compared to 83.1 % in the surgery alone group.[16] A poor tolerance to mFOLFOX6 was observed in this trial, with only 36 % of the patients completing all planned 6 treatment months due to severe adverse effects. The authors argued that this may have led to a disadvantageous effect on the overall survival, and based on the significant prolongation of DFS, argued for a shorter post-operative treatment period (e.g., 3 months). Similarly, the postoperative component of mFOLFOX4 in the EORTC 40983 trial had a lower completion rate.

A notable outcome in the survey is that 15 % of the respondents used anti-EGFR therapy despite recommendations in the ESMO guidelines, disadvising the use of targeted agents during perioperative therapy. *Bringwater et al.* showed in a mature analysis of the New-EPOC trial that the overall survival was 26 months shorter for patients receiving cetuximab and chemotherapy than for those receiving chemotherapy alone.[24] Due to the closed questions of the survey, it was not possible for respondents to elaborate further on their answer. Future studies should evaluate the use of anti-EGFR therapy since the publication of the new European Society for ESMO guidelines.

Although available studies do not demonstrate improved overall survival of multimodal treatment strategies in resectable CRLM, the role of preoperative systemic therapy undoubtedly adds to the assessment of sensitivity of the tumor for specific regimens, helps to downsize CRLM, thereby reducing the required resection magnitude, and may also adequately diminish micrometastatic disease.[12,25] On the downside, it induces liver toxicity, potentially resulting in higher rates of inadequate future liver remnant after surgery.[26] It seems likely that the use of systemic therapy in resectable CRLM will become a personalized treatment strategy based on well-defined oncological parameters.

This study demonstrates the heterogeneity in the treatment of resectable CRLM between surgeons and different countries. The outcomes of large trials, such as EORTC 40983 and JCOG0603, might explain the lack of unanimity because of the significant improvement in PFS, but lack thereof in OS.[15,16] Additionally, the heterogeneity of the study population of the trials poses another challenge. Molecular and risk scores are becoming increasingly important for treatment strategy decisions. This highlights the need for well-conducted trials to obtain sufficient information for this discussion.

Thermal ablation was available for most respondents. Notably is the outcome that 77 % of the respondents used thermal ablation as adjunct to parenchymal-sparing treatment for deeper lesions and only 2.4 % stated that thermal ablation and surgical resection are equally suitable. The last decades series were published with comparable OS for thermal ablation in smaller lesions.[27,28] However, in this survey, thermal ablation was rarely

used as a local treatment, despite its minimally invasive nature. The COLLISION trial might provide more evidence for the standard use of thermal ablation for resectable and ablatable CRLM $\leq$3 cm.[29]

The results of this survey should be interpreted in light of several limitations. First, the variety of answers to the different treatment strategies demonstrated the difficulty in using a multiple-choice questionnaire. This was obviated by the option of clarification but may have caused even more heterogeneity. Second, no clinical outcomes were related to any of the different treatment strategies. The last limitation is the relatively low number of respondents and small mean number of respondents per country. Heterogeneity within countries may be under-represented because of the relatively limited number of respondents per country. The present survey tried to clarify the current perception and treatment policy for colorectal liver metastases. However, in overall, it was difficult to make a strong statement which could make influence for future studies or discussions. Our survey shows that there is a general agreement on resectability, based both on technical-anatomical criteria and tumor biology. Furthermore, the survey shows that there is still heterogeneity on treatment strategies, most based on one positive study supporting peri-operative chemotherapy which is 15 years old.[15] In this trial resectability criteria are used, which do not hold nowadays. Therefore the results of our survey should form the perfect basis for prospective observational studies and a multinational trial evaluating current best treatment practices.

Conclusion

Although there is general agreement between surgeons on the definition of resectability, there is large variability in the current views on the treatment of upfront resectable CRLM across Europe. Heterogeneity in treatment practices is specifically prevalent in the choice of systemic therapy, use of direct local treatment, and treatment strategies. Additional evidence clarifying the effects and indications of perioperative systemic therapy could help align the views on this topic, resulting in more standardized and personalized care.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2024.01.007.