Colorectal liver metastases: partial hepatectomy or thermal ablation

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COLORECTAL LIVER METASTASES:
PARTIAL HEPATECTOMY OR THERMAL ABLATION

Robbert Staffan Puijk

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COLORECTAL LIVER METASTASES: PARTIAL HEPATECTOMY OR THERMAL ABLATION

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. J.J.G. Geurts,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op dinsdag 7 november 2023 om 13.45 uur
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De Boelelaan 1105

door
Robbert Staffan Puijk
geboren te Zeist

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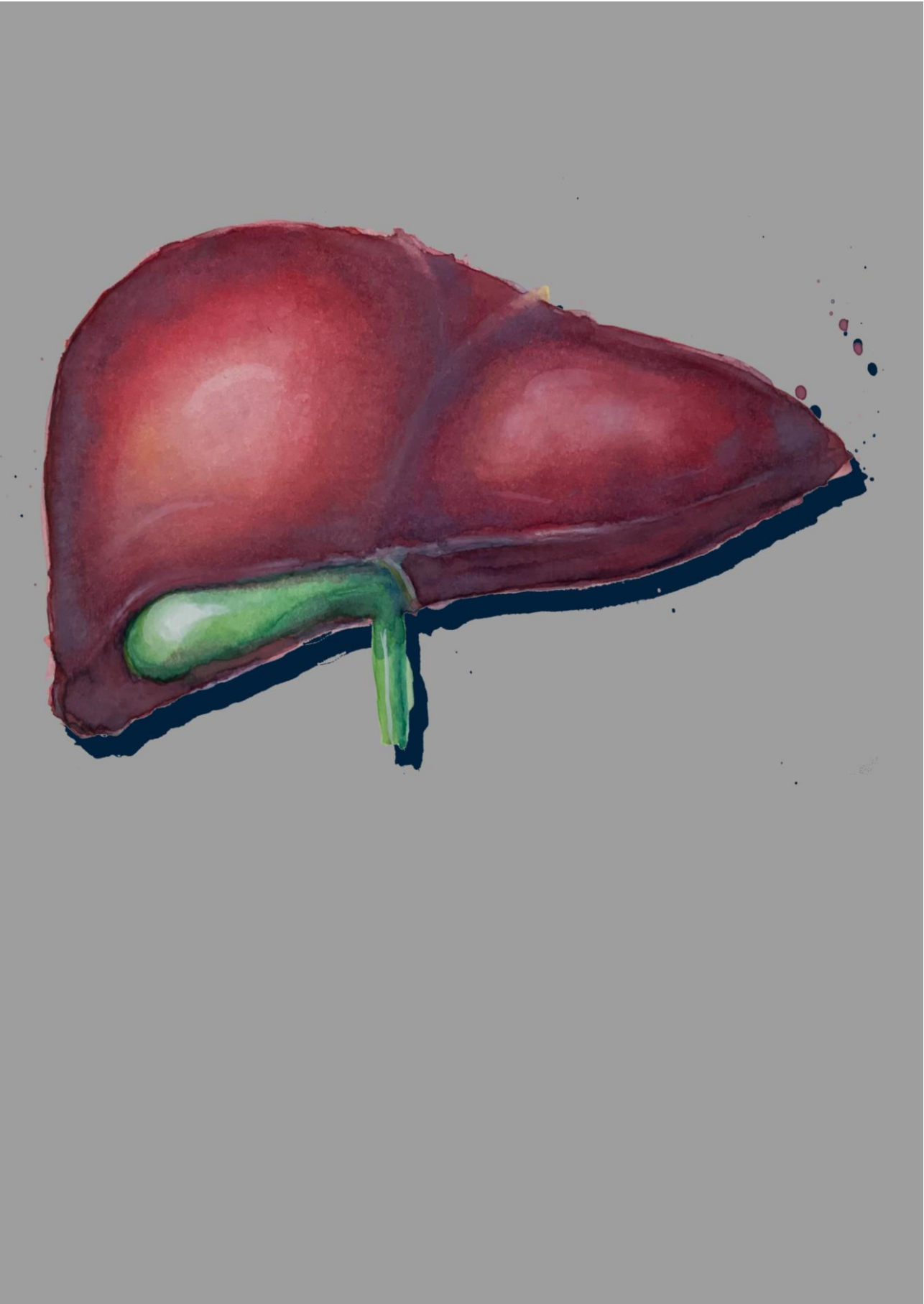
	prof.dr. J.J. van der Vliet

Voor mijn ouders

"If I have seen further, it is by standing on the shoulders of Giants"

Isaac Newton (1643-1727)

CONTENTS



GENERAL INTRODUCTION

AND THESIS OUTLINE

The existence of the liver was already described in the Greek mythology, where the liver was seen as the “seat of life” - the central organ in both Gods and humans.[1] The foundation of medicine started with the philosophy of Hippocrates (c. 460-377 BC) and Claudius Galenus (c. 130-201 AD), who also, although to a limited extent, defined the first anatomical characteristics of the liver as a central organ in human beings. Their philosophy has dominated medical understanding and practice for over fifteen centuries. More detailed anatomical observations in humans followed much later when Andries van Wesel (1515-1564), better known as Andreas Vesalius, presented the widely adopted first, systematic anatomical atlas: *Humani Corporis Fabrica* in 1543 (Figure 1). A change from dogmatic thinking to scientific thinking. In his work the liver was illustrated in its true shape: a two-lobed organ.

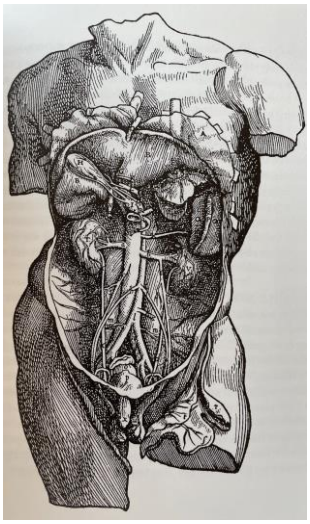


Figure 1. Humani Corporis Fabrica Libri Septum, Bazel (Oporinus), 1543, boek V, fig. XX (1).

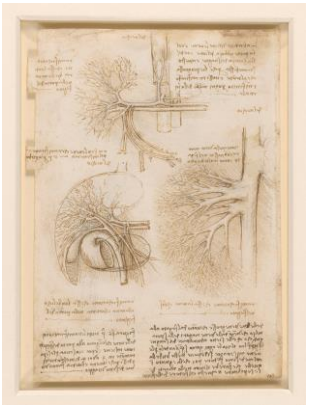


Figure 2. Illustrations of the liver and surrounding vascular structures by Leonardo da Vinci, 1507. From Clayton and Philo 2017, p. 95)

Almost parallel to Vesalius, the universal intellect from the Renaissance, Leonardo da Vinci (1452-1519), also made an essential contribution to the further examination and knowledge of the liver as a crucial organ by performing an autopsy on a deceased centenarian man (Figure 2). In the eighteenth century, physiology became an important new progress within the field of medicine, with Albrecht von Haller (1708-1777) and Claude Bernard (1813-1878) being the forefathers of the modern liver physiology by demonstrating that the liver contributes to the metabolic processes involved in digestion.

A small jump in time to the second half of the nineteenth century, where it became possible to perform abdominal surgical procedures under general anesthesia. However, after this milestone, the liver remained a forbidden area for surgeons due to the high risk of serious hemorrhage due to its extensive vascularization. In the following century, the introduction of imaging modalities, such as X-ray, ultrasound and computed tomography, was the most important development in the more minimally invasive treatment of focal liver diseases.

The potential of angiographic catheters in performing minimally invasive non-diagnostic procedures was first highlighted in 1963 by Charles T. Dotter, who is still praised for the final introduction of the nowadays well-known percutaneous transluminal angioplasty technique (Figure 3).[2] It was four years later when Alexander Margulis introduced the concept "interventional radiology" – referring to an umbrella term for treatments using the same basic techniques, like abscess drainages, biopsies, central venous line insertion, etcetera. A step forward in time brings us to one of the latest developments in interventional radiology: the field of interventional oncology. This includes targeted minimally invasive, real-time image-guided, (loco)regional treatment options for a variety of cancer types and is nowadays known to be the fourth pillar in clinical oncological care, along with medical oncology, surgery and radiotherapy, and one of the fastest growing medical subspecialties in health care in general.[3-5]

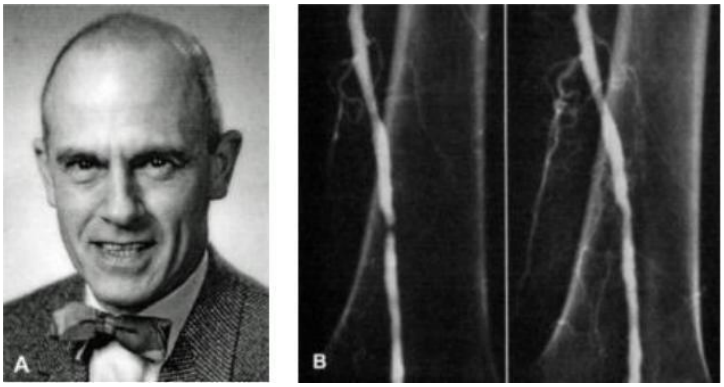


Figure 3. (A) Charles Dotter. (B) The first percutaneous transluminal angioplasty technique.

Within the arsenal of interventional oncology related anti-cancer therapies, the use of targeted minimally invasive image-guided tumor ablation, with radiofrequency ablation (RFA) and microwave ablation (MWA) being the most widely adopted methods, has expanded significantly over the last two decades.[5-7] These needle-guided treatment options are characterized by the local delivery of thermal energy at a high dosage directly affecting the tumor tissue in order to treat cancer more effectively.[8,9]

Oncological outcomes, such as safety, efficacy and survival time, of thermal ablation are most being studied in patients with primary and secondary liver malignancies, hepatocellular carcinoma (HCC) and colorectal liver metastases (CRLM) respectively, who underwent open surgical procedures. For patients with very early-stage HCC (BCLC 0, ≤2 cm), image-guided tumor ablation is already recommended when surgical options are precluded and has replaced resection in selected patients.[10] For patients with CRLM, the long-term results of the randomized controlled EORTC-CLOCC trial emphasized that thermal ablation has replaced the stand-alone treatment of chemotherapy and has been globally adopted as standard of care to eliminate unresectable small-size tumors (≤3 cm).[11] Despite this worldwide adoption and similar survival outcomes for patients treated with partial hepatectomy for CRLM[12-16], interventional radiology and surgical oncology societies generally state that thermal ablation cannot be considered an alternative to resection.

To date, thermal ablation is being performed as adjunct to liver resection or as stand-alone treatment when complete surgical removal of all metastatic sites is not feasible.[17,18] More specifically, for patients with an impaired performance status, high comorbidity score, history of extensive abdominal surgery, (loco)regional tumor progression after prior local liver treatment, and for patients with deep-seated anatomically unresectable tumors or with deep-seated anatomically resectable limited disease otherwise requiring major resection (parenchyma-sparing), thermal ablation offers a safe and effective means to eradicate smaller-size (≤3 cm) CRLM.[9,10,19]

Liver ablations can be performed via an open, laparoscopic or percutaneous approach.[18] The percutaneous approach is rapidly gaining popularity because of its minimally invasive parenchyma-sparing nature, favorable safety profile with a low complication rate (1.3% – 2.4%), acceptable efficacy rate (7.6 – 22.2%), and repeatability.[19-23] Periprocedural management has developed rapidly in terms of extensively upgraded device specifications, optimization of anesthetic techniques, use of real-time image guidance tools and 3-dimensional (3D) image fusion and ablation confirmation software platforms for quantitative volumetric assessment of the ablation zone.[19,24,25] These innovations should let to better tumor visibility, detection of surrounding critical structures, and more accurate real-time applicator guidance and ablation zone monitoring. Given all these advancements and the fact that the more recent series in literature report comparable survival outcomes of surgical

resection and thermal ablation, the ongoing debate for the best curative intent treatment option has revitalized and led to the situation that the golden standard, surgical resection, seems no longer be the only curative intent treatment option for upfront resectable smaller-size CRLM.

AIMS OF THIS THESIS

The studies in this thesis seek to answer the following main clinical issues: (1) 'In general, is it feasible to standardize time-to-event outcome measures in image-guided tumor ablation?', (2) 'What is the current status, in terms of long-term oncological outcomes, of thermal liver ablation in clinical practice for patients with CRLM?', (3) 'How can we further optimize periprocedural management in order to improve the local effectiveness of thermal liver ablation and thereby reduce LTP rates?', (4) 'Can thermal ablation eventually replace the present-day standard of care partial hepatectomy for patients with resectable small-size (≤3 cm) CRLM?'

THESIS OUTLINE

The first two chapters describe two documents that form either a novel foundation for standardized definitions of oncologic outcome measures in the scientific field of image-guided tumor ablation and a practical guideline and decision-tree of resectability and ablatability criteria.

Chapter 1 provides a consensus document proposing standardized definitions for a broad range of oncologic outcome measures in the scientific field of image-guided tumor ablation. It addresses recommendations on how to uniformly document, analyze, and report outcomes as well as when to assess outcomes per patient, per session, or per tumor. Furthermore, recommendations were given regarding definitions of starting and ending time, survival time, and time-to-event end points. These guidelines were developed to facilitate a clear interpretation of results and to standardize worldwide communication among researchers and clinicians.

Chapter 2 gives an overview of experts' recommendations regarding resectability and ablatability criteria for the treatment of CRLM, created by a multidisciplinary Delphi consensus study.

In **Chapter 3** the current treatment status for small-size (≤3 cm) and intermediate-size (3-5 cm) (un)resectable CRLM is given by means of two systematic reviews and meta-analyses. **Chapter 3.1** describes the current clinical status of systemic chemotherapy, and local treatment options thermal ablation (RFA and MWA) and partial hepatectomy in the treatment of CRLM. **Chapter 3.2** gives an overview of MWA, RFA, irreversible electroporation (IRE), and stereotactic ablative body radiotherapy (SABR) for intermediate-size (3-5 cm) unresectable CRLM.

Chapter 4 provides an overview of our clinical experience with thermal ablation in the treatment of CRLM. Data was obtained from the prospective Amsterdam Colorectal Liver Met Registry (AmCORE). A comparative study aimed to analyze long-term oncological (survival) outcomes following open and percutaneous thermal liver ablation in patients treated for CRLM over the last 10 years.

In **Chapter 5** a comprehensive overview of the technical features of thermal ablation systems is given for quality control and endpoint assessment purposes, as well as multiple supportive tools for the percutaneous approach, such as the use of real-time image guidance, 3D image fusion, ablation confirmation.

The results of our clinical studies regarding optimization of percutaneous liver tumor ablation are presented in the next two chapters.

Chapter 6 sums up the outcomes of three different anesthetic techniques in terms of local disease control, safety, and their effect on periprocedural perception of pain during percutaneous computed tomography (CT)-guided procedures in patients treated for primary and secondary liver malignancies.

Chapter 7 describes our clinical experience with the additional administration of intra-arterial, intrahepatic contrast agent during each percutaneous ablation procedure – the so called 'transcatheter CT hepatic arteriography (CTHA)' technique. **Chapter 7.1** shows a comparison of CTHA and conventional CT fluoroscopy guidance in percutaneous liver tumor ablation procedures, in terms of local disease control and safety. The clinical illustrations in **Chapter 7.2** highlight the additional value of CTHA guidance in terms of the ability to improve detectability of the liver tumor, detect additional tumors intraprocedurally, identify surrounding critical vascular structures, detect vanished tumors after induction chemotherapy, differentiate local tumor progression (LTP) from non-enhancing scar tissue, and to promptly detect and respond to iatrogenic liver hemorrhage. In **Chapter 7.3** two historical cohorts were compared in order to investigate the added diagnostic value of CTHA for the intraprocedural detection of previously unknown CRLM and the impact on the definitive treatment plan.

Chapter 8 involves the potential further implementation of thermal liver ablation in clinical day practice. **Chapter 8.1** presents the study protocol and design of the COLLISION trial. An international phase-III, randomized controlled trial that will explore potential non-inferiority of thermal ablation compared to surgical resection for patients with small-size (≤3 cm) resectable CRLM. Patients with at least 1 resectable and ablatable CRLM (≤3cm, also known as target tumor), up to ten lesions, a good performance status, no extrahepatic disease and no prior liver treatment are considered eligible. The primary endpoint is overall survival, according to an intention-to-treat analysis. Secondary endpoints were adverse events, mortality, local tumor progression-free survival, local control allowing repeat treatments, distant progression-free survival, length of hospital stay and assessment of quality of life and cost-effectiveness.

The results of the first pre-planned interim analysis (n = 200 randomized patients) of the COLLISION trial are presented in **Chapter 8.2.**

The following chapters, **Chapter 8.3** and **8.4**, underline the clinical relevance and necessity of this time-honored question: ‘‘thermal ablation or surgery for colorectal liver metastases?’’ In case thermal ablation comes out as non-inferior (i.e., equal or superior), a switch in treatment method will undoubtedly lead to a reduction in morbidity and mortality, length of hospital stay and incremental costs without compromising oncological outcome for patients.

In line with the objective of Chapter 8, **Chapter 8.5** shows a comparison of repeat thermal ablation and repeat surgical resection in patients with recurrent CRLM. Data was obtained from the AmCORE database with the intent to assess for safety, efficacy and survival outcomes of the two treatment options concerned.

Current knowledge and open issues regarding thermal ablation for small-size CRLM are discussed in a broader perspective in **Chapter 9**. The major findings in this thesis are summarized in **Chapter 10**.

Disclaimer

Chapter 8.2 is based on lectures and presentations given at CIRSE 2021 (virtual meeting), MIOLive 2022 (virtual meeting), Spectrum 2022 (Miami, United States), ECIO 2022 (Vienna, Austria), SIO 2022 (San Francisco, United States), ECR 2022 (Vienna, Austria), and NVIR Wetenschapsavond 2022 (Utrecht, the Netherlands). All data in this chapter belongs to the principle investigators of the trial. The data presented is publicly accessible via the websites of the conference organizations concerned and will be fully published when the study is completely finalized.

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CHAPTER 1

Standardized definitions of time-to-event end points in image-guided tumor ablation

1.1

Consensus guidelines for the definition of time-to-event end points in image-guided tumor ablation: results of the SIO and DATECAN initiative.

R.S. Puijk, M. Ahmed, A. Adam, Y. Arai, R. Arellano, T. de Baère, R. Bale, C. Bellera, C.A. Binkert, C.L. Brace, D.J. Breen, E. Brountzos, M.R. Callstrom, G. Carrafiello, J. Chapiro, F. de Cobelli, V.M.H. Coupé, L. Crocetti, A. Denys, D.E. Dupuy, J.P. Erinjeri, D. Filippiadis, A. Gangi, D.A. Gervais, A.R. Gillams, T. Greene, B. Guiu, T. Helmberger, R. Iezzi, T. Wook Kang, A. Kelekis, H.S. Kim, T. Kröncke, S. Kwan, M.W. Lee, F.T. Lee, E.W. Lee Jr, P. Liang, B.I. Lissenberg-Witte, D.S. Lu, D.C. Madoff, G. Mauri, M.F. Meloni, R. Morgan, G. Nadolski, G. Narayanan, I. Newton, B. Nikolic, F. Orsi, P.L. Pereira, U. Pua, H. Rhim, J. Ricke, W. Rilling, R. Salem, H.J. Scheffer, C.T. Sofocleous, L.A. Solbiati, S.B. Solomon, M.C. Soulen, D. Sze, R. Uberoi, T.J. Vogl, D.S. Wang, B.J. Wood, S.N. Goldberg, M.R. Meijerink

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ABSTRACT

There is currently no consensus regarding preferred clinical outcome measures following image-guided tumor ablation or clear definitions of oncologic end points. This consensus document proposes standardized definitions for a broad range of oncologic outcome measures with recommendations on how to uniformly document, analyze, and report outcomes. The initiative was coordinated by the Society of Interventional Oncology in collaboration with the Definition for the Assessment of Time-to-Event End Points in Cancer Trials, or DATECAN, group. According to predefined criteria, based on experience with clinical trials, an international panel of 62 experts convened. Recommendations were developed using the validated three-step modified Delphi consensus method. Consensus was reached on when to assess outcomes per patient, per session, or per tumor; on starting and ending time and survival time definitions; and on time-to-event end points. Although no consensus was reached on the preferred classification system to report complications, quality of life, and health economics issues, the panel did agree on using the most recent version of a validated patient-reported outcome questionnaire. This article provides a framework of key opinion leader recommendations with the intent to facilitate a clear interpretation of results and standardize worldwide communication. Widespread adoption will improve reproducibility, allow for accurate comparisons, and avoid misinterpretations in the field of interventional oncology research.

INTRODUCTION

Interventional oncology is one of the fastest growing disciplines in clinical oncology and health care in general.[1] Its success is chiefly based on the minimally invasive nature of the needle-, applicator-, and catheter-based image-guided procedures with lower complication rates, superior toxicity profiles, and often comparable or superior mid- and long-term oncologic outcomes compared with conventional treatment modalities such as surgical resection and systemic therapy.[2-7] In clinical oncology, the most objectively defined time-to-event end point to address clinical benefit is overall survival. However, a proliferation of pharmacologic treatments and dosing strategies has led to the use of surrogate end points to measure interim treatment efficacy. Depending on the disease setting, these include disease-free, recurrence-free, and progression-free survival; local tumor progression-free survival; organ-specific progression-free survival and distant progression-free survival; time to progression; time to local (tumor) progression and time to organ-specific progression; primary and assisted technique efficacy rates; local tumor progression rate; and local control.[8,9]

Throughout the interventional oncology literature, these survival terms are loosely defined and are often incorrectly used interchangeably. Accurate comparisons between studies are hampered by the heterogeneous and unclear reporting of oncologic outcome parameters, which includes variability in the interpretation and use of time-to-event end point terms and definitions of starting and ending times.

In 2014, Ahmed et al.[8] updated their keystone consensus report regarding the standardization of terminology and reporting criteria, improving the precision of communications in this field. Although their article and the supplement to the consensus document concisely mention that *(a)* reporting of overall survival from start of ablation and from time of diagnosis is required for all intermediate and long-term studies; *(b)* survival at specified time points and median survival times should be reported, as well as time to progression and progression-free survival; and *(c)* local time to progression and local (tumor) progression-free survival should be differentiated from organ-specific time to progression and progression-free survival, clear definitions and recommendations on how to use and interpret these parameters were not provided. Thus, in the field of image-guided tumor ablation, standardization of terms is required to facilitate effective communication.

The purpose of this modified Delphi consensus project was to provide standardized definitions of patient-, session-, and tumor-related parameters and to offer recommendations on how to uniformly collect, analyze, and report oncologic outcomes for patients treated with image-guided tumor ablation. This project is a collaboration between the Society of Interventional Oncology and the Definition for the Assessment of Time-to-Event End Points

in Cancer Trials Initiative, or DATECAN, group, whose final intention is to obtain harmonized consensus definitions that advance intersociety communications.[9]

STUDY METHODOLOGY

The initial methodology was developed and previously applied in four disease-specific projects, including pancreatic cancer,[10] sarcoma and gastrointestinal stromal tumor,[11] breast cancer,[12] and renal cell cancer[13] initiatives. Institutional review board approval was not required as this study does not involve human participants. This article should be considered a supplement to the standardization of terminology reporting criteria recommended by Ahmed et al.[8]

Coordinating committee

The coordinating committee (Table E1 [online]) was composed of Society of Interventional Oncology research committee members (M.R.M., S.N.G., M.A., M.C.S., J.C., J.P.E., G. Nadolski, I.N.), one representative from the Definition for the Assessment of Time-to-Event End Points in Cancer Trials Initiative (C.B.), one health economist (V.M.H.C.), two epidemiologists (V.M.H.C., B.I.L.W.), one study coordinator (R.S.P.), and one operations manager (T.G.). The coordinating committee was responsible for the methodologic protocol and conduct (M.R.M., R.S.P., S.N.G., M.A., M.C.S., J.C., J.P.E., G. Nadolski, I.N., C.B.), survey and questionnaires (all coordinating committee members), data collection and analysis (M.R.M., R.S.P., S.N.G., M.A., C.B., V.M.H.C., B.I.L.W.), and guideline and manuscript preparation (all coordinating committee members).

Evaluating committee

The coordinating committee reached out to at least one active board member of the following international scientific groups or organizations: Society of Interventional Oncology, Technology Assessment Committee of the Society of Interventional Radiology, Standard of Practice Committee of the Cardiovascular and Interventional Radiological Society of Europe, Interventional Oncology Sans Frontières Expert Panel, and Asian Society of Tumor Ablation. The board members were asked to provide us with a list of key opinion leaders. All potential participants in the evaluating committee (Table E2 [online]) were required to confirm that they had at least 5 years of experience in the field of clinical oncology research, published at least one article for a given cancer site, and participated in at least three clinical oncology trials. After having confirmed these requirements in the online questionnaire, all were asked

if they could think of further participants. A total of 62 key opinion leaders from Europe (*n* = 29), the United States (*n* = 25), and Asia (*n* = 8) working in 48 centers eventually joined the evaluating committee. Data on experts' demographics, such as year of birth, current job position, professional membership, country of residence, time (in years) working in the field of interventional oncology, and familiarity with oncologic outcomes metrics, were collected.

Literature review and questionnaire construction

A PubMed literature search resulted in a list of short-, mid-, and long-term oncologic outcome measures and time-to-event end points (Appendix E1 [online]). This list was used by the coordinating committee to generate the first questionnaire. The formal consensus method involved the following steps (Figure 1): *(a)* definition of problems, literature review, and appointing the experts' committees (by the coordinating committee); *(b)* development of definitions and recommendations (by the coordinating committee); *(c)* a three-round rating process and evaluation of responses (by the coordinating committee plus evaluating committee); *(d)* presentation of results and final attempt to reach consensus during in person teleconference; and *(e)* creation of a final report with definitions plus recommendations.

Consensus process

A modified Delphi consensus is a structured and validated measurement instrument used for evaluation of expert opinion on health and medical topics.[14] It has been widely used to establish consensus across a range of subject areas. The Delphi process formalizes the degree of agreement among experts by using a series of surveys that are iterated with feedback until consensus is reached.

The guidelines were developed in four coordinating committee meetings (April 2019, June 2019, October 2019, and January 2020). Two rating rounds and one in-person web-based conference call were scheduled to develop the recommendations. A total of three survey rounds, or fewer if consensus was reached sooner, were prechosen as this enables adequate reflection on group responses and is considered optimal to reach consensus. The questionnaires were internet-based and sent by e-mail. All panelists received a deadline for completing the survey and were sent weekly reminders to encourage participation.

Before the first round, panelists agreed to review three additional documents: *(a)* the standardization of terminology reporting criteria by Ahmed et al.[8], *(b)* the list of relevant definitions as suggested by the coordinating committee (Appendix E1 [online]), and *(c)* the key instructions for filling in the consensus document.

In round 1, statements were evaluated using a 9-point Likert scale (where 1 = totally disagree and 9 = totally agree) to produce stable findings in Delphi consensus projects (9). For each

statement, panelists were given a free-text response option. Relevant items previously defined by Ahmed et al.[8] were presented, and panelists were asked whether the items could use adjustments. Items with strong consensus were locked and archived. Consensus was considered strong if all responses to a certain item were between 7 and 9, allowing up to two outliers. Strong consensus for the remaining single-answer multiple choice questions was defined as having reached at least 80% agreement among panelists. Data were analyzed anonymously.

The first-round answers were gathered and reported back to the panelists in the second round, where panelists rated only those items for which consensus had not been reached. Based on the first-round dispersal of scores (minimum, maximum, and median scores), each panelist was encouraged to reassess his or her initial judgments. Finally, for items remaining without consensus, a third round was organized. This in-person teleconference, led by a representative of the coordinating committee (M.R.M.), involved members of the coordinating committee and evaluating committee. The remaining items were discussed, and a preliminary draft of the recommendations was composed for validation by all panelists.

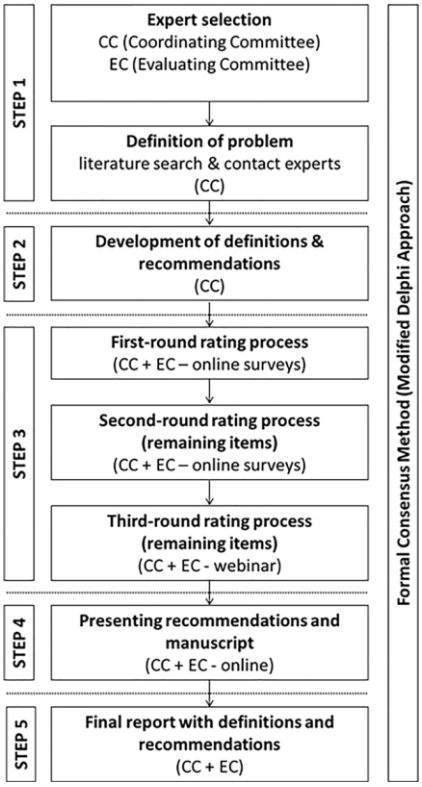

Figure 1. Flowchart of study design. The formal Delphi consensus method consisted of five steps: step 1, definition of problems, literature review, and appointing the experts' committees (by the coordinating committee [CC]); step 2, development of definitions and recommendations (by the coordinating committee); step 3, three-round rating process and evaluation of responses, including a final third round to reach consensus during a webinar (by the coordinating committee and evaluating committee [EC]); step 4, presentation of recommendations and manuscript to the evaluating committee; and, step 5, creation of the final manuscript.

RESULTS

The coordinating committee drafted a list of 62 key opinion leaders in the field of interventional oncology. Thirty-six of those 62 experts (58%) participated in the first round. All panelists are board-certified interventional radiologists. The panelists had an average of 20.9 years of experience (standard deviation, 7.7 years) in the field of interventional radiology, 11.1 years of experience (standard deviation, 7.7 years) in clinical trials serving as principal investigator, and 17.7 years of experience (standard deviation, 6.7 years) in clinical trials serving as collaborator. All panelists were familiar with oncologic outcome measures in their practice: 78% (28 of 36 panelists) always use them and 22% (eight of 36 panelists) use them occasionally. Additional detailed information regarding the panelists and their affiliated institutions is listed in Tables E1 and E2 (online). The experts rated a total of 62 items. A detailed comprehensive overview of the results, including all items and the level of agreement, is shown in Figure E1 (online).

Response rates were 58% (36 of 62 panelists), 56% (24 of 43 panelists), and 54% (23 of 43 panelists) in rounds 1 (July to October 2019), 2 (November 2019 to January 2020), and 3 (March 30, 2020), respectively. In round 1, consensus was reached on 27 of the 60 items (45%). The remaining 33 items were reiterated in the second round and two additional items, which emerged in the first round, were added. After two rounds, consensus was reached on 56 of the 62 items (90%). The remaining six items were discussed face-to-face in a videoconference (round 3; March 30, 2020). No consensus was reached regarding the recommended validated classification system to register complications, adverse events, quality of life, and health economics–related issues, although the panelists did agree to recommend the following statement: To document complications, adverse events, quality of life, and health economics–related issues, one should use and report the most recent version of a validated patient-reported outcome questionnaire.

In the first round, several panelists requested clarification regarding the use of the terms *to document, to analyze,* and *to report*. Accordingly, for future rounds the steering committee reached consensus regarding the following definitions: *(a)* to document means to collect and store patient-, procedure-, or tumor-related parameters in a centralized (preferably electronic, secure, and anonymized) study or registry database; *(b)* to analyze means to calculate, assess, and interpret congregated data derived from the documented patient-, procedure-, and tumor-related parameters; and *(c)* to report means to disclose the analyzed patient-, procedure-, and tumor-related parameters in relation to the study outcomes with the intent to publish one's findings.

The consensus items were translated into the following recommendations by the coordinating committee to which the evaluating committee anonymously agreed.

RECOMMENDATIONS

Addressing outcomes per patient, per procedure, or per tumor

When assessing time-to-event data in randomized controlled trials, single-arm prospective studies, and/or retrospective comparative and non-comparative series, the following definitions should be analyzed per patient and not on a per-tumor or per procedure basis: overall survival, disease-specific overall survival, disease-free survival, recurrence-free survival, progression-free survival, and distant progression-free survival (Table E3 [online]). Parameters that address both procedure-related adverse effects and direct costs should be addressed per procedure. This includes short-terms complications, anesthesia techniques, hospital-stay characteristics, and laboratory tests that, for example, assess organ function and the presence or absence of infectious complications. Technical success should be addressed per tumor and per procedure and not per patient. The term *session* can be used as a synonym for procedure. To assess the local efficacy of an ablative intervention, regardless of the oncologic outcome(s), one should address and report the following parameters per patient and per tumor: local tumor progression-free survival, time to local (tumor) progression, freedom from local or organ-specific recurrence, primary and secondary or assisted technique efficacy, residual disease, local progression, recurrence rates, and local control. Multiple index tumors (e.g., multiple colorectal metastases or multifocal hepatocellular carcinoma) within one unique patient cannot be regarded as independent as these tumors are potentially correlated and hence study outcomes hypothetically interlinked. When using standard survival estimates (Kaplan-Meier or cumulative incidence functions), in cases with multiple index tumors in one patient, the dependency of partially correlated or clustered data is ignored and this potential limitation should be reported and stated in the discussion.

Starting and ending time definitions

When assessing time-to-event data in randomized controlled trials, patients who did not receive the allocated treatment should be included in the intention-to-treat analysis. According to the intention-to-treat analysis, the starting time should be the date of randomization. In trials where all patients, regardless of the eventual randomization arm, are treated with induction or neoadjuvant therapy, randomization should be performed after completion of the neoadjuvant therapy. In addition, adding a per-protocol analysis should be considered, including only patients who actually received the allocated treatment, especially if a potential bias due to exclusion of patients exists. According to the specific per-protocol analysis, when assessing time-to-event data in randomized controlled trials, the starting time should also be the date of randomization. In addition, it should be considered to add data

regarding the time from the intervention, intervention is long or heterogeneous or if a large number of crossovers and/or patient dropouts exist.

For single-arm prospective studies and for retrospective comparative and noncomparative series, the starting time should be the date of the first intervention even if the therapy may require completion procedures (e.g., completion ablation for insufficient margins). In case of sequential procedures (e.g., a preplanned two stage ablation followed by transarterial chemoembolization), the starting time should be the date of the first intervention.

When focusing on single-arm prospective series, where patients receive strict and homogeneous neoadjuvant or induction chemotherapy and/or radiation therapy regimens, one should document the time from (a) the date of detection of disease (diagnosis), (b) the date of the start of neoadjuvant or induction therapy, and (c) the date of the first interventional procedure.

If the risk of including a certain referral bias, lead-time bias, or immortality-time bias is present, then one should report time-to-event data both from the date of diagnosis and from the date of the start of the intervention.

To assess mid- to long-term outcomes following a given interventional procedure, one should document (a) the date of unequivocal presence of the event and (b) the date of an alternative event that excludes or alters the probability for a future event to occur (competing risk). During follow-up after a given interventional procedure, one should separately document (a) the date of the last contact moment (e.g., laboratory tests, phone calls, consultations) that reliably confirms or excludes the presence of a given event, (b) the date of the last cross-sectional imaging or surrogate test that reliably confirms or excludes the presence of the event, and (c) (non)physical contact moments (e.g., non-tumor-specific laboratory tests, phone calls, consultations) that reliably exclude death, but not the presence or absence of disease.

Survival time definitions

If the patient's likelihood of dying from causes other than the disease being studied is substantial (e.g., as with elderly patients or those with early-stage disease with a good prognosis), one should document and report both overall survival and disease-specific overall survival. In the statistical analysis, death due to causes other than the disease being studied should be considered a competing risk for the disease-specific survival analysis.

For early disease stages, when the intervention is likely curative (e.g., ablation of small renal tumors), one should use recurrence-free survival. For intermediate disease stages, when the intervention is considered potentially curative (e.g., ablation of colorectal liver metastases),

one should use disease-free survival. For advanced disease stages, when the intervention is considered palliative, one should use progression-free survival.

Time to progression is defined as the time between the starting time and any disease recurrence (local, regional, or distant). Distant progression-free survival is defined as the time between the starting time and distant tumor progression, but not local or regional progression. Local tumor progression-free survival is defined as the time between the starting time and local tumor progression per tumor treated (per-tumor analysis) or per patient treated (per-patient analysis). Time-to-local (tumor) progression is defined as the time between the starting time and local tumor progression per tumor treated, resulting in a horizontally flipped survival curve (1 - local tumor progression-free survival). Death due to any cause without documented signs of local, regional, or distant disease progression should be considered a competing risk.

Time-to-event outcome definitions and data censoring

To calculate the survival probability, one should use the Kaplan-Meier survival estimate method, including the number of events and the numbers at risk at each evaluation time point. Cumulative incidence function curves are preferred or should be added to the Kaplan-Meier estimates if the number of competing risks in a certain (sub)group is substantial, showing the cumulative failure rates over time due to a particular cause. With respect to data censoring, one should report the type of data censoring (right-, left-, or interval-censored observations). The date of cross-sectional imaging or any other technique that unequivocally demonstrates a certain event should be considered the date of the event (left-censored data). Both for interim and final analyses, the date of assessment should be predefined either at a fixed point in time after inclusion of a certain number of individuals or after reaching a certain number of events. Any individuals remaining event-free and at risk should be right censored. Interval-censored observations, where a virtual halftime date between two cross-sectional imaging examinations is considered as the actuarial date of the event, should be avoided.

Eligibility

In prospective randomized and nonrandomized studies, the number of eligible patients (who fulfill the inclusion criteria and who do not meet the criteria for exclusion) should be documented and reported, as well as the number of eligible patients who eventually do not participate. If possible, the reason for nonparticipation (e.g., refusal or failure to meet the inclusion and exclusion criteria during work-up and/or during neoadjuvant or induction therapy) before formal recruitment (inclusion) should be documented and reported.

Recruited (included) patients who signed informed consent are considered active study participants during the predefined time they are "within the study." Active study participants who, for any reason (patient's wish to end study participation or loss to follow-up), fail to continue participation in the period predefined as "within the study" should be considered study dropouts, regardless of whether they dropped out before or after randomization.

If active study participants refuse to undergo the allocated treatment arm, then the patient undoes their trial enrollment. To eliminate any undesired impact on study-related outcomes, the investigators should formally end patients' active participation before they receive any alternative therapy. Patients who cross over from their allocated treatment arm to another study treatment arm, but who remain "within the study," should be regarded as crossover patients. The number of patients who cross over to another treatment arm should always be minimized.

Technical success, technique efficacy, local control, and ablation confirmation

Technical success addresses whether the tumor was treated according to protocol and covered completely by the ablation zone, if possible by using ablation confirmation techniques (see explanation below). One should document and report the technical success rates. Technique efficacy refers to a prospectively defined point in time when complete ablation of macroscopic tumor was achieved, as evidenced by imaging follow-up or any alternative technique (i.e., biopsy or serologic criteria). If a patient died due to any cause before that point in time, then the event should be analyzed and reported as a competing risk. Primary efficacy rate refers to the percentage of target tumors successfully eradicated following the initial ablation, whereas secondary or assisted technique efficacy rate refers to the percentage of target tumors eventually eradicated, including with repeat ablations, using the ablative method being studied. Local control is equivalent to assisted technique efficacy, with the exception that repeat treatments using alternative methods (other ablative methods, radiation therapy, or surgical excision) are allowed. Residual unablated tumor refers to the presence of residual viable tumor at the ablative margin at initial follow-up imaging, whereas local tumor progression refers to reappearing viable tumor provided that at least one contrast-enhanced follow-up study did not reveal residual viable tumor at the ablative margin.

Ablation confirmation refers to postprocedural imaging, or any alternative technique, that is implemented with the intent to allow for additional overlapping (completion) procedures either within the same procedure or in a complementary completion session in the days or weeks hereafter. For percutaneous ablations, one should attempt to document and report the minimum tumor-free margin. For CT-guided ablations, rigid or non-rigid image fusion and registration should be performed to confirm complete ablations, including circumferential safety margins of treated peri-ablational tissue.[8,15,16] One should attempt to report the method

of assessment of complete tumor coverage and safety margins (e.g., image fusion software) as close to the time of ablation as possible, ideally immediately, or at least within 24 hours after ablation.

Complications, adverse events, quality of life, and health economics–related outcomes

Complications, defined as any unexpected departure from a (post)procedural course, and adverse events, defined as any actual or potential injury related to a procedure, should be documented and reported, citing the most recent version of the used validated classification system so that they can be categorized consistently according to severity, time of occurrence (e.g., intraprocedural, postprocedural, or late), and likelihood of the event being related to the procedure. Although not meant to represent an exclusive list, the following classification systems are used to report complications and adverse events: *(a)* Common Terminology Criteria for Adverse Events standards, *(b)* Clavien-Dindo classification, *(c)* Society of Interventional Radiology classification, and *(d)* Cardiovascular and Interventional Radiological Society of Europe Quality Assurance Document and Standards for Classification of Complications.[17-20] In accordance with the previous standardization of terminology consensus document by Ahmed et al.[8], pain should be reported using the most recent version of the Common Terminology Criteria for Adverse Events of the National Cancer Institute.

Quality of life should be stratified according to disease stage and patient's functional status. One should document and specifically cite the most recent version of the validated classification system used. Quality of life should be assessed both before (baseline) and after treatment, regardless of disease progression. Although not meant to represent an exclusive list, the following standardized questionnaires have been issued for assessing the quality of life: *(a)* European Organization for Research and Treatment of Cancer, *(b)* Functional Assessment of Chronic Illness Therapy or Cancer Therapy, *(c)* World Health Organization Quality of Life scale (WHOQOL-BREF), *(d)* Health Utilities Index, *(e)* Short Form Health Surveys (SF-36, SF-12), *(f)* Nottingham Health Profile, *(g)* Quality of Well-Being Scale, and *(h)* Consumer Assessment of Healthcare Providers and Systems. Irrespective of the chosen method, one should always attempt to use general measures; cancer-, treatment-, and symptom-specific questionnaires; and non–cancer-specific (satisfaction) questionnaires.

For health economics–related outcomes, both a cost-effectiveness analysis and a comparative-effectiveness analysis are essential for defining the position of tumor ablation in relation to its alternatives. Health economics–related outcomes should be documented and reported, specifically citing the most recent version of a validated classification system used. Although not meant to represent an exclusive list, standardized questionnaires that can be used include the generic EuroQoL Group (Rotterdam, the Netherlands) forms for the

assessment of quality-adjusted life years (EQ-5D; EuroQol Group) and the Productivity and Disease Questionnaire, or PRODISQ, for the assessment of cost-effectiveness.

DISCUSSION

Over the past 2 decades, image-guided thermal and non-thermal tumor ablation techniques have become indispensable therapeutic options for a variety of cancer types. For certain smaller-size malignant tumors (e.g., hepatocellular carcinoma, colorectal and other liver and lung metastases, renal cell carcinoma, prostate cancer, and neuroendocrine tumors), international guidelines have already adopted thermal ablation as a first-line treatment option.[21-23] The continuing emergence of novel treatment options and growing demand for minimally invasive image-guided tumor ablation techniques have raised the need for evidence-based interventional oncology, and with that comes the need for clear documentation of oncologic outcome parameters.

The response rates in our study were 58%, 56%, and 54% in rounds 1, 2, and 3, respectively. After three rounds, consensus was reached for all items but three (95%; 59 of 62 items). Consensus was not reached for the preferred validated classification system to document, analyze, and report complications and adverse events, quality of life, and health economics–related issues. Nonetheless, the panelists unanimously agreed on the statement that "complications and adverse events, quality of life, and health economics–related issues should be documented and reported specifically citing the most recent version of the validated classification system used." Review of the literature and discussions within the committees made it clear that outcome assessment in interventional oncology can be challenging. To date, neither a specific outcome nor a specific outcome measure is a widely accepted standard tool in interventional oncology. The disproportionate interest in the local effectiveness of a certain ablative technique and the complexity of correctly analyzing treatment methods that can be repeated and that can be used to treat multiple index tumors in a single individual can explain this. However, it does not relieve treating physicians of their duty to provide hard and unequivocal evidence that our treatments prolong survival, improve quality of life, or reduce costs.

These guidelines for the definition of time-to-event end points have been developed as an in-depth supplement to the more concise standardization of terminology and reporting criteria in image-guided tumor ablation published by Ahmed and colleagues.[8] The participation of independent epidemiologists and members of the Definition for the Assessment of Time-to-Event End Points in Cancer Trials initiative study group and the large number of international key opinion leaders from various institutions in the expert panel, as well as the relatively high response rates for all survey rounds, strengthen our methodology and indicate its importance.

As stated by the Centre for Evidence-based Medicine, Delphi consensus studies are considered level 5 evidence.[24] As an anonymous technique, it prevents expert participants from conforming to the opinion of others.[25] Depending on the participant selection tools, the number of rounds and what to do in which round, the specific cutoff values applied, and whether to discuss with the experts has led to several variants of the original Delphi method. The coordinating committee chose to use the well-documented three-step modified Delphi consensus method as proposed by Jones and Hunter[14], which is also used in the development of various national clinical guidelines.

One potential drawback of our study was the relative homogeneity of the academic and professional background of the panelists (all interventional radiologists). This may impair the generalizability and validity of the recommendations made herein. Nonetheless, image-guided tumor ablation is most often performed by interventional radiologists, and the responsibility to attend multidisciplinary tumor boards, to have a thorough understanding of the guidelines and available evidence, to establish periprocedural care, and to provide robust evidence for new oncologic interventions has previously been emphasized by many, thus minimizing this limitation. General limitations of the Delphi consensus method are the lack of guidance and agreed standards on how to select participants and the fact that it is time-consuming and laborious for participants, which explains why it is vulnerable to dropouts. Participants might also drop out due to the long temporal commitment, distraction between rounds, or disappointment with the process.

This study provides a framework of key opinion leader recommendations regarding patient-, procedure-, and tumor-related definitions, starting and ending time definitions, survival time definitions, time-to-event end points, and patient-reported outcome measures. Clear definitions will provide the necessary foundation for scientific reproducibility between studies as they will ensure an objective and reliable interpretation of results, allow for accurate comparison of outcomes, and avoid misinterpretations. We encourage all of our colleagues to adopt the recommendations outlined in this proposal to facilitate worldwide communication of scientific advances in the field of interventional oncology.

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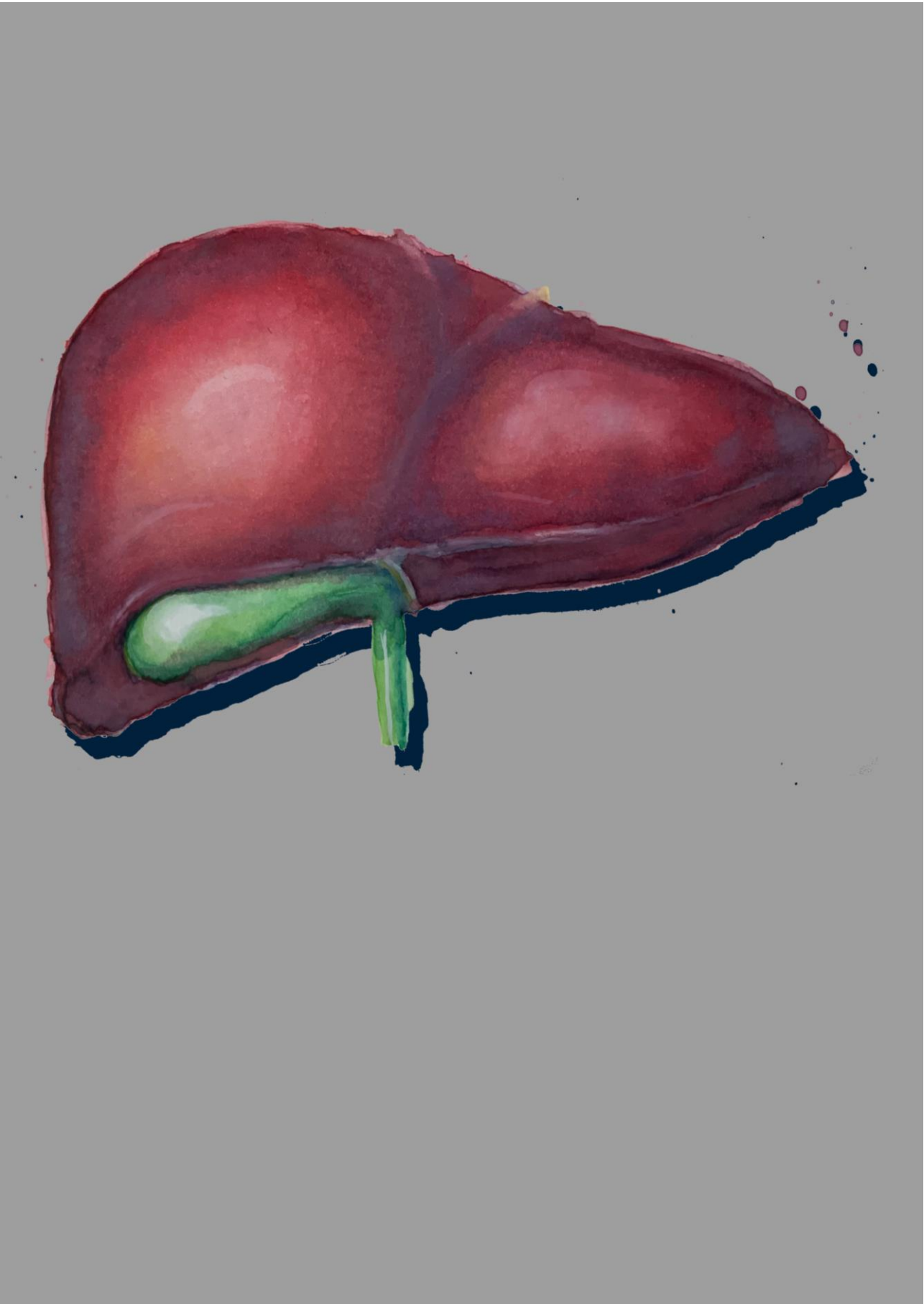

CHAPTER 2

Resectability and ablatability criteria

2.1

Resectability and ablatability criteria for the treatment of liver only colorectal metastases: multidisciplinary consensus document from the COLLISION Trial Group

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Cancers 2020

ABSTRACT

The guidelines for metastatic colorectal cancer crudely state that the best local treatment should be selected from a 'toolbox' of techniques according to patient- and treatment-related factors. We created an interdisciplinary, consensus-based algorithm with specific resectability and ablatability criteria for the treatment of colorectal liver metastases (CRLM). To pursue consensus, members of the multidisciplinary COLLISION and COLDFIRE trial expert panel employed the RAND appropriateness method (RAM). Statements regarding patient, disease, tumor and treatment characteristics were categorized as appropriate, equipoise or inappropriate. Patients with ECOG ≤ 2, ASA ≤ 3 and Charlson comorbidity index ≤ 8 should be considered fit for curative-intent local therapy. When easily resectable and/or ablatable (stage IVa), (neo)adjuvant systemic therapy is not indicated. When requiring major hepatectomy (stage IVb), neo-adjuvant systemic therapy is appropriate for early metachronous disease and to reduce procedural risk. To downstage patients (stage IVc), downsizing induction systemic therapy and/or future remnant augmentation is advised. Disease can only be deemed permanently unsuitable for local therapy if downstaging failed (stage IVd). Liver resection remains the gold standard. Thermal ablation is reserved for unresectable CRLM, deep-seated resectable CRLM and can be considered when patients are in poor health. Irreversible electroporation and stereotactic body radiotherapy can be considered for unresectable perihilar and perivascular CRLM 0-5cm. This consensus document provides per-patient and per-tumor resectability and ablatability criteria for the treatment of CRLM. These criteria are intended to aid tumor board discussions, improve consistency when designing prospective trials and advance intersociety communications. Areas where consensus is lacking warrant future comparative studies.

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent cancer in the world and, with nearly 881,000 deaths in 2018, the second leading cause of cancer related death.[1] The liver is the most common site of metastases, present at the time of diagnosis in roughly 20% and developed during the course of disease in an additional 40%.[2-5] Around 40% of patients with colorectal liver metastases (CRLM) have metastatic disease confined to the liver at first discovery. Curative-intent local treatments are currently considered the only realistic treatment options that can provide long-term disease control and cure in a select group of patients.[6,7] Advances in systemic regimens greatly contributed by downstaging patients for liver surgery and/or tumor ablation.[8] Furthermore, it opens a window to identify biologically aggressive fast disseminating cancers that cannot be controlled by local invasive treatments.

Although the eligibility for hepatic resection continues to expand, in approximately 80% upfront surgical excision of all CRLM is not possible.[2] Nowadays, the decision to opt for resection is not only predicated upon tumor-related factors such as size, number, location and distribution, but also upon retaining a sufficient future liver remnant (FLR).[2-9] Induction systemic therapy for disease that can potentially be downstaged, combined resection plus ablation, portal vein embolization with or without venous deprivation, lobar trans-arterial Yttrium-90 radio-embolization and a variety of two-stage procedures for bilobar disease have greatly contributed to this development.[10] Radiofrequency ablation (RFA) and microwave ablation (MWA) are heat-based thermal ablation modalities, currently adopted as standard of care to treat unresectable small (0-3cm) CRLM.[11] Two recently published systematic reviews and meta-analyses comparing thermal ablation to chemotherapy alone and to partial hepatectomy, both labelled thermal ablation superior to chemotherapy alone but inferior to surgery with regards to overall survival.[11-12] Global guidelines state that thermal ablation should be reserved for unresectable disease. However, in the absence of generally accepted recommendations, the option of thermal ablation as a safe and fair alternative for small deep-seated resectable CRLM has further blurred the definition of resectable disease. Although most superficial, shallow- and deep-seated, small-size CRLM seem to be suitable for thermal ablation, peritumoral vicinity of the common, left or right hepatic bile duct are considered absolute contra-indications as this is associated with an unacceptable risk of inducing biliary tract injuries.[13] Irreversible electroporation (IRE), a predominantly non-thermal ablation technique assumed to spare blood vessels, bile ducts and adjacent organs, engenders ultra-short high-voltage currents that create lethal nanopores in the cell membrane of tumor tissue.[14-16] With stereotactic body radiotherapy (SBRT), high radiation doses are delivered to a target volume within the liver, while minimizing collateral damage to healthy surrounding tissue.[17-19]

Although several clinical staging and classification systems provide prognostic information to predict outcome based on available parameters, and notwithstanding several attempts to postulate resectability criteria, clearly defined and combined resectability and ablatability criteria are absent. As a result, local treatment strategies for liver only metastatic CRC patients are exceedingly heterogeneous and the quality depends upon local expertise and the existence of regional or national referring networks. In light of the increasingly complex patient and disease characteristics and the ever-expanding toolbox of treatment options, there is a necessity to establish criteria that reflect both the technically feasible, the safest and the most effective local treatment option for CRLM patients. The purpose of this project was to create multidisciplinary resectability and ablatability consensus criteria amongst a large group of experts and to postulate a therapeutic decision model for patients with CRLM based on the highest available evidence levels and classified according to patient, disease and tumor characteristics.

METHODS

Expert panel

Members of the expert panels collaborating in the COLLISION trial[20] (registered at ClinicalTrials.gov *NCT03088150*), an international phase III randomized controlled trial comparing partial hepatectomy with thermal ablation for small-size resectable CRLM, the COLLISION-XL trial[21] (registered at ClinicalTrials.gov *NCT04081168*), a multicenter phase II/III randomized controlled trial comparing MWA with SBRT for intermediate-size unresectable CRLM and the COLDFIRE-2 trial[22] (registered at ClinicalTrials.gov *NCT02082782*), a two-center phase IIb prospective clinical trial, first composed a list of patient, disease, tumor and previous treatment characteristics that can potentially influence the decision of the preferred local treatment strategy. Panelists had to fulfill the following requirements: minimum experience of 3 years performing and/or supervising procedures in CRLM patients as surgeons, interventional oncologists or radiation oncologists, having performed and/or supervised over 100 procedures, good clinical practice (GCP) certified and local investigator for at least one of the abovementioned studies. The panel eventually consisted of 19 liver surgeons, 21 interventional radiologists, two radiation oncologists, one technical physician trained to perform ablations and two medical oncologists specialized in colorectal cancer.

Patient, disease, tumor and previous treatment characteristics

Potentially decision-affecting patient characteristics assessed were age, Eastern Cooperative Oncology Group (ECOG) performance status[23], American Society of Anaesthesiologists (ASA) physical status classification system[24], underlying liver disease (none, mild or severe)[25] and the Charlson Comorbidity Index (CCI)[25]. The Disease characteristics evaluated were synchronous versus metachronous disease and for the latter the time elapsed between primary tumor diagnosis and the first detection of CRLM (taking into account any (neo)adjuvant systemic treatments following bowel surgery), (y)pT-stage and (y)pN-stage for previously resected primaries, (y)cT-stage and (y)cN-stage for potentially resectable and for upfront unresectable primaries, CEA levels, K-RAS, N-RAS or BRAF mutational status, microsatellite (in)stability, the clustered consensus molecular subtype[26] (CMS1 (microsatellite instability immune), hypermutated, microsatellite unstable and strong immune activation; CMS2 (canonical), epithelial, marked WNT and MYC signaling activation; CMS3 (metabolic), epithelial and evident metabolic dysregulation; and CMS4 (mesenchymal)), the location of the primary tumor (right versus left sided and colon versus rectum), the clustered and validated clinical risk score (CRS) by Fong and colleagues[27] and the modified CRS[28], more recently suggested by the MD Anderson medical center. We classified CRLM into four stages:

(1) Stage IVa disease: easily resectable/ablatable requiring minor hepatectomy and/or ablations;

(2) Stage IVb disease: difficultly resectable/ablatable requiring major hepatectomy (+/– ablations);

(3) Stage IVc disease: initially unresectable/unablatable, but potentially downstageable CRLM where induction systemic therapy and/or future remnant augmentation are appropriate;

(4) Stage IVd disease: permanently unresectable/unablatable CRLM in patients ineligible to receive systemic therapy or after unsuccessful downstaging.

Tumor characteristics such as number, size, location (segment, exophytic versus superficial versus deep seated) anatomical relationship to critical structures such as hepatic arteries, portal and systemic veins and the central bile ducts and tumor distribution (scattered or clustered, mono- or bilobar) of CRLM and volume of the FLR were analyzed, as was the preference to opt for less-invasive parenchyma-sparing versus en-bloc major hepatectomy. Further features that potentially impact the therapeutic decision concerned the surgical and medical history, such as abdominal adhesions, recovery from previous abdominal surgery,

the objectified response to previous lines of systemic therapy and the number of earlier cycles of chemotherapy and/or biological agent(s). Although trans-arterial therapy such as Yttrium-90 (Y90) or Holmium-66 (H66) selective internal radiotherapy and trans-arterial chemo-embolization have demonstrated the ability to downstage patients for curative-intent surgery and/or ablation, this sequence as well as radiation segmentectomy, cryo-ablation, laser-induced thermal therapy, needle-based brachytherapy and high-intensity-focused ultrasound for CRLM were considered evolving treatments under investigation and were hence disregarded. Extrahepatic disease was considered off-scope for the current project.

STUDY DESIGN

We employed the RAND Corporation/University of California Los Angeles Appropriateness Method (RAM) to measure the appropriateness of different local treatment strategies for specific patient, disease and tumor characteristics.[29] In this "modified Delphi" process, experts from multiple disciplines use the available scientific evidence and supplement this evidence with their expert opinions. Each item could be rated on a scale from 1 to 9 (Likert scale), where 1 indicates that the treatment is highly inappropriate (expected harms greatly outweigh the expected benefits) and 9 indicates that it is very appropriate (expected benefits greatly outweigh the expected harms). Within each item the average patient was considered. A median score ranging 1–3 means a treatment is inappropriate, 4-6 means it is uncertain (equipoise) and 7–9 means the treatment is considered appropriate. When at least 80% of panelist scored in the same range, the consensus was defined as strong. When 70–80% scored in the same range, the consensus was defined as moderate. Below 70%, a consensus was not reached.

The coordinating committee performed a PubMed literature search on a point-by-point basis in February 2020 for studies in English concerning the treatment of CRLM. Although no formal systematic review was conducted, the search was conformal to the PRISMA guidelines with regards to the information sources used, the search performed and the studies selected (identification, screening and verification by two independent authors). The search can be found in Supplementary File S1. We selected the most relevant papers in order of priority: meta-analysis, systematic review, randomized controlled trials, non-randomized controlled trials, prospective cohort studies, case-control studies, case series, and expert opinions. The levels of evidence of the retrieved articles were independently assessed by the two senior authors (MPvdT, MRM) conformal to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system. Discrepancies were resolved by consensus. All relevant characteristics were identified and included in a comprehensive list of (contra-)indications (see Supplementary File S1). The evaluating committee participated in two rating rounds. Before starting the first round, panelists received a list with

definitions (see Supplementary File S2) and three articles that they were asked to read as preparation.[11,30,31] In the first round, panelists privately rated the statements using an online questionnaire. The statements that did not achieve strong consensus in round 1 were discussed during a video conference. Panelists could voice their doubts about statements and if deemed necessary by the majority of the panel statement were rephrased. Afterwards the panelists that responded to the first round of the survey received the second and final round of the survey with the statements that did not reach consensus in the first round and the results of the first round were reported back beneath the statements.

RESULTS

For rounds 1 and 2, response rates were 44/48 (92%) and 33/44 (75%), respectively. In the first round, consensus was reached for 12/25 statements. Based on discussions during the video conference, 5/13 statements were textually rephrased, and 1 statement was completely rephrased (Supplementary File S1, statement 21). In round 2, strong consensus was reached for 8/13 remaining statements, moderate consensus in 4/13 statements and no consensus in 1/13 statements (see online Supplementary File S3 for all statements plus results). Substantiated by the established criteria from the expert panel's assessments per-patient (Figure 1) and per-tumor (see Figure 2) flowcharts for the treatment of CRLM were created.

Agreements

Patient Characteristics

Local therapy should not be withheld from patients based on age alone (evidence level low to moderate—strong consensus).[32-35] Partial hepatectomy, thermal ablation, IRE and SBRT are appropriate treatment options for liver only metastatic CRC patients with ECOG ≤2, ASA ≤3 and CCI ≤8; SBRT can be considered for select patients with ECOG 3 (if life expectancy >1 year), ASA 4 or CCI-9-10 (evidence level low—strong consensus).[36-50] Local therapy is appropriate for patients with no or mild underlying liver disease; for patients with severe underlying liver disease the risks of the procedure do not outweigh the benefits (evidence level low—moderate consensus).[51-52]

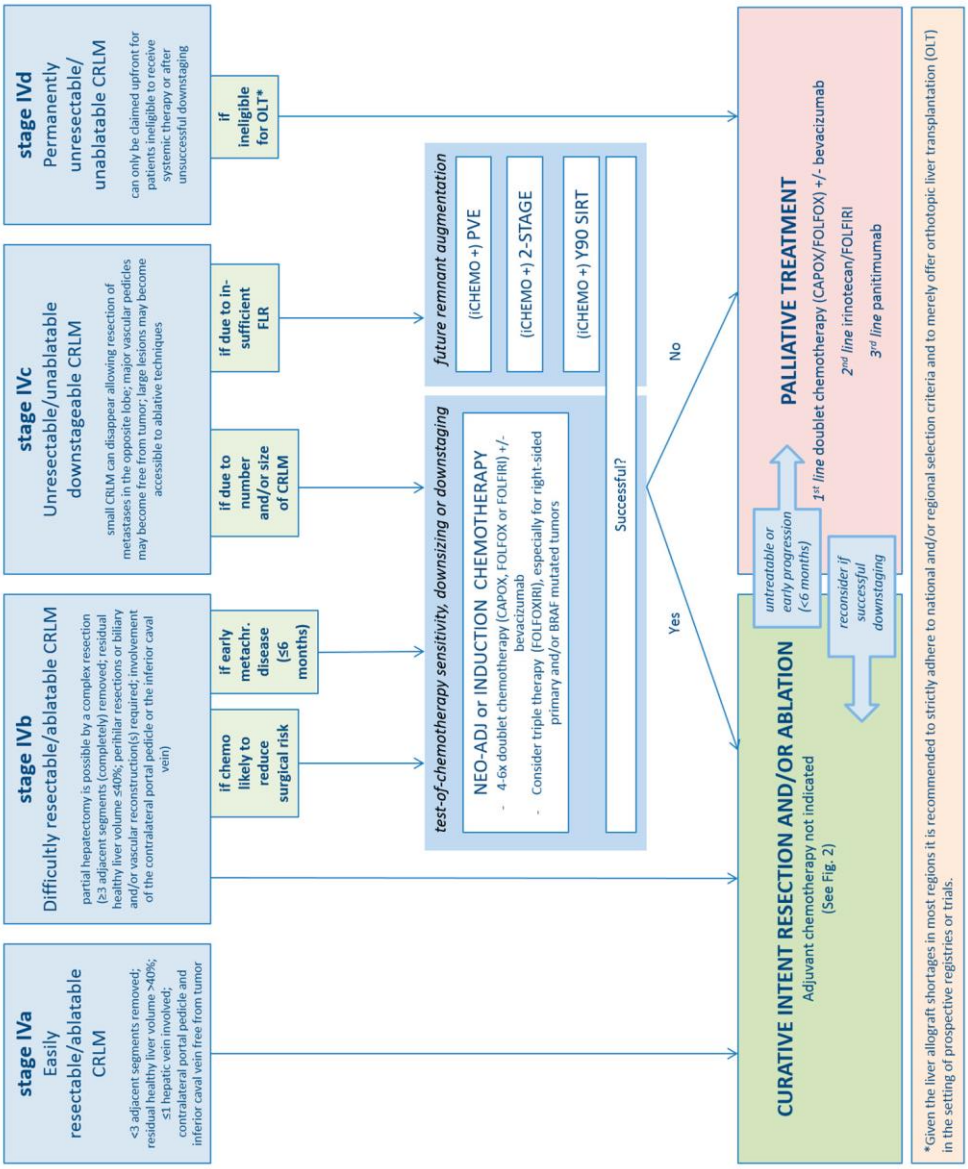

Figure 1. Per patient flowchart

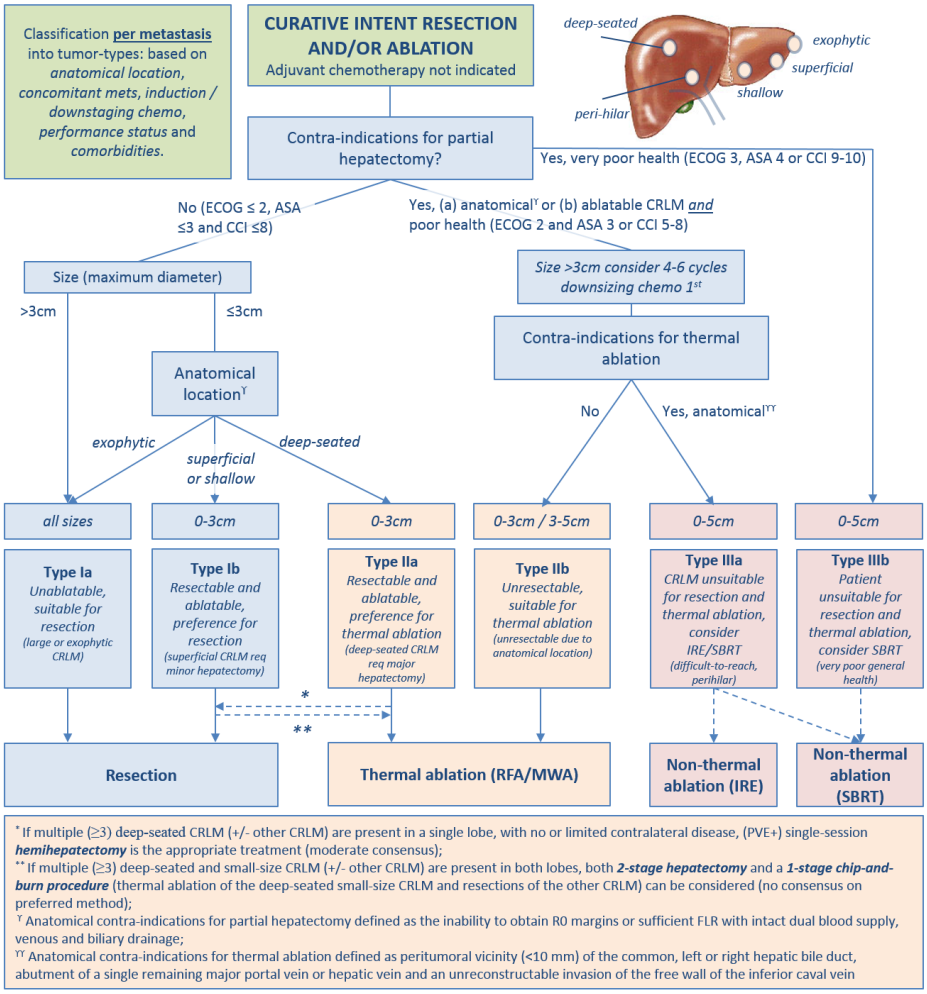

Figure 2. Per tumor flowchart

Disease Characteristics

For patients with stage IVa and stage IVb disease, defined as disease requiring minor hepatectomy/ablations versus disease requiring major hepatectomy, the appropriate treatment is upfront surgery and/or ablation without peri-procedural systemic therapy (evidence level high— strong consensus).[53-54] However in stage IVb disease, there are two exceptions where pre-procedural systemic therapy is indicated: (1) when downsizing of CRLM is likely to reduce the procedural risk (induction systemic therapy) and (2) in chemo-naïve patients that did not have CRLM at time of diagnosis of the primary tumor, who developed multiple CRLM that would require major hepatectomy within six months, indicating aggressive and fast disseminating tumor biology (neo-adjuvant systemic therapy). Neo-adjuvant systemic therapy would prevent patients from receiving futile invasive local therapy if early disease progression under systemic therapy is present (evidence level low—strong consensus).[55-58] In stage IVc, defined as initially unresectable but potentially downstageable CRLM, induction systemic therapy is appropriate until (a) curative-intent local treatment has become possible or (b) when additional downsizing will not (further) decrease procedural risk (evidence level high—strong consensus).[6-8,59-62] Stage IVd disease, defined as permanently unsuitable for curative intent local therapy, should be reserved for unresectable/unablatable patients who fail downstaging chemotherapy and for unresectable/unablatable patients who do not qualify for downstaging systemic therapy (evidence level moderate—strong consensus).[63] Orthotopic liver transplantation (OLT) can be considered for highly select patients permanently unsuitable for local treatment, at the prerequisite that a suffcient number of liver allografts is available and merely in the setting of prospective registries and/or trials. Although promising prognosticators, liquid and tissue biomarkers as well as validated classification systems such as the CRS by Fong and colleagues and the modified CRS have not yet shown additive value in the selection of specific local treatment options (no evidence—strong consensus).[27,28,64-66] Patients cannot be disqualified for local therapy based on a certain number and/or size of CRLM; the upper limit is defined by respecting the thresholds of the estimated future liver remnant volume and/or function (evidence level low—consensus strong).[67-70]

Tumor Characteristics

Partial hepatectomy is the standard of care for liver only colorectal metastases (evidence level low—consensus strong).[71-75] However, in patients with a poor general health status (ECOG 2 and ASA 3 or CCI 5-8) thermal ablation can be considered as an alternative treatment option (evidence level low—consensus high).[9,11,76-78] For small-size and resectable CRLM that are deep seated requiring major hepatectomy, thermal ablation is the appropriate treatment (evidence level low—consensus strong).[79] Unresectable CRLM ≤3cm should be treated by thermal ablation. Thermal ablation can be considered for unresectable CRLM 3–5

cm when further downsizing systemic therapy is unfeasible (evidence level moderate to high—consensus strong).[9,11,12,76,80-82] IRE and SBRT can be considered for patients with unresectable and not thermally ablatable CRLM (evidence level low—consensus moderate).[14-16,83-85] IRE is appropriate for perihilar and/or perivascular CRLM ≤3 cm, and 3–5 cm if further downsizing therapy is unfeasible (level of evidence low—consensus moderate).[14-16,84] SBRT can be considered for select patients with a limited disease burden (≤3 CRLM) and tumors ≤5 cm, at the prerequisite that an ablative dose can be delivered without jeopardizing liver function or other organs at risk and that ECOG is ≤3, ASA is ≤4 or CCI is ≤10 (level of evidence low—consensus strong).[83]

Three distinct types of CRLM that are eligible for local treatment emerged: 1) CRLM that should be resected (type I), 2) CRLM that should be treated with thermal ablation (type II) and 3) CRLM eligible for non-thermal ablation (type III). The following subtypes were categorized: CRLM that are unablatable but suitable for resection (type Ia), CRLM that are resectable and ablatable with a preference for resection (type Ib), CRLM that are resectable and ablatable with a preference for thermal ablation (type IIa) and CRLM that are considered unsuitable for resection (type IIb). The last category entails the anatomically unresectable and not thermally ablatable CRLM, eligible for IRE or SBRT (type IIIa) and the patients with a very poor general health status but fair life expectancy >1 year, eligible for SBRT (type IIIb) (see Table 1).

Type I *Resection*	Type II *Thermal ablation RFA/MWA*	Type III *Non-thermal ablation IRE/SBRT*
Ia: Unablatable, suitable for resection	**IIa:** Resectable and ablatable, preference for thermal ablation	**IIIa:** Unresectable and unablatable, consider IRE or SBRT
Ib: Resectable and ablatable, preference for resection	**IIb:** Unresectable, suitable for thermal ablation	**IIIb:** Unresectable and unablatable, consider SBRT

Table 1. Type of CRLM for which locoregional therapy should be considered.

Intertumor or Clustered Dependency Characteristics

When multiple (≤3) deep-seated CRLM (+/- other CRLM) are present in a single lobe, with or without limited contralateral disease, and remnant liver volume and/or function are adequate, single-session partial hepatectomy is the appropriate treatment (evidence level low—consensus moderate). When multiple (≤3) deep-seated and small-size CRLM (+/- other CRLM) are present in both lobes, and remnant liver volume and/or function would be inadequate, both a "2-stage hepatectomy" and a 1-stage "chip-and-burn" procedure (thermal ablation of the deep-seated small-size CRLM and resections of the other CRLM) can be considered (no consensus on preferred method).[86-88]

Treatment Characteristics

The anatomical contra-indications for partial hepatectomy are as follows: (1) inability to obtain R0 margins (R1 margins in case of vascular involvement), (2) inability to preserve a sufficient FLR volume and/or function, (3) inability to preserve the dual blood supply and the venous and biliary drainage from the FLR and (4) inaccessibility of the abdominal cavity due to excessive abdominal adhesions (strong consensus).[30,68,89] The anatomical contra-indications for thermal ablation are as follows: (1) peri-tumoral vicinity (<10 mm) of the common, left or right hepatic bile duct or (2) peri-hepatic critical structures that cannot be distanced using surgical or interventional dissection methods, (3) the abutment or encasement of a single remaining major portal or systemic vein following surgery and (4) invasion of the free wall of the inferior caval vein. The maximum tumor size is 3 cm, although thermal ablation can be considered for 3–5 cm unresectable CRLM after failure to (further) downsizing with systemic therapy (strong consensus).[90] The contra-indications for IRE are CRLM >5 cm, ventricular arrhythmias, cardiac stimulation devices and congestive heart failure (strong consensus).[22] Contra-indications for SBRT are >3 CRLM and the inability to deliver an ablative radiation dose without jeopardizing liver function and adjacent organs or structures at risk (moderate consensus).[91]

DISCUSSION

This article describes the development of a multidisciplinary expert panel consensus-based treatment algorithm for patients with liver-only colorectal cancer metastases. Given the rapidly changing landscape and the multitude of novel local, regional and systemic treatments, a guideline with directive rules of decision cannot be expected to be truly complete or to remain permanent. Similarly, the items of consensus do not encompass the full spectrum of interpatient variability and individual exceptions. The postulated agreements are contemporary and intended to guide multidisciplinary team meetings, optimize future prospective studies and improve intersociety communications.

Although several attempts to propose resectability criteria have been reported, combined resectability and ablatability criteria have not been postulated. [68,89,92] An early effort to classify CRLM patients was proposed by Nordlinger and colleagues in ‘the European Colorectal Metastases Treatment Group staging system’, and subdivided patients into resectable (M1a), potentially resectable (M1b) and metastases unlikely to become resectable (M1c).[89] More recently the ESMO consensus guidelines stated that “the best local treatment should be selected from a ‘toolbox’ of procedures according to disease localization, treatment goal, treatment-related morbidity and patient-related factors such as comorbidities and

age".[30] However, the ESMO guidelines do not define the appropriate local treatment option based on specific patient, disease and tumor characteristics.

Nineteen surgeons, 21 interventional radiologists, two radiation oncologists, two medical oncologists and one technical physician reached strong consensus on 20/25 statements and moderate consensus on another four statements. With respect to patient characteristics, strong consensus was reached for the ECOG performance status, ASA score and CCI thresholds; moderate consensus was reached on the statement that local treatment should be withheld from patients with severe underlying liver disease. Regarding disease characteristics, strong consensus was eventually reached on all items (subgroup definitions, discouraging the use of prognostic biomarkers, and size and number of CRLM as predictive parameters). Considering tumor characteristics, strong to moderate consensus was reached on the majority of items regarding the preferred local treatment per specific anatomical location. Although strong consensus was reached regarding hepatectomy as the preferred treatment option for patients with multiple deep-seated CRLM in one lobe, no consensus was reached for patients with multiple deep-seated CRLM in both lobes. After some textual adjustments following round 1, a strong consensus was eventually reached on the contra-indications for partial hepatectomy, thermal ablation and IRE and moderate consensus on SBRT. The lower consensus regarding SBRT to treat CRLM may be a result of the paucity of disease-specific and/or comparative studies with hard oncological endpoints throughout the literature.[93-95] However, a fair amount of studies did show promising results regarding toxicity and local control to treat tumors within the liver and the results seem to be improving.[18,19,96] Given the partially overlapping indications, the exact role of IRE and SBRT in the treatment of unresectable and not thermally ablatable CRLM needs to be clarified in future prospective studies.

An equal distribution amongst panelists existed for a '2-stage hepatectomy' versus a 'single-session chip-and-burn procedure' in this subgroup of patients with advanced disease. Although the historical gold standard represents a 2-stage hepatectomy with future liver remnant augmentation, a trend towards parenchyma sparing procedures exists.[86] As the complication rate and outcomes of these complex procedures strongly depend on operator experience, in the absence of comparative studies it is recommended to leave the decision up to local expertise.

In the prospective SECA-I and -II trials, 36 patients with unresectable colorectal cancer liver only metastases underwent liver transplantation. Under very strict selection criteria, promising results were reported with 5-year overall survival from transplantation reaching 83%.[97-100] These results led to conditional and preliminary acceptation of liver transplantation in a highly select subgroup of patients with CRLM permanently unsuitable for local treatment in several countries. However, given the liver allograft shortages in most regions, it is

recommended to strictly adhere to the national or regional selection criteria and to merely offer this treatment in the setting of prospective registries or trials.

Hopefully, in the near future the outcomes of studies such as the phase III non-inferiority randomized controlled COLLISION trial that seeks to compare partial hepatectomy to thermal ablation for resectable CRLM, the COLLISION-XL trial that compares MWA to SBRT for intermediate-size unresectable CRLM, an RCT in Denmark (*NCT03654131*) and an RCT in Italy (*NCT02820194*) for CRLM <4 cm that compare SBRT to MWA, and the COLDFIRE-2 trial that investigates the role of IRE for perihilar and perivascular CRLM will be able to shed light on these issues.[20-22]

The high number of expert participants, the multidisciplinary approach, the good response rates and the high level of strong consensus add value to this consensus guideline. Although the items of agreement aimed to cover both patients with and without a history of local therapy for CRLM, the reported evidence mainly focused on the first metastatic episode. Hence, the outcomes are less applicable to patients with distant recurrences in the liver, given the presumed higher complexity of surgical procedures in a previously accessed abdominal cavity and given the often reduced liver remnant volume.[101] One potential shortcoming of our study was the underrepresentation of some professions in the multidisciplinary expert panel (two radiation oncologists, two medical oncologists and one technical physician, compared to 19 surgeons and 21 interventional radiologists), which potentially weakens the generalizability of the agreements. Furthermore, the fact that the work represents opinions from predominantly Dutch physicians may have contributed to a skewed view on the role of peri-procedural systemic therapy for CRLM as this is still controversial. Another drawback is that despite our efforts to postulate clear criteria based on the anatomical location of CRLM, the assessment of the specific location (e.g., exophytic, superficial, shallow and deep seated) remains largely subjective.

In this consensus guideline we did not discuss the approach of surgery or ablation (e.g., open, laparoscopic, robot assisted and percutaneous). We feel this choice should be made by the specialists performing the procedure, as this decision depends on local knowledge, skills and resources.

Several treatments for the local or regional treatment of CRLM were considered ‘off-scope’, such as cryoablation, Y90 or H66 selective internal radiation therapy, trans-arterial chemo-embolization, high-intensity-focused ultrasound, laser-induced thermotherapy, hepatic artery infusion (pump) chemotherapy and brachytherapy. Although all represent promising techniques, research is ongoing and the exact role in the treatment of CRLM will need to be defined in future prospective controlled studies.

Conclusions

This paper provides a framework of key opinion leader agreements concerning resectability and ablatability criteria for CRLM. We encourage all of our colleagues to adopt the recommendations outlined in order to aid tumor board discussions, to improve consistency in the design of future prospective trials and to advance intersociety communications.

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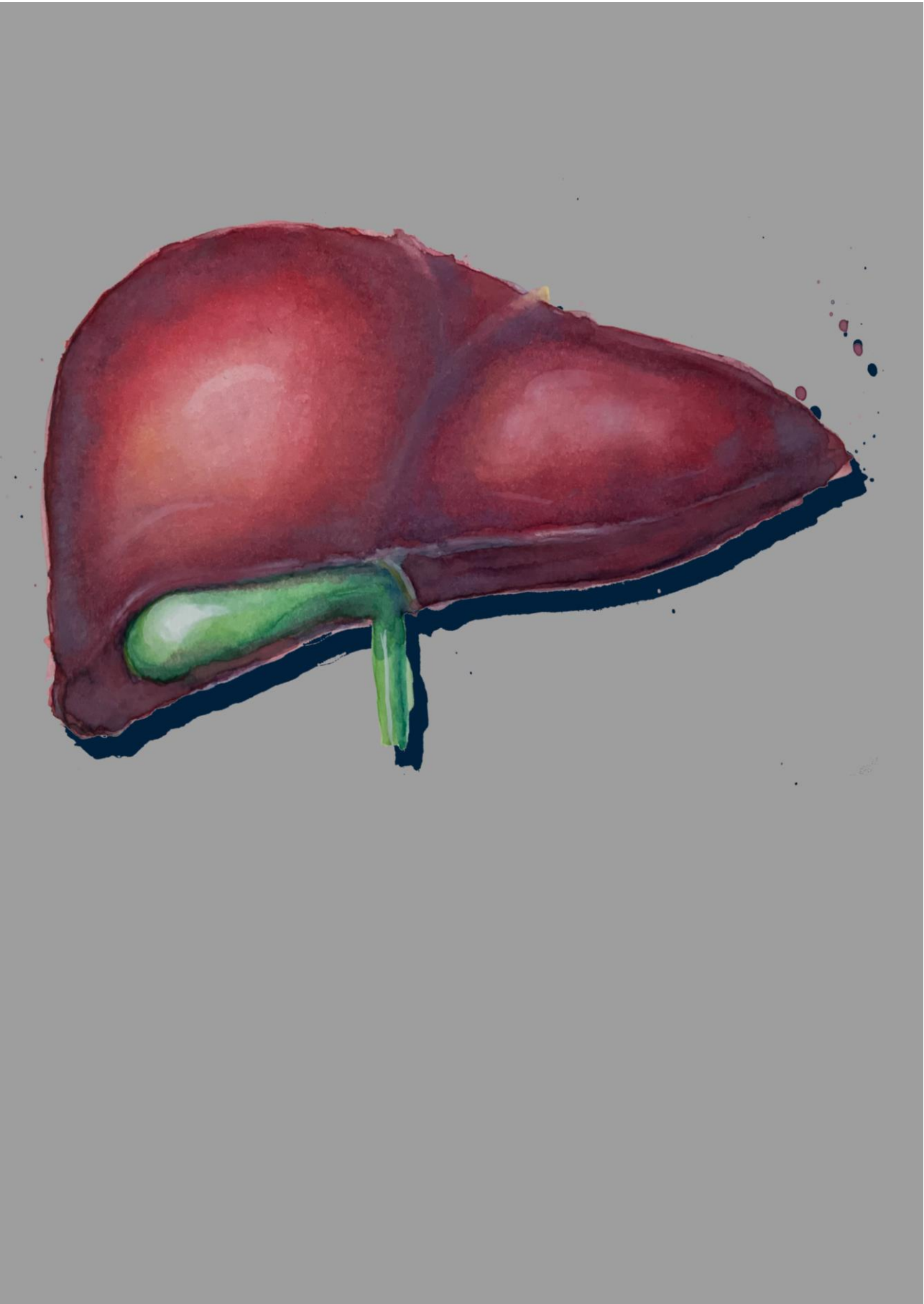

CHAPTER 3

Current treatment status

3.1

Radiofrequency and microwave ablation compared to systemic chemotherapy and to partial hepatectomy in the treatment of colorectal liver metastases: a systematic review and meta-analysis

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ABSTRACT

Purpose: To assess safety and outcome of radiofrequency ablation (RFA) and microwave ablation (MWA) as compared to systemic chemotherapy and partial hepatectomy (PH) in the treatment of colorectal liver metastases (CRLM).

Methods: MEDLINE, Embase and the Cochrane Library were searched. Randomized trials and comparative observational studies with multivariate analysis and/or matching were included. Guidelines from National Guideline Clearinghouse and Guidelines International Network were assessed using the AGREE II instrument.

Results: The search revealed 3530 records; 328 were selected for full-text review; 48 were included: 8 systematic reviews, 2 randomized studies, 26 comparative observational studies, 2 guideline-articles and 10 case series; in addition 13 guidelines were evaluated. Literature to assess the effectiveness of ablation was limited. RFA + systemic chemotherapy was superior to chemotherapy alone. PH was superior to RFA alone but not to RFA + PH or to MWA. Compared to PH, RFA showed fewer complications, MWA did not. Outcomes were subject to residual confounding since ablation was only employed for unresectable disease.

Conclusion: The results from the EORTC-CLOCC trial, the comparable survival for ablation + PH versus PH alone, the potential to induce long-term disease control and the low complication rate argue in favor of ablation over chemotherapy alone. Further randomized comparisons of ablation to current-day chemotherapy alone should therefore be considered unethical. Hence, the highest achievable level of evidence for unresectable CRLM seems reached. The apparent selection bias from previous studies and the superior safety profile mandate the setup of randomized controlled trials comparing ablation to surgery.

INTRODUCTION

Colorectal cancer is the second most common cause of cancer-related death in developed countries and the third most common malignancy worldwide.[1] Roughly 50% of patients develop colorectal liver metastases (CRLM), yet only a minority (10–15%) can undergo partial hepatectomy (PH). Five-year survival following PH ranges between 31 and 58% in carefully selected patients.[2,3] The remainder is usually offered chemotherapy and/or local tumor ablation alone or in combination with PH. Especially radiofrequency (RFA) and microwave ablation (MWA) are commonly employed and widely available. Median overall survival (OS) following systemic treatment nowadays reaches 20–22 months in patients who receive sequential chemotherapy regimens often with biological agents; 5-year survival remains <15%.[4-8] Five-year survival following ablation varies between 17 and 53%.[9-13] Although recent studies[13-16] have reported similar survival for patients treated with thermal ablation or PH, interventional radiology and surgical oncology communities generally state that thermal ablation cannot be considered an alternative to PH. They recommend the use of open, laparoscopic or percutaneous RFA and MWA for small CRLM (≤3 cm) in patients who are unsuitable for resection due to (1) an impaired general health status (age, comorbidities), (2) a history of extensive abdominal surgery, (3) the presence of lesions with an unfavorable location or (4) an insufficient future liver remnant to resect all lesions.[11,17,18] In light of these recommendations the Dutch National Health Care Institute (ZiNL) and representatives from the Dutch societies for interventional radiology, surgical and medical oncology commissioned a systematic review and meta-analysis with the following research questions: (1) what is the evidence regarding safety and effectiveness for RFA and MWA in the treatment of CRLM? and (2) what is the status of RFA and MWA in international guidelines?

MATERIALS AND METHODS

Search Strategies

The search strategies and inclusion criteria were based on the following PICOS question: P (population): patients with resectable and unresectable CRLM; I (intervention): RFA and MWA; C (comparison): for resectable disease PH and for unresectable disease systemic chemotherapy; O (outcomes): critical endpoints were OS, complications and quality of life (QoL), important endpoints were disease-free survival (DFS), local progression-free survival (LPFS), and ablation-site recurrence rate (ASR); S (study designs): (systematic reviews), randomized studies, controlled studies, comparative observational studies with multivariate analysis and/or matching, non-comparative studies if an insufficient number of comparative studies was found. To assess the relative importance of outcomes (critical, important but not

critical or limited) the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used.[19] We used Cochrane systematic review methods to identify studies that met the inclusion criteria. MEDLINE, Embase and the Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment database, CENTRAL) were searched (last update September 26th 2017) using a combination of text words and medical subheadings (search strategies: Table 3 online appendix). No time limit was used. Searches were limited to studies involving humans and published in English or Dutch. Abstracts were only taken into consideration when their methodological quality could be sufficiently evaluated and data extraction could be entirely completed. Studies also describing primary liver tumours and/or non-colorectal liver metastases were only included if data about CRLM could be extracted separately. Only studies reporting on the following outcomes were considered: (1) critical outcomes: OS, QoL and complications; (2) important outcomes: DFS, LPFS, ASR.

Study selection and quality criteria

All retrieved studies were evaluated for inclusion by two reviewers (JV, KHH) independently. First, studies were evaluated on title and abstract. Studies potentially eligible for inclusion were ordered in full text for a comprehensive evaluation.

For the included studies, the methodological quality was evaluated independently using the AMSTAR tool for systematic reviews and the risk of bias tool of the Cochrane Collaboration for randomized trials and controlled studies. For uncontrolled studies (including case series) the following criteria were judged: adequate definition of disease, clear baseline characteristics, inclusion of a representative cohort, adequate disease confirmation using validated methods, standardized data collection and objective outcome measurement.

All discrepancies were resolved by consensus. If no consensus was reached, the opinion of a third researcher (LGF) was the overriding factor.

Data extraction

Data were extracted by one reviewer (KHH or LGF) and checked by a second (JV). The results were displayed as described in the article, allowing for recalculations based on the data extracted from the article if needed.

Data analysis

Based on clinical criteria, such as population, intervention, control group and outcome, an assessment was made whether the studies were sufficiently comparable to perform a meta-analysis. A random effects model was chosen, unless there was no statistical heterogeneity. Individual results were presented in a forest plot. The following comparisons and outcomes allowed for a meta-analysis: (1) RFA versus PH alone regarding OS, DFS, LPFS, 30-day mortality and complications, and (2) RFA + PH versus PH alone regarding OS, DFS, LPFS and 60-day mortality. For time-to-event outcomes (survival), the generic inverse variance method was used. Only corrected hazard ratios (HR; e.g. based on a multivariate analysis) were imputed. For dichotomic results (complications), the Mantel–Haenszel method was used to calculate risk ratios (RR). When ≥ 10 studies were available for inclusion in the meta-analysis a funnel plot was used to assess for publication bias. The meta-analysis was conducted using Review Manager 5.3.

Levels of evidence

To appoint a level of evidence, the GRADE system was used taking into account the quality assessment and the results from data extraction.[20,21] We classified the level of evidence into 4 GRADE categories: high, moderate, low and very low (Table 1). Quality elements evaluated for downgrading were study limitations, inconsistency, indirectness, imprecision and publication bias.

Two independent researchers graded the evidence levels (JV, KHH). If consensus was not reached, the opinion of a third independent researcher was decisive (LGF). The reasons for appointing evidence levels were documented.

Guidelines

(Inter)national guidelines about RFA and MWA for CRLM were searched in the following database: National Guideline Clearinghouse and Guidelines International Network as well as on websites of (inter)national guideline organizations and scientific societies. Two reviewers (JV, LGF) selected and judged the guidelines using the AGREE II instrument (Table 2 online appendix).[22] If consensus was not reached, the opinion of a third independent researcher (KHH) was decisive.

RESULTS

The literature search resulted in 3530 records. After excluding 1121 duplicate papers and 459 documents written in a non-English language, a total of 1950 unique references remained (Fig. 1). Based on title and abstract 1622 references were excluded. A total of 328 articles were selected for full-text review. This led to the exclusion of 280 articles for the following reasons: single cohort without comparison (n = 115); wrong comparator, comparison, intervention or outcome (n = 48); no separate results for CRLM (n = 22); systematic review without quality appraisal (n = 20); narrative review (n = 17); observational study without matching or multivariate analysis (n = 16); and other (n = 42) (Table 4 online appendix). A total of 48 articles were included: eight systematic reviews, two randomized studies, twenty-six comparative observational studies and ten case series. Two references were included as guideline. Seven out of eight systematic reviews were classified as high quality[1-3,9,23-35], one was judged as poor quality[26] (Fig. 2).

Updated search resulted in three new comparative observational studies.[13,27,28]

Table 1: Grading of Recommendations Assessment, Development and Evaluation (GRADE*).[19,20]

Endpoint	Conclusion	Literature review	GRADE level
Overall Survival	RFA (+/-PH) + chemotherapy is superior to chemotherapy alone	1 RCT *(downgraded; serious imprecision)*	Moderate
	RFA + chemotherapy is superior to chemotherapy alone	1 RCT *(downgraded 2x; serious indirectness & serious imprecision)*	Low
	RFA (for unresectable CRLM) + PH is equivalent to PH alone	Observational comparative studies	Very low
	RFA alone (for unresectable CRLM) is inferior to PH alone	Observational comparative studies	Very low
	MWA is equivalent to PH	1 RCT *(downgraded; very serious risk of bias)*	Very low
	MWA (for unresectable CRLM) + PH is equivalent to PH alone	One observational comparative study	Very low
Complications	RFA alone (for unresectable CRLM) is superior to PH	Observational comparative studies	Very low
	Studies on RFA (for unresectable CRLM) + PH versus PH alone show conflicting results	Observational comparative studies	-
	MWA alone is equivalent to PH	1 RCT *(downgraded; very serious risk of bias)*	Very low
Quality of Life	There are no comparative studies on the effect of RFA or MWA	-	-

* GRADE definitions: high quality—further research is very unlikely to change our confidence in the estimate of effect (randomized controlled trials); moderate quality—further research is likely to have an important impact on

our confidence in the estimate of effect and may change the estimate (controlled trials, no randomization), low quality—further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate (observational studies); very low quality—any estimate of effect is very uncertain (any other type).

[a] Serious imprecision: in case of low optimal information size (OIS; number of included patients did not meet sample size), dichotomous outcomes, low number of events, wide confidence intervals with uncertainty about magnitude of effect, or when there is a lot of variation in the effects among the participants in continuous measures.

[b] serious indirectness: very important differences in populations, interventions, outcome measures, or indirect comparisons.

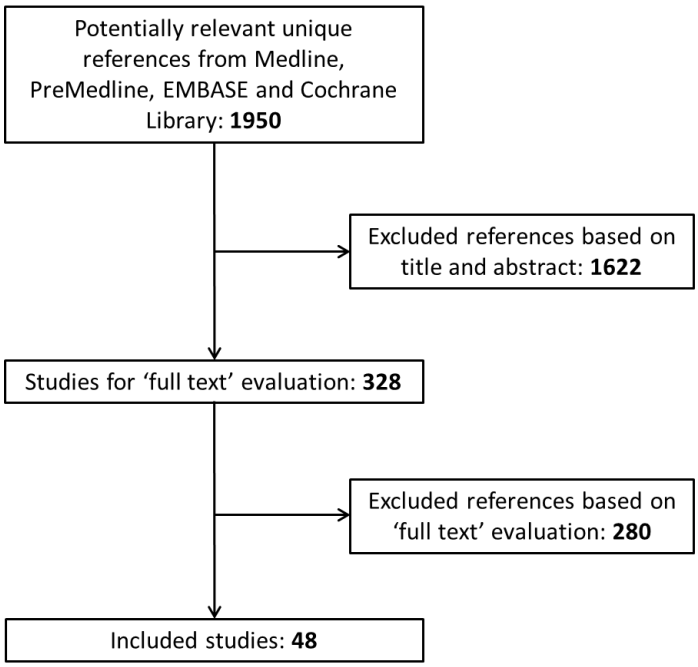

Figure 1. Results of selection: effectiveness of thermal ablation versus surgical resection or systemic chemotherapy in treating patients with CRLM

RFA

One randomized controlled trial (EORTC-CLOCC trial) compared systemic chemotherapy (FOLFOX [Folinic acid, Fluorouracil, Oxaliplatin] and from October 2005 FOLFOX + bevacizumab) with or without RFA in 119 patients with unresectable CRLM (Fig. 3).[29] Median number of CRLM was 4 (systemic + RFA) and 5 (systemic alone); 25.0% of patients in systemic + RFA group had solitary metastases, 11.9% in the systemic only group. Due to

slow recruitment the trial was downgraded to a phase II study. Twenty-four observational studies compared RFA for unresectable CRLM to PH for resectable disease (Fig. 4). Fourteen studies compared RFA with surgery alone[13,30-42], eight studies compared RFA + PH with PH alone[13,15,16,18,27,28,43,44], and four studies compared RFA to RFA + PH or PH alone[13,45-47]. A total number of 5020 patients were included in these observational studies (RFA: N = 1103; RFA + PH: N = 541; PH alone: N = 3376). For none of these studies, it could be excluded that therapy selection was based on patient and/or tumor characteristics and/or physician preference (confounding by indication). Moreover, the methods used to describe outcomes were heterogeneous and, although all included studies used multivariate analysis or data matching based on prognostic factors, these factors differed from study to study. None of the studies blinded patients or outcome assessors. In eleven studies, data collection was retrospective.

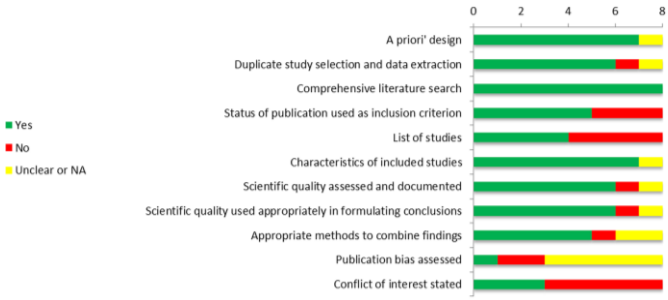

Figure 2. Risk of bias of included reviews for RFA

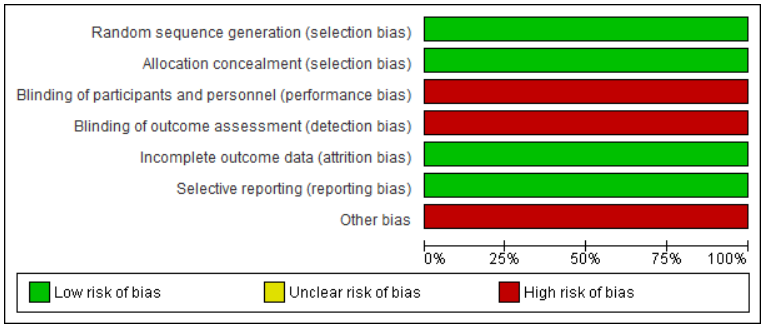

Figure 3. Risk of bias of Ruers et al.[29]

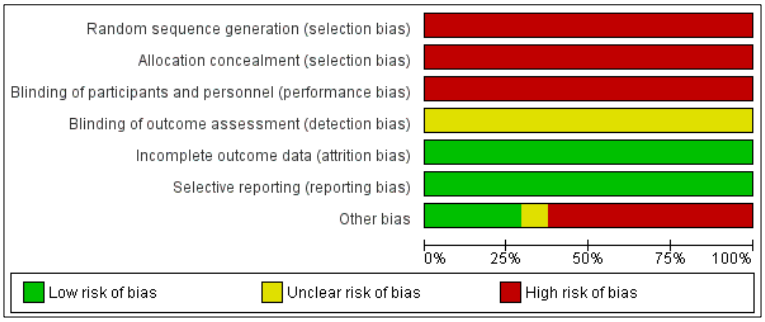

Figure 4. Risk of bias of comparative observational studies for RFA

Overall survival

RFA plus chemotherapy versus chemotherapy alone

The EORTC-CLOCC trial reported a 30-month OS of 61.7% (95% confidence interval (CI) 48.2–73.9%) for the combination group versus 57.6% (95%CI 44.1–70.4%) in the chemotherapy alone group.[29] After a median follow-up of 9.7 years, OS was significantly better in the RFA + chemotherapy group (HR = 0.58; 95%CI 0.38–0.88) with an 8-year OS of 35.9 versus 8.9% for chemotherapy alone.[29] In the RFA arm 27 out of 50 patients also underwent hepatic resection(s) which may have confounded results.

RFA versus PH alone

Ten observational studies (N = 1824 reported corrected hazard ratios for OS (Fig. 5).[13,30,31,33-35,37,39,45,46] Pooling of the results showed that RFA was associated with an inferior OS (HR = 1.78; 95%CI 1.35–2.33)). Two other studies only reported non-corrected HRs, treatment type was not associated with prognosis based on univariate analysis.[41,47] Adding these studies to the meta-analysis did not substantially alter the results (HR = 1.62; 95%CI 1.29–2.03).

Five articles allowed for pooling of OS results for solitary metastases. Again, RFA was associated with a less favorable outcome (HR = 1.77; 95%CI 1.18–2.65).[31,33-35,39] The corrected odds ratio as reported by Aloia et al. also showed better results for PH alone (odds ratio 3.22; 95%CI 1.74–5.96).[32]

RFA plus PH versus PH alone

Seven observational studies (N = 1918 reported corrected hazard ratios and allowed for pooling of OS results (Fig. 6).[13,15,16,18,27,45,46] No significant difference in OS was found (HR = 1.24; 95%CI 0.84–1.84). One other article reported only non-corrected hazard ratios, treatment type was not associated with prognosis based on univariate analysis. Adding this

study to the meta-analysis did not meaningfully alter the results: (HR = 1.27; 95%CI 0.90–1.81).[47] Govindarajan et al. reported the OS for recurrent CRLM, and did not detect a significant difference between PH and PH + RFA for both solitary CRLM (p = 0.49) and multiple CRLM (p = 0.18).[43]

Adverse events and quality of life

Ruers et al. reported one fatality (sepsis) in the RFA + chemotherapy group.[29] Ten observational studies (N = 1795) comparing RFA and PH alone reported post-procedural or 30-day mortality.[30-32,34-39,47] Meta-analysis did not show a difference (RR = 0.64; 95%CI 0.21–1.95), although the funnel plot did suggest publication bias (Fig. 7). Of the observational studies comparing RFA + PH and PH alone, one study (N = 113) reported 30-day mortality[39], two studies (N = 232) reported 60-day mortality[18,44] (Fig. 8) and two studies (N = 709) reported 90-day mortality[15,27] (Fig. 9). No significant differences were detected (30-day: no events; 60-day: RR = 0.80; 95%CI 0.09–6.90; 90-day: RR = 1.02; 95%Cl 0.27–3.76). Govindarajan et al. reported two deaths within 100-days post-resection in a group of 96 patients versus no deaths in the combination group.[43] Hof et al. only reported the 30-day mortality rate for both interventions (5 of 707 patients).[13]

In the EORTC-CLOCC trial, no significant difference in chemotherapy-induced toxicity between the groups was found.[29] In the observational studies comparing RFA and PH alone, complications were more common after PH compared to RFA (10 studies; RR = 0.47; 95%CI 0.28–0.78) (Fig. 10)[30,31,33-36,39-41,47] Of the observational studies comparing RFA + PH and PH alone, Faitot et al. reported serious adverse events in 28% after PH (C grade 3) versus 13% in the combination group (p = 0.017).[15] Imai et al. reported major complications in 18.6% in the PH alone group (C grade 3) versus 22% after PF + RFA (p = 0.656).[27] Kim et al. reported adverse events in 21% after PH (278 patients: 13 hemorrhage, 17 abscesses, 10 wound infections, 8 respiratory failure, 11 ileus) versus 37% in the combination group (27 patients: 3 hemorrhage, 3 abscess, 3 wound infection, 1 respiratory failure) (p < 0.001).[47] Sasaki et al. and Hof et al. didn't report complications.[13,28]

Ruers et al. reported the effect of RFA on quality of life using EORTC QLQ-C30 questionnaires.[29] With 110 out of 119 patients included in the analysis, overall quality of life decreased 27 points on average after the procedure to partially restore (to 10 points under baseline) prior to starting chemotherapy (4–8 weeks after RFA) and completely restored hereafter. No formal statistical comparison was done.

Local progression-free survival, disease-free survival and ablation-site recurrence

RFA plus chemotherapy versus chemotherapy alone

Ruers et al. reported a significantly longer median DFS of 16.8 months (95%CI 11.7–22.1) in the combination group versus 9.9 months (95%CI 9.3–13.7) in the chemotherapy alone group corresponding to a HR of 0.63 (95%CI 0.42–0.95, p = 0.025).[29] The percentage of patients treated for the first progression was comparable between both arms, 37 out of 42 patients (88.1%) in the combination treatment group and 46 out of 53 patients (86.8%) in the systemic treatment group. The long-term results, confirmed an overall DFS favoring RFA + chemotherapy (HR 0.57; 95% CI 0.38–0.85; p = 0.005). The 8-year DFS for RFA + chemotherapy versus chemotherapy alone was 22.3% (95%CI 12.7–33.7) versus 2.0% (95%CI 0.2–9.0).[29]

RFA versus PH alone

Three and five observational studies (N = 406 and N = 1253), respectively, reported corrected hazard ratios for DFS[30,36,37,46,47] and LPFS[34,40,45] (Figs. 11, 12). RFA was inferior to PH regarding LPFS and DFS (HR = 5.36 [95%CI 1.64–17.52] and 1.49 [95%CI 1.23–1.81], respectively). One study specifically included patients with solitary CRLM; again PH was superior (HR = 4.61; 95%CI 1.16–18.32).[34] Most studies did not report corrected data for the number of recurrences. However, Gleisner et al. performed a matched-control and propensity score analysis.[46] At 1 year any disease recurrence was more commonly detected after RFA compared to PH alone (66 vs. 24%; p < 0.001) with a high rate of ASR after RFA (41 vs. 2%; p < 0.001). Lee et al. also included a propensity score analysis; ASR rate was higher after RFA compared to resection (p = 0.021).[36]

RFA plus PH versus PH alone

Four and two observational studies (N = 1261 and N = 465), respectively, reported corrected hazard ratios for DFS[15,27,46,47] and LPFS[16,45] (Figs. 13, 14). RFA + PH was associated with a poor LPFS compared to PH alone (HR = 1.64; 95%CI 1.22–2.20). No significant difference in DFS between RFA + PH versus PH alone was found (HR = 1.14; 95%CI 0.82–1.60). One study used a matched-control and propensity score analysis which revealed a higher rate of overall and treatment site recurrences after RFA at 1 year (overall 61 vs. 24%; p < 0.001 and ASR 10 vs. 2%; p < 0.001)[46] Sasaki et al. and Hof et al. didn't report corrected hazard ratios for LPFS or DFS[13,28]

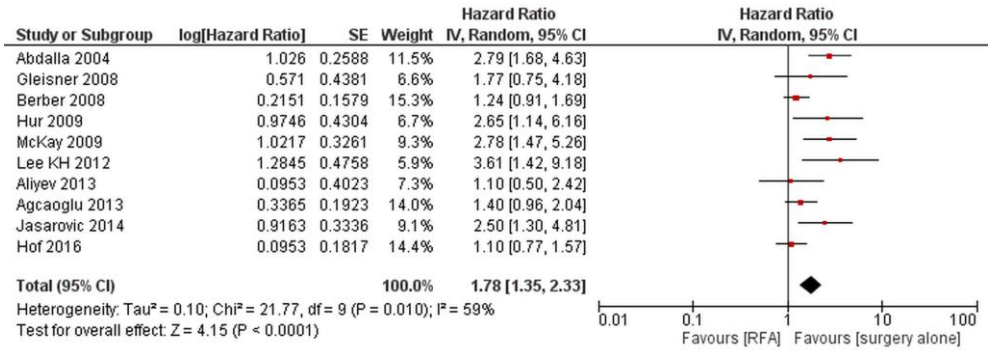

Figure 5. RFA versus PH alone: overall survival (OS)

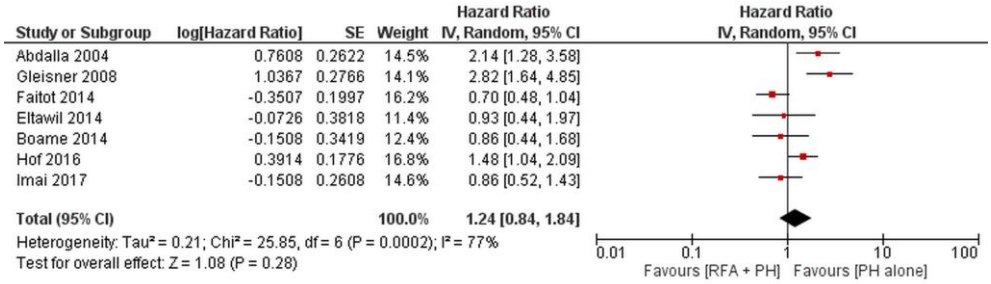

Figure 6. RFA + PH versus PH alone: overall survival (OS)

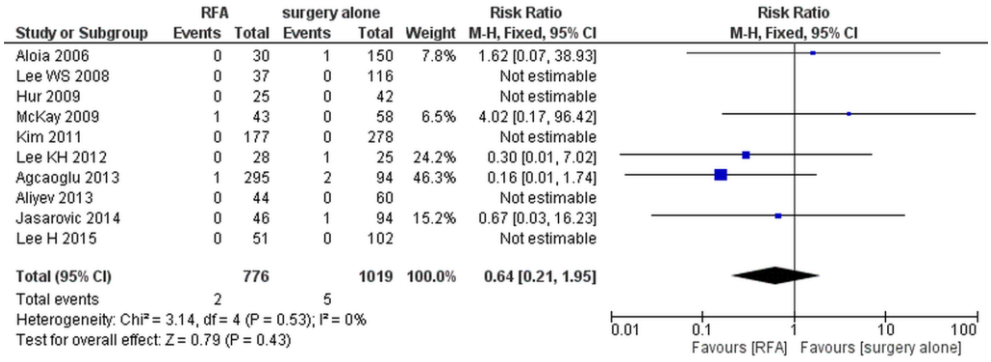

Figure 7. RFA versus PH alone: 30-day mortality

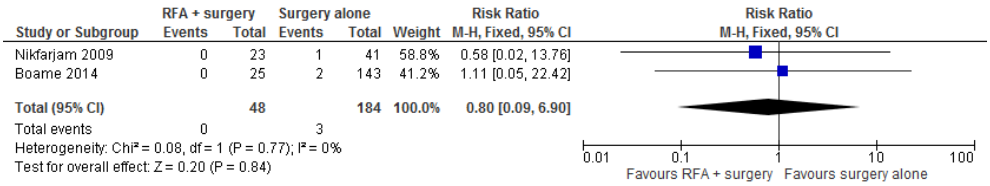

Figure 8. RFA + PH versus PH alone: 60-day mortality

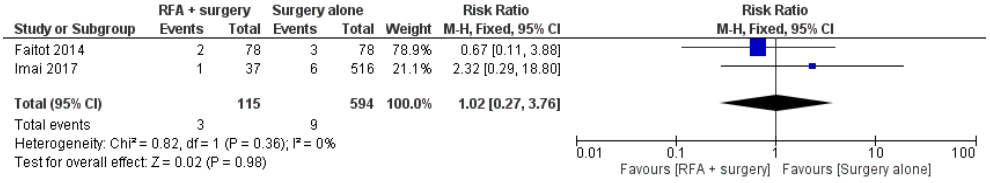

Figure 9. RFA + PH versus PH alone: 90-day mortality

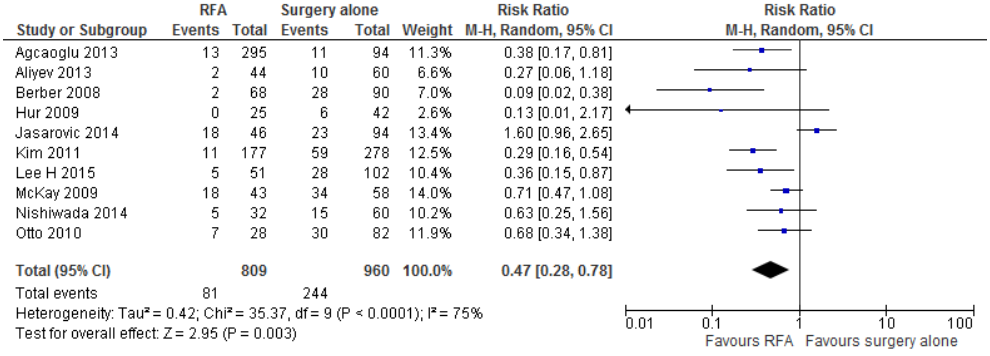

Figure 10. RFA versus PH alone: complication rate

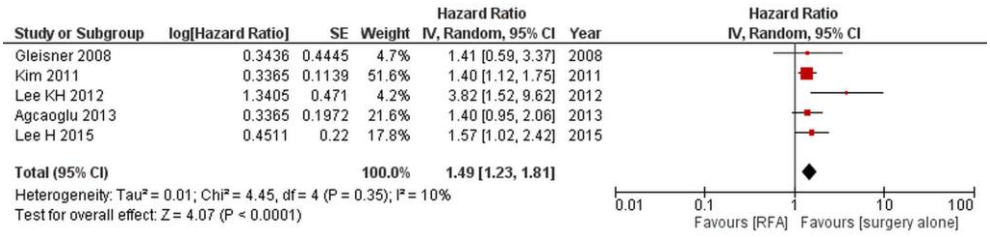

Figure 11. RFA versus PH alone: disease-free survival (DFS)

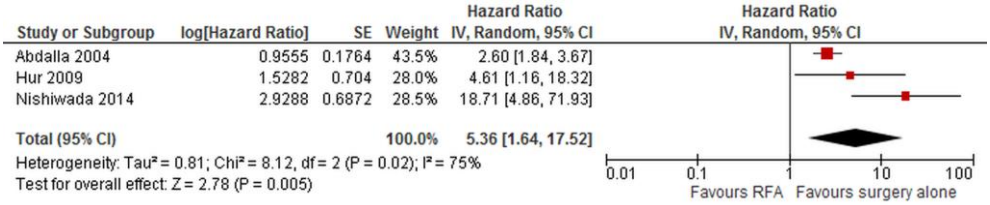

Figure 12. RFA versus PH alone: local progression-free survival (LPFS)

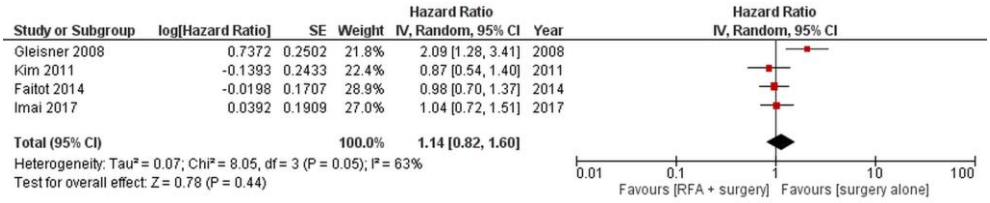

Figure 13. RFA + PH versus PH alone: disease-free survival (DFS)

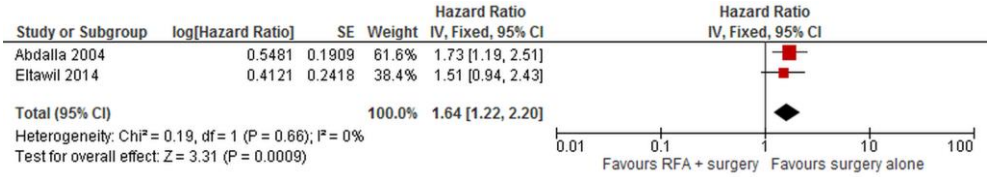

Figure 14. RFA + PH versus PH alone: local progression-free survival (LPFS)

MWA

One randomized controlled trial (RCT) compared MWA to hepatectomy in 30 patients with resectable CRLM (Fig. 15)[48] The absence of an intention-to-treat analysis makes this study at high risk of bias; 25% (10/40) of the randomized patients were not included in the analysis and the precise randomization method remains unclear.

One observational study compared MWA + PH to PH alone in 53 consecutive patients with at least 5 bilobar CRLM.[49] MWA was performed for unresectable lesions. Another observational study compared a group of 20 patients who underwent MWA for multiple unresectable CRLM with two historical cohorts: 36 patients who had resection and 25 patients who only received systemic treatment.[50] Both studies are at risk of bias due to the absence of a randomization process and the retrospective data collection (Fig. 16).

Finally, an additional number of ten case series were included (N = 689) (Fig. 17).[51-60] In seven of these, the majority of patients underwent combined resections + MWA[51-55,57,59] Seven studies have a high risk of bias due to retrospective data collection and/or contamination of results after complementary PH[51-55,57,59]; in the three other studies risk of bias remains unclear because selection bias cannot be excluded.[56,58,60] Only two studies separately reported results for solitary CRLM.[56,58] Last updated search revealed no extra articles for MWA.

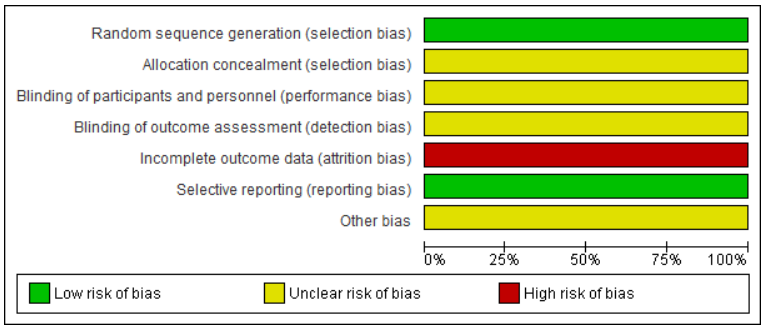

Figure 15. Risk of bias of Shibata et al.[48]

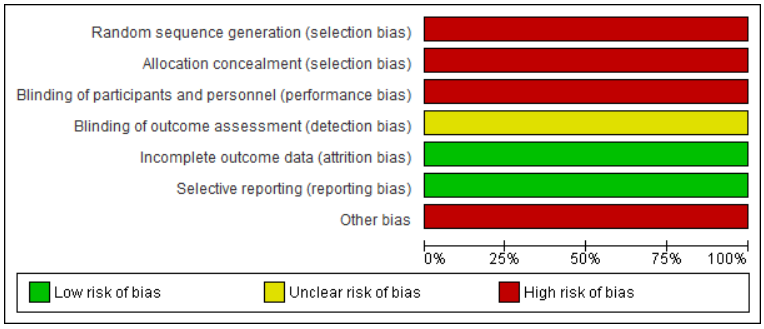

Figure 16. Risk of bias of observational studies for MWA

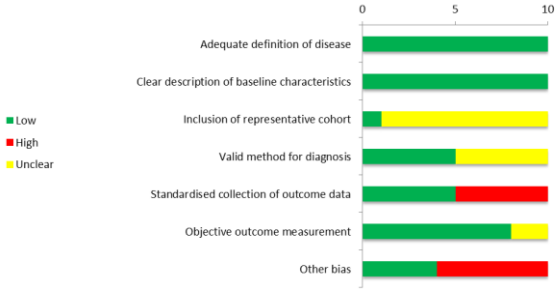

Figure 17. Risk of bias of case series for MWA

Overall survival

Shibata et al. reported a 3-year OS of 23% after hepatectomy and 14% after MWA.[48] Median OS was 25 versus 27 months (p = 0.83).

Engstrand et al. reported a 4-year OS of 41% for the MWA group versus 4% in the historical cohort treated with chemotherapy alone.[50] Treatment modality was found to be a prognostic factor in multivariate analysis (HR = 0.56; 95%CI 0.33–0.96). The 4-year OS in the PH alone cohort was 70%, but no formal statistical comparison was reported.

Tanaka et al. did not detect a significant difference in OS between MWA + PH versus PH alone (3-year OS: 50.9 vs. 48.8%).[49] Median OS was 39 months after PH and 28 months after MWA + PH. In multivariate analysis, MWA was no prognostic factor for OS.

Median OS in five case series ranged between 24 and 36 months.[53,54,57-59] The reported 3-,4- and 5-year OS varied between 35–79%[53,54,59,60], 35–58%[52,55] and 17–18%[53,59], respectively.

Mortality, adverse events and quality of life

Both Shibata et al. and Tanaka et al. did not detect any mortality after MWA or PH within 60 days after the procedure.[48,49] Reported mortality in the case series ranged from 0 to 2%.[55,57,59] Shibata et al. reported complications in 2/14 patients in the MWA group (1 liver abscess, 1 biliary fistula) and in 3/16 in the PH group (1 intestinal obstruction, 1 biliary fistula, 1 wound infection) (p = 0.87).[48] Tanaka et al. found complications in 6/37 patients undergoing liver PH versus 3/16 in the combination group (no p = value reported).[49] In the case series, the documentation of complications was heterogeneous.

Complication rates varied between 0 and 54%.[51,52,54,56,57,59] No studies reported the effect on quality of life.

Disease-free survival and ablation-site recurrence

Shibata et al. reported a median DFS of 13.3 months following PH versus 11.3 months following MWA.[48] Tanaka et al. did not detect a significant difference in DFS (4-year DFS: 39 vs. 35%; p = 0.86).[49] After a median follow-up of 21 months, 28/34 (19 in the liver) patients in the PH group had a recurrence versus 11/15 (9 in the liver) in the MWA group after a median follow-up of 19 months.

Eng et al. reported a 3.5-year DFS of 19%.[52] Stattner et al. found a 3-year DFS of 22% for the entire MWA group and 32% for the MWA alone subgroup.[59] Two studies found a median DFS of 8 and 12 months.[57,59] Groeschl et al. reported a 3- and 5-year DFS of 34 and 9%, respectively.[53] In a second series Groeschl et al. found a 3-year DFS of 0%.[54] Overall recurrence was present in 39–72%.[52-54,57,59] In 8 case series ASR varied between 2 and 30%.[51-54,56-59]

Guidelines

The search for guidelines resulted in 15 references, out of which two were excluded because they were updated by a more recent version.[61,62] Thirteen references were evaluated based on their full text; all were included and assessed according to the AGREE II instrument (Table 2 online appendix).[63-75] In 4 guidelines RFA and MWA was not mentioned.[63-66] In 1 guideline RFA was mentioned but without clear recommendations.[67] The American College of Radiology (ACR) guideline does not include specific recommendations, but RFA was described as unsuitable for CRLM, although scientific support for this statement is lacking.[68] The US National Comprehensive Cancer Network (NCCN) guidelines do not provide well-defined recommendations for RFA and MWA, although they do write the following: ‘‘The panel does not consider ablation to be a substitute for resection in patients with completely resectable disease. In addition, resection or ablation (either alone or in combination with

resection) should be reserved for patients with disease that is completely amenable to local therapy. Use of surgery, ablation, or the combination, with the goal of less-than-complete resection/ablation of all known sites of disease, is not recommended''.[69,70] References to the EORTCCLOCC trial and to several observational studies were used to support these statements.[3,29,46,76-80] The European Society for Medical Oncology (ESMO) considers RFA suitable for CRLM <4 cm if surgery is contraindicated and refers to the EORTC-CLOCC trial and a systematic review.[29,71,78] The UK National Institute for Health and Care Excellence (NICE) guideline considers the current evidence on safety and efficacy adequate to support the use of this procedure in patients unfit or otherwise unsuitable for hepatic resection, or in those who have previously had hepatic resection, provided that normal arrangements are in place for clinical governance, consent and audit.[72] The Scottish Intercollegiate Guidelines network (SIGN) commends that ablation should be considered for CRLM.[73,81] The Belgian Health Care Knowledge Center (KCE) recommends the use of RFA in combination with PH to preserve sufficient future liver remnant and refers to the NICE, SIGN and CCO guidelines.[74] The most comprehensive recommendations were reported in the Dutch Comprehensive Cancer Centre (IKNL) guideline: thermal ablation cannot be considered a substitute for resection, but represents a suitable treatment option for unresectable CRLM if the goal is a complete eradication of all lesions with curative intent.[75] Percutaneous ablation can be considered for patients who are less suitable for surgery because of high-age, comorbidity, unfavorable location or a history of extensive abdominal surgery. The ablation technique of the first choice is RFA. MWA can be considered a good alternative, especially for lesions in proximity of large blood vessels where heatsink, when heat is carried away by the flowing blood, may enable tumor cells to survive after RFA. IKNL refers to the EORTC-CLOCC trial, the Cochrane review and several observational studies.[3,26,29,82-85]

DISCUSSION

Contradictory to the many available comparative observational studies and case series on thermal ablation for CRLM, the literature to reliably assess its effectiveness compared to chemotherapy and surgery is limited. Although one RCT was identified for RFA[29], GRADE valuation required downgrading the quality of evidence regarding OS. When comparing RFA (± PH) + chemotherapy to chemotherapy alone, quality was downgraded to moderate, especially because both the optimal information size (OIS; number of included patients did not meet sample size) and the reduced relative risk (RRR = 100 * [1 - upper limit of the 95%CI for the HR (0.88)] = 12%) was too low (serious imprecision; Table 1). When comparing RFA + chemotherapy to chemotherapy alone, quality was further downgraded to low, because a substantial part of the ablated patients also underwent PH (serious indirectness). However, the remarkable differences in 8-year OS (8.9 vs. 35.9%) and 8-year

DFS (22.3 vs. 2.0%) seem to validate the eradication of all macroscopically visible CRLM and to justify the adoption of thermal ablation for unresectable CRLM for this indication.[29] The very serious risk of bias of the one MWA trial required downgrading to very low-quality evidence.

Comparing PH alone for resectable lesions with RFA for unresectable lesions, RFA was associated with significantly fewer complications but also with an inferior survival. In contrast, RFA in addition to PH for patients with unresectable disease, resulted in a comparable survival to resection alone for patients with resectable disease. In other words, for patients with unresectable disease, in whom palliative chemotherapy used to denote the only treatment option, RFA is able to offer patients a DFS and OS comparable to or approaching that of surgical candidates. Out of the eight studies published after 2012, seven showed a similar OS when comparing ablation (± PH) to PH alone (Figs. 5, 6), which may advert to ablative technique improvements. Although MWA compared to chemotherapy alone was associated with a superior OS for patients with unresectable CRLM, this is based on a single retrospective study at risk of bias due to the unclear randomization process, which seriously demotes quality of evidence.[50]

In contrast to RFA, the number of comparative studies for MWA was limited. For this reason, we incorporated more restrictions for the RFA studies, including only RCTs and observational studies that performed either case matching or multivariate analysis for prognostic factors.

The included observational studies were by definition all confounded by indication, since ablation was only performed for unresectable lesions. Reasons for choosing ablation over PH were comorbidity (0–41%), inadequate future liver remnant and/or technical factors such as difficult anatomical location (5–67%), patient's choice (0–61%) or extrahepatic disease for studies where this was no exclusion criterion (0–19%). Two other methods to adjust for confounding, namely restricting inclusion to patients from one prognostic category (for example bilobar CRLM) or stratification into subgroups were not allowed, because these methods only take one prognostic factor into account. All outcome measures were heterogeneously reported and follow-up periods ranged between 19 and 61 months in observational studies on RFA. The documentation of tumor load and disease status was strongly variable as were the definitions of progression-, recurrence and disease-free survival.

The reporting of complications was heterogeneous, which is why it is difficult to identify the most frequent complications for thermal ablation. Of the 24 observational studies, only two were published prior to 2008. In recent years, several technical advancements were implemented in the field of RFA, although the same can be assumed for surgical techniques. The impact of these two older reports on the global results is probably limited. For MWA this effect may be greater, because the only RCT was published in 2000 and one of two observational studies in 2006. Although technical factors such as an unfavorable anatomical

location were used to choose for thermal ablation, clear definitions for resectability were not provided in any of the included studies, with the exception of Ruers et al., who defined resectability as ''the possibility to completely resect all CRLM''.[29] For this reason, subgroup analysis was impossible and the risk for potential confounding by indication remains high. In the thermal ablation studies, the number of procedures necessary to reach local control was heterogeneously reported.

At the time of literature review, there was only one series comparing RFA to MWA for CRLM.[86] Of 243 patients there were no differences regarding OS and ASR between RFA and MWA (p = 0.559 and 0.078, respectively), although the complication rate for peribiliary CRLM was higher after MWA (p = 0.002).

Conclusions drawn from previous meta-analyses are comparable to ours with regard to patients with resectable CRLM, but differ for patients with unresectable disease. The review from Sutherland et al.[25] (published in 2006) was probably too old to find sufficiently relevant studies. Belinson et al.[2] and Cirocchi et al.[3] concluded: ''Evidence from the included studies are insufficient to recommend RFA for a radical oncological treatment of CRLMs''. Gurusamy et al. did not find any RCTs.[9] Bala et al.[1] and Loveman et al.[23] found one RCT for MWA (Shibata et al.[48] published in 2000) and concluded: ''Evidence is insufficient to show whether microwave coagulation brings any significant benefit in terms of survival or recurrence compared with conventional surgery for CRLM patients''. Smith et al.[24] did not assess RFA separately. Pathak et al.[26] were more positive in their conclusions, although their analysis primarily included case series.

The results from this analysis should be judged with caution. Although systematically obtained, there are no guarantees that all available evidence was identified. Furthermore, the inclusion of observational studies increases the risk for publication bias, for which objective indications were detected for the complication rate. Although (for RFA) only studies using randomization, matching or multivariate analysis was included, this does not exclude residual confounding.

To conclude, this article is the first systematic review that supports the widespread adoption of thermal ablation to treat small unresectable CRLM. The (1) recently published long-term survival results from the EORTC-CLOCC trial[29], the (2) comparable survival results after ablation versus resection for the series reported after 2012, the (3) comparable survival after ablation + resection versus resection alone, the (4) potential to induce long-term disease control and the (5) low complication rates all argue in favor of thermal ablation over chemotherapy alone. Further randomized comparisons of thermal ablation with curative intent to current-day palliative chemotherapy alone should therefore be considered unethical. As a consequence, the highest achievable evidence level for unresectable CRLM seems to have been reached.

Although ablation for unresectable CRLM seems inferior to PH for resectable lesions, the lower complication rate combined with the apparent selection bias stresses the need to conduct a randomized controlled trial. Currently, PH for resectable CRLM is being challenged by thermal ablation in a large multicentre, phase III, randomized controlled trial (COLLISION trial; *NCT03088150*). This study assesses overall- and disease-free survival, time to (local) progression, primary and assisted technique efficacy rates, adverse events, quality of life and incremental costs.

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3.2

Microwave ablation, radiofrequency ablation, irreversible electroporation, and stereotactic ablative body radiotherapy for intermediate size (3-5 cm) unresectable colorectal liver metastases: a systematic review and meta-analysis

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ABSTRACT

Purpose of Review: Based on good local control rates and an excellent safety profile, guidelines consider thermal ablation the gold standard to eliminate small unresectable colorectal liver metastases (CRLM). However, efficacy decreases exponentially with increasing tumour size. The preferred treatment for intermediate-size unresectable CRLM remains uncertain. This systematic review and meta-analysis compare safety and efficacy of local ablative treatments for unresectable intermediate-size CRLM (3–5 cm).

Recent Findings: We systematically searched for publications reporting treatment outcomes of unresectable intermediate-size CRLM treated with thermal ablation, irreversible electroporation (IRE) or stereotactic ablative body-radiotherapy (SABR). No comparative studies or randomized trials were found. Literature to assess effectiveness was limited and there was substantial heterogeneity in outcomes and study populations. Per-patient local control ranged 22–90% for all techniques; 22–89% (8 series) for thermal ablation, 44% (1 series) for IRE, and 67–90% (1 series) for SABR depending on radiation dose.

Summary: Focal ablative therapy is safe and can induce long-term disease control, even for intermediate-size CRLM. Although SABR and tumuor-bracketing techniques such as IRE are suggested to be less susceptible to size, evidence to support any claims of superiority of one technique over the other is unsubstantiated by the available evidence. Future prospective comparative studies should address local-tumour-progression-free-survival, local control rate, overall survival, adverse events, and quality-of-life.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide and the second leading cause of cancer-related mortality, with almost 1.850.000 new cases worldwide and 881.000 deaths in 2018.[1] Colorectal liver metastases (CRLM) will develop in 25–30% of these patients during the course of their disease and is the main cause of death in CRC patients.[2-5] When left untreated, the 5-year overall survival (OS) rate is dismal, with survival rates around 0–3%.[6-8] Although systemic therapy alone clearly improves survival, the only treatments that can provide long-term disease control or in a subset of patients even cure, are local eradication of the tumour.

Following resection of CRLM, 5-year survival rates of 40–55% can be achieved.[3-5,9-12] Unfortunately, only 20–30% of patients are considered eligible for partial hepatectomy.[3,4,13] Induction chemotherapy can downstage another 10–30% to resectable disease.[13-16] Although generally accepted guidelines are lacking, unresectability of CRLM can be roughly defined as follows: (1) an insufficient volume and function of the future liver remnant after resection, (2) inability to spare the arterial or portal venous blood supply to or the venous or biliary drainage from the future remnant, due to the anatomical location of the lesion(s), (3) an impaired general health status and/or serious cardiopulmonary comorbidities, and (4) an inaccessible abdominal cavity due to extensive previous abdominal surgery.

In the last two decades several radical intent thermal and non-thermal ablative therapies to treat unresectable CRLM emerged. The most well-known are radiofrequency ablation (RFA), microwave ablation (MWA), irreversible electroporation (IRE), and stereotactic ablative body radiotherapy (SABR).[17-24]

There is an ample amount of studies that have shown needle-guided thermal ablation to be effective and safe in the treatment of CRLM ≤ 3 cm.[17] After a median follow-up of 9.7 years, the EORTC-CLOCC trial reported a superior OS of RFA plus chemotherapy over chemotherapy alone (*HR* = 0.58; 95%*CI* 0.38–0.88) with an 8-year OS of 35.9% vs. 8.9%.[25] The efficacy of thermal ablation is even being compared to resection in CRLM < 3 cm to prove non-inferiority in the ongoing RCT COLLISION.[26] Conversely, for larger (> 3 cm) CRLM, the primary technique efficacy decreases exponentially, manifesting in higher rates of local tumour progression for all techniques.[27-33]

The radiation oncology community has suggested SABR to represent a feasible alternative as local treatment option for a limited number of unresectable CRLM. Although SABR can be effective to establish local control, a tradeoff exists between tumour control and collateral damage to surrounding tissue and structures.[34-36] As the efficacy is unaffected by the proximity of large blood vessels and less affected by lesion size and a difficult-to-reach

anatomical location, authors have suggested SABR as an alternative to thermal ablation for perivascular, sub-diaphragmatic, and larger CRLM.[37,38]

IRE is a relatively new non-thermal ablative method, where cell death is caused by using high-voltage electric pulses that induce permanent disruption of the membrane.[39] It is thought to be a safe ablation method for tumours adjacent to vascular and biliary structures because it spares the extracellular matrix and as a result preserves critical tubular structures.[40]

Extrapolating treatment results of small-sized CRLM, local ablative therapies are also often presumed to prolong survival for unresectable intermediate-size CRLM (3–5 cm). However, given the exponential decrease in local efficacy with increasing lesion size, this presumption requires validation. To ensure patients receive the optimal treatment method, knowledge about the preferred local ablative technique is indispensable. This multidisciplinary systematic review and meta-analysis critically assess and compare the outcomes of local treatment in patients with unresectable intermediate-size CRLM treated with the most widely used thermal and non-thermal ablation techniques.

METHODS

This systematic review and meta-analysis was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and PICO (patients, interventions, comparisons, outcomes) protocol.[41]

Search

A literature search was performed in the databases PubMed and Embase from January 1st 2008 till November 11th 2020. Keywords used in the search were as follows: colorectal liver metastases, microwave ablation, radiofrequency ablation, stereotactic body radiotherapy, and irreversible electroporation. The full search strategy is presented in appendix 1. The subsequent PICO question was used for the search strategy: P(population): patients with intermediate-size CRLM; intervention: RFA, MWA, IRE, and SABR with or without systemic therapy; comparison: systemic therapy alone; outcome: *critical* endpoints were local-tumour-progression-free survival/local control (LTPFS/LC), complications/toxicity, overall survival (OS), and *important* endpoints were disease-free survival (DFS) and quality of life. The interventional oncology society prefers the use of the term LTPFS (to describe the time from the initial treatment to the first recurrence, regardless of whether the recurrence was reablated), where the radiation oncology society prefers the use of the term local control.[42] Conference abstracts, reviews, meta-analyses, and studies not concerning humans were excluded.

Study selection

The abstracts retrieved by this literature search were independently screened by two authors (SN and RP). If the abstracts appeared to adhere to the in- and exclusion criteria, a full-text evaluation was performed. The references of relevant publications were reviewed. References appearing eligible were also submitted to a full-text evaluation. Manuscripts also containing information on efficacy and safety of primary liver carcinoma and non-colorectal liver metastases were allowed if they reported their data on CRLM separately. Studies were excluded if they did not report on at least one of the abovementioned outcome measures distinctly for intermediate size CRLM and if the sample size was less than five. Discrepancies between authors were resolved by consensus.

Data extraction

Two authors (SN and MD) extracted the data from the included studies. This concerned the following variables: name author, publication year, years of inclusion, total number of patients, and number of patients with CRLM 3–5 cm, whether patients received prior local treatment of the liver, presence of extrahepatic disease, size of CRLM, amount of CRLM 3–5 cm and/or ≥ 3 cm, treatment modality, and concomitant resections with thermal ablation. The collected data pertaining to study outcomes were for example median follow up, dose and fractions in SABR and biologically equivalent dose (BED10), local control, LTPFS, complications/toxicity, DFS, OS, and quality of life. This data was checked by a third author (RP). In case of discrepancies, these were discussed and resolved by consensus. Additional data of subgroups with intermediate size CRLM was requested and collected from authors that reported results of the comparison of SABR to thermal ablation.

Data analysis

Quality assessment criteria per study were based on clinical criteria, such as the included number and specific reporting of intermediate-size CRLM, the population, and the outcome measures used. Pooled analyses were allowed if results from studies were sufficiently similar with regards to these criteria. Studies potentially sufficient to perform meta-analysis were assessed and a random effects model was used to account for statistical heterogeneity. Analysis with the Mantel–Haenszel method was performed to calculate risk ratios (RR) of local tumour progression. Review Manager 5.3 was used to perform the meta-analysis.

Guidelines

CRLM guidelines were searched using Guideline Central and Guidelines International Network databases.

RESULTS

The search strategy yielded 1685 abstracts after removal of duplicates. After screening the abstracts for eligibility, 151 articles remained for full-text analysis, of which 124 were excluded. This left 27 articles that met our inclusion criteria for qualitative synthesis and 2 articles for quantitative synthesis with meta-analysis (see flowchart in Figs. 1 and 2). Very few publications reported on the outcomes of intermediate-size CRLM (3–5 cm) specifically. Therefore, we allowed publications reporting on the outcomes of CRLM ≥ 3 cm. Series that discontinued including patients before 2008 were excluded, due to the likelihood of outdated results.

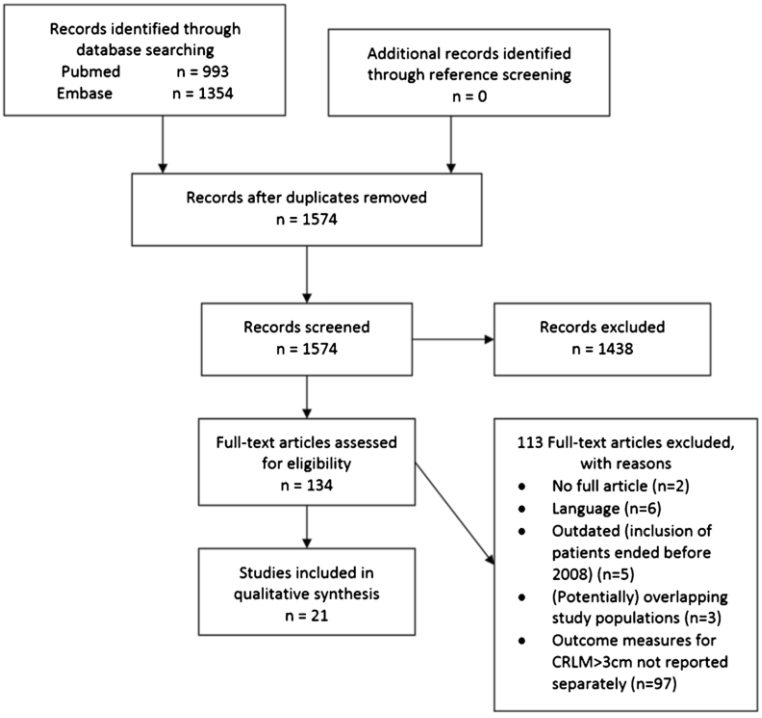

Figure 1. Flowchart of systematic search and selection according to PRISMA.

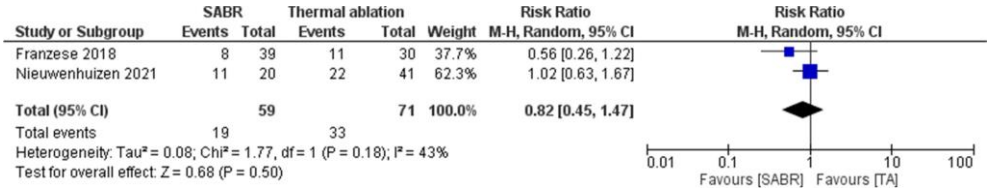

Figure 2. Risk ratio of local tumour progression comparing SABR to thermal ablation (TA)

Study characteristics

There were no randomized controlled trials on ablative treatment methods for intermediate-size CRLM. Of 27 included articles, 20 retrospective series[27,43-61], and 1 prospective cohort[62] reported on thermal ablation for CRLM > 3 cm: 14 on RFA[27,43,45-49,51,53,56-59,62], 5 on MWA[44,52,54,60,61], and 2 on both RFA and MWA.[50,55] One phase II trial[35] and two retrospective series[63,64] report the outcome of SABR for CRLM > 3 cm. One study reported outcomes for intermediate-size CRLM treated with IRE.[65] Two retrospective series compared SABR to thermal ablation and were included in the meta-analysis.[66,67] All publications were issued between 2011 and 2020. In the absence of comparative studies, a formal meta-analysis could not be performed. The study population (patient, disease, and lesion characteristics), the use of periprocedural systemic therapy, and oncological outcome measures were highly variable and heterogeneously reported.

Thermal ablation

Patient and lesion characteristics

At per patient level, eleven studies reported on 323 patients with at least one ablated CRLM > 3 cm (see Table 1).[45-49,51,53,54,58,59,62] Although simultaneous resections of concomitant resectable CRLM were allowed in 6 studies, none reported outcomes specifically for ablated intermediate-size CRLM with versus without concomitant partial hepatectomy.[27,44,45,48,55,57] Half of the studies stated whether patients had received prior focal liver treatment(s) (range 9.1–100%).[27,43,46,50,51,53,56-59] Extrahepatic disease was allowed in 11 studies[27,45-47,51-53,55-59,62], disallowed in 5[43,48,49,54,60], and not reported in 3.[44,50,61] On a per-lesion basis, 18 studies reported on 760 ablated CRLM > 3 cm: 544 with RFA; 160 with MWA; 56 RFA or MWA.[27,43-50,52-61]

Author/ year	Type of study	Yrs inclusion	MWA / RFA	No pts in tot	No pts CRLM >3cm	Age* yrs	Lap/ open / perc *	EHD *	Prior local treatment of liver *	Concurrent surgery*	Median FU in months *
Bale/ 2011[43]	Retro	2005-2011	RFA	63	-	Med 66	perc	No	38% of pt	No	25
Eng / 2015[44]	Retro	2009-2013	MWA	33	-	Med 61	open	-	-	28 pt (85%)	17
Erten/ 2020[61]	Retro	2014 - 2019	MWA	94	-	Mean 61.6	Lap / open	-	-	-	18
Fan / 2016[62]	Prosp	2003-2010	RFA	49	18	-	-	Yes	-	-	-
Gwak / 2011[45]	Retro	2004-2008	RFA	35	10	Med 62	Perc 26 pt/ open 9 pt	7 pt 20%	No	9 pt (26%)	31
Hamada / 2012[46]	Retro	2002-2010	RFA	84	31	Med 64.6	perc	23 pt 27%	21 pt (25%)	No	26
Jiang / 2019[47]	Retro	2012-2016	RFA	76	22	-	perc	40 pt 53%	-	No	32
Kennedy / 2012[48]	Retro	2000-2010	RFA	130	46	Med 65	lap	No	-	42pt (32%)	42
Kim / 2011[49]	Retro	1996-2008	RFA	177	14	Mean 60.4	Perc / open	No	-	-	41
Liu / 2017[50]	Retro	2004-2013	RFA/ MWA	101	-	Mean 58.2	Perc	-	25 pt, (25%)	No	-
Mao / 2019[51]	Retro	2006-2016	RFA	61	25	Med 59	Perc	8pt 13.1%	61 pt (100%)	No	29
Nielsen / 2013[27]	Retro	2000-2010	RFA	128	-	Mean 62.6	Perc / open	Yes	12 pt (9%)	64	36
Qin/ 2018[52]	Retro	2013-2017	MWA	137	-	Mean 54.9	Perc	34 pt 25%	-	No	18
Shady/ 2015[53]	Retro	2002-2012	RFA	162	26	-	Perc	51 pt 31%	116 pt (72%)	No	55
Shi / 2020[54]	Retro	2010-2017	MWA	210	68	Mean 59	Perc	No	-	No	48
Takahashi/2018[55]	Retro	2011-2014	RFA/ MWA	105	-	-	Lap	Yes	-	24pt (23%)	MWA 17 RFA 18
Valls/ 2015[56]	Retro	2005-2012	RFA	59	-	Mean 64.1	Perc	Yes	59 pt (100%)	-	25
Veltri/ 2012[57]	Retro	1996-2009	RFA	248	-	Med 67	Perc 243 pt / open 19 pt	51 pt (20%)	102 pt (41%)	19 pt (8%)	19
Wang / 2020[58]	Retro	2013-2018	RFA	85	37	Mean 59	Perc	22 pt (26%)	20 pt (24%)	No	30
Wang / 2020[59]	Retro	2012-2016	RFA	80	26	Mean 59	Perc	28 pt (35%)	12 pt (15%)	No	51
Zhang/ 2016[60]	Retro	2009-2014	MWA	199	-	Med 60	Perc	No	-	No	30

Table 1. Overview of included studies reporting on thermal ablation. * of total amount of patients.

Overall survival

Colorectal liver metastases 3–5 cm

Seven studies reported on OS in patients with at least one intermediate-size CRLM.[43,45,51,54,58,60,62] Median survival ranged 24–39 months.[43,45,51,54,58,60,62] Fan et al. reported the lowest median OS of 24 months.[62] However, in this study patients received cytoreductive RFA with palliative intent in salvage setting. Excluding the outlying results from Fan et al., OS ranged 26–39 months. The 1-, 2-, 3-, and 5-year OS ranged 73–92%[43,54,58,62], 41–72%[43,54,58,62], 20–40%[43,45,54,58,62], and 10–36%[43,45,54,62], respectively.

Colorectal liver metastases > 3 cm

Median OS ranged 21.7–37 months in seven retrospective series.[27,43,46,48,53,57,59] The lowest median OS was reported by Veltri et al.[57], a relatively old study that included patients over a longer period of time from 1996 to 2009. More than 40% of their study population had received prior local hepatic treatment and almost 20% of patients presented with extrahepatic disease. The 1-, 2-, 3-, and 5-year OS ranged 74–93%, 30–70%, 20–34%, and 8–31%.[48,49,53,57,59] See Table 2 for an overview of the survival outcomes.

Author	Lesion size (range) cm *	No. CRLM 3-5cm	No. CRLM >5cm	No. CRLM >3cm	Median OS in months 3-5cm	>3cm	1yr OS 3-5cm	2 yr OS 3-5cm	3yr OS	5yr OS
Bale[43]	2 (0.5-13)	36	23	59	32	>3cm: 31 >5cm 29	86% ^	72% ^	36% ^	36% ^
Fan[62]	NS (till 5cm)	-	-	-	24		73% ^	41% ^	20% ^	10% ^
Gwak[45]	2.4 (1-5)	-	-	-	Mean 39		-	-	40%	27%
Hamada[46]	2.3 (0.5-9.0)	-	-	35		31	-	-	-	-
Kennedy[48]	2.9 (1-8)	-	-	46	-	29	>3cm 93%	>3cm 70% ^	>3cm 34%	>3cm 8%
Kim[49]	2.1 (0.5-6.2)	-	-	14	-	-	>3cm 84% ^	>3cm 53% ^	>3cm 31% ^	>3cm 31% ^
Mao[51]	2.7 (0.9-4)	-	-	-	32	-	-	-	-	-
Nielsen[27]	2.2 (0.2-8.0)	49	20	69	-	37	-	-	-	-
Shady[53]	1.8 (0.5-5.7)	-	-	32		25	>3cm 88% ^	>3cm 50% ^	>3cm 26% ^	>3cm 18% ^
Shi[54]	2.7 (till 5 cm)	68	-	-	26	-	92% ^	55% ^	32% ^	20% ^
Veltri[57]	2.5 (NS)	-	-	137	-	21.7	>3cm 74% ^	>3cm 39% ^	>3cm 30% ^	>3cm 14% ^
Wang[58]	2.8 (0.8-5)	52	-	-	26	-	90% ^	42% ^	33% ^	-
Wang[59]	2.5 (1-6.4)	-	-	32	-	22	>3cm 80% ^	>3cm 30% ^	>3cm 20% ^	>3cm 10% ^
Zhang[60]	3 (1-5)	51 (4-5 cm)	-	-	36	-	-	-	-	-

Table 2. Overview of OS outcomes in thermal ablation. NS, not stated. * All-size CRLM included in study. ^ Percentages retrieved and estimated from OS curves.

Complications and quality of life

None of the studies reported the complication rate or the effect of thermal ablation on quality of life specifically for patients with CRLM > 3 cm. Irrespective of lesion size studies reported a major complication rate of 2–17% for percutaneous ablation.[43,46,47,50,52,53,56] Most reported major complications were: pleural effusion, pneumothorax, hepatic abscess, hepatic hematoma, perihepatic bleeding, or ileal perforation. Both Qin et al. and Veltri et al. did not find a correlation between the development of complications and lesion size.[52,57] Qin et al. found a mean lesion size of 1.8 cm vs 1.5 cm for patients with versus without complications ($p = 0.101$).[52] Similarly, Veltri et al. found a mean size of 2.7 cm in both groups.[57]

Disease-free survival, local-tumour-progression-free survival, and local control

Colorectal liver metastases 3–5 cm

Two retrospective series reported DFS.[45,60] Gwak et al. reported a median DFS of 19 months[45] and Zhang et al. a median DFS of 12 months for patients with CRLM of 4–5 cm.[60] One prospective cohort found a median DFS of 15 months.[62] In four retrospective series, LTP rate varied between 25 and 62% with a median follow up time of 25–36 months.[27,43,51,58] Eventual local control following repeat-ablations was not reported specifically for intermediate-size CRLM. See Table 3 for an overview of the efficacy of thermal ablation.

Colorectal liver metastases > 3 cm

Bale et al.[43] reported a median DFS of 12.4 months from stereotactic RFA. Shady et al. found a median LTPFS of 6 months[53] and Wang of 9 months.[59] Kim et al. found a 5-year DFS rate of 23%.[49] LTP was reported by nine retrospective series and ranged 14–78% with a median follow up time of 17–55 months.[44,46,48,50,52,53,55,56,61] The 1- and 2-year LTPFS varied between 34.8–69% and 17.4–62%, respectively.[46,47,53,55,59]

Author	Lesion size (range) cm *	No. CRLM 3-5 cm	No. CRLM >3cm	LTP 3-5cm	LTP >3cm	1yr LTPFS	2yr LTPFS	DFS/LTPFS (in months)
Bale[43]	2 (0.5-13)	36	59	11%	-	-	-	DFS >3cm 12 DFS >5cm 11
Eng[44]	NS (till 5.5)	-	7	-	14%	-	-	-
Erten[61]	NS (0.2-6.6)	-	21	-	19%	-	-	-
Fan[62]	NS (till 5cm)	-	-	-	-	-	-	Med DFS 3-5cm: 15
Gwak[45]	2.4 (1-5)	-	-	-	-	-	-	Mean DFS 3-5cm 19, 3-yr 20% 5-yr 10%
Hamada[46]	2.3 (0.5-9.0)	-	35	-	69%	35%	17%	-
Jiang[47]	2.3 (0.9-5.7)	-	33	-	-	67%	62%	-
Kennedy[48]	2.9 (1-8)	-	46	-	20%	-	-	-
Kim[49]	2.1 (0.5-6.2)	-	14	-	-	-	-	DFS rate 23%
Liu[50]	2.1 (0.7-6.0)	-	23	-	65%	-	-	-
Mao[51]	2.7 (0.9-4)	-	-	25% per tumor, 28% per pt	-	-	-	-
Nielsen[27]	2.2 (0.2-8.0)	49	69	27%	-	-	-	-
Qin[52]	1.5 (0.5-6.7)	12	13	-	38%	-	-	-
Shady[53]	1.8 (0.5-5.7)	-	32	-	78%	36% ^	25% ^	Med LTPFS 6
Takahashi[55]	≥3-NS	-	33	-	45%	69% ^	40% ^	-
Valls[56]	3-5.8	-	25	-	52%	-	-	-
Wang[58]	2.8 (0.8-5)	52	-	62%	-	60% ^	39% ^	-
Wang[59]	2.5 (1-6.4)	-	32	-	-	-	-	Med LTPFS 9
Zhang[60]	3 (1-5)	51 (4-5cm)	-	-	-	-	-	Med DFS 4-5cm 12

Table 3. Overview of efficacy outcomes of thermal ablation. NS, not stated. * Of total amount of patients. ^ Percentages retrieved from graphs.

Stereotactic ablative body radiotherapy

Patient and lesion characteristics

Strict adherence to the inclusion criteria resulted in two retrospective series, as most SABR series do not report separate results based on tumour type and tumour diameter > 3 cm.[63,64] Doi et al. compared SABR with a conventional fractionated schedule and included 24 patients in total, 15 patients with 21 CRLM > 3 cm and 16 patients (66.7%) with a history of focal hepatic resection(s) and/or thermal ablation(s) (see Table 4).[63] Joo et al. included 70 patients in total, half of the study population had received prior local hepatic treatment, and 19 patients (27%) presented with extrahepatic disease.[64] It was not stated how many patients had intermediate size CRLM.

To collect more data, one prospective phase II trial that studied the efficacy of SABR for 27 CRLM patients with a *cumulative* gross tumour volume (GTV) diameter > 3 cm unsuitable for surgery and thermal ablation was eventually added.[35] Cumulative GTV diameter here

means either at least 1 CRLM > 3 cm or multiple smaller CRLM with a cumulative size > 3 cm. Twenty-four CRLM > 3 cm were included. In this study, 11 patients (26%) had extrahepatic disease (EHD) and half of the patients had undergone prior focal liver treatment(s).

Overall survival

No study reported OS specifically for CRLM 3–5 cm. Doi et al. reported results both for SABR as for non-ablative radiotherapy and found a median OS of 45 months for patients with at least one CRLM > 3 cm.[63] Conversely, for patients with small-size CRLM ≤ 3 cm, they found a median OS of 27 months.[63] Scorsetti et al. reported a 1-, 2-, and 3-year OS from SABR of 68, 40, and 17%, respectively, for patients with CRLM > 3 cm (Tables 5 and 6).[35]

Toxicity and quality of life

No studies reported the complication rate or the effect of SABR on quality of life for patients with CRLM > 3 cm. Two studies reported no grade ≥ 3 toxicity.[35,64] Scorsetti et al. found grade 2 acute toxicity in 78% of the study population (55% fatigue, 25% transient hepatic transaminase increase, 12% nausea).[35] One series reported 2/24 patients with grade 3 toxicity, 1 patient with grade 3 γ-glutamyl transpeptidase (GGT) elevation, and 1 patient with grade 3 GGT and blood bilirubin elevation presumably caused by cholangitis due to a recurrent tumour.[63]

Disease-free survival and local control

Doi et al. found a 1- and 2-year local control of 50.4% and 10.5% for intermediate-size CRLM and 71.4% and 26.8% for large-size CRLM > 5 cm, respectively.[63] Joo et al. reported a local control for CRLM > 3 cm that correlated with the delivered radiation dose (BED < 132 Gy vs. ≥ 132 Gy): 67% vs 90% ($p = 0.06$).[64]

Author/ year	Type of study	Yrs of inclusion	Treatment modality	No pts in tot	No pts CRLM >3cm	Age* yrs	Dose, fractions, (BED10)	EHD*	Prior local treatment of liver *	Lesion size (range) cm	Median FU in months *
Doi/ 2017[63]	Retro	2007-2014	LINAC	24	15	64 med	45.0-72.0 Gy, 4-33 fr (71.7 - 115.5Gy)	-	16 pt (66.7%)	3.5 (0.7-11.69)	16.5
Joo/2017[64]	Retro	2007-2014	LINAC	70	-	65 med	30-60Gy, 3-5 fr (58.4-180Gy)	19 pt (27%)	35 pt (50%)	2.9	34.2
Scorsetti/ 2015[35]	*Phase II*	*2010-2012*	*LINAC*	*42*	*27pt^*	*67 mean*	*45.6-85.7Gy/ 3fr (262.5Gy)*	*11 pt (26%)*	*21 pt (50%)*	*3.5 (1.1-5.4)*	*24*

Table 4. Overview of included studies reporting on SABR. *Of total amount of patients. ^ 27 patients with cumulative GTV ≥ 3 cm, not actual lesion size > 3 cm.

Author	No. CRLM 3-5cm	No. CRLM >5cm	No. CRLM >3cm	Median OS >3cm	1yr OS	2 yr OS	3yr OS	LC >3cm	1yr LC	2 yr LC	LTPFS
Doi (63)	13	8	21	45 mo	-	-	-	-	3-5 cm 50.4% >5cm 71.4%	3-5cm 10.5% >5cm 26.8%	15 mo
Joo (64)	-	-	42	-	-	-	-	BED<132Gy 67%, BED>132Gy 90%	-	-	
Scorsetti (35)	-	-	*24*	-	*>3cm 68%*	*>3cm 40%*	*17% ^*	-	-	-	

Table 5. Overview of OS and local control for SABR. ^ Percentages retrieved from graphs

Irreversible electroporation

Patient and lesion characteristics

The search resulted in one retrospective series specifically reporting on treatment of intermediate-size CRLM.[65] Fruhling et al. reported on 30 patients in total, of which nine patients had 9 CRLM of 3–4 cm in size. More than half of the patients had received previous local treatment(s) of the liver and all patients were treated by percutaneous IRE. Median follow-up was 22.3 months.

To extend data on IRE for CRLM > 3 cm we included the final results of an as of yet unpublished prospective multicenter phase IIb single-arm study (COLDFIRE-2 trial) where 51 patients were treated with IRE in 62 procedures. Although currently under review, the trial protocol was previously published[68], the results have been presented at ECIO 2019 in Amsterdam, and the outcomes are available as online abstract.[69] Twenty-one (27.6%) out of the 76 IRE-treated CRLM were 3–5 cm in size.

Overall survival

Fruhling et al. reported a median OS from IRE for intermediate-size CRLM of 19.7 months.[65] Meijerink et al. reported a median OS from IRE of 32.4 months (95% *CI* 19.2–45.6 months), although they did not report median OS specifically for the subgroup of patients with intermediate-size CRLM.

Complications and quality of life

Fruhling et al. reported four complications in nine patients after IRE of intermediate-size CRLM. Three patients with CTCAE grade I/II complications (episode of shortness of breath, of increased blood pressure and ECG changes during IRE and chest pain requiring morphine) and one patient with a CTCAE grade III complication, namely, a portal vein and biliary duct stricture in the IRE ablated zone. A stent was placed for the portal vein stricture and a percutaneous trans-hepatic cholangiography (PTC) drainage catheter was placed for the biliary duct stricture. Meijerink et al. did not report complications for CRLM 3–5 cm and both series did not report the effect of IRE on quality of life.[65]

Disease-free survival, local-tumour-progression-free survival, and local control

DFS was not reported specifically for CRLM > 3 cm. After a median follow up of 22.3 months, in five out of nine patients (55.6%), local-tumour-progression was detected.[65] Meijerink et al. did not find a significant difference in LTPFS between small- and intermediate-size CRLM (HR 1.72; *CI* 0.73–4.06; $p = 0.22$).[69] With a minimum follow-up of 1 year, median per-patient and per-tumour LTPFS was not reached. Including repeat procedures, local control was eventually realized in 74% (37/50) of patients.

Comparison of SABR to thermal ablation

Local tumour progression

Franzese et al. performed a propensity score–based comparison of SABR to MWA in 135 patients with CRLM with freedom from local progression (FFLP) as primary endpoint.[66] Stratified analysis by lesion size showed that SABR improved FFLP in patients with lesions > 3 cm and FFLP was similar for both treatment techniques in patients with lesions ≤ 3 cm. Additional data collection showed FFLP specifically for intermediate-size CRLM, suggesting a benefit in local control of SABR compared to MWA in the treatment of larger lesions. After at least 1 year of follow-up, local tumour progression was reported in 8 of 39 CRLM for SABR and 11 of 30 CRLM for MWA of intermediate-size lesions.

Nieuwenhuizen et al. performed a multivariate analysis of thermal ablation compared to SABR for unresectable CRLM to evaluate local tumour progression in the prospective AmCORE registry.[67] Subgroup analyses were performed for larger size lesions (> 3 cm) and additional data collection showed local tumour progression in 11/20 tumours following SABR and 22/41 tumours following thermal ablation with at least 1 year of follow-up.

Overall comparison of local tumour progression following SABR and thermal ablation showed no significant difference ($p = 0.50$).

Author/ year	Type of study	Yrs of inclusion	No pts SABR/ TA	Age * yrs	Median size SABR/ TA	Local tumour progression SABR/ TA	Median time to local tumour progression SABR/ TA	Dose range SBAR	Median FU in months *
Franzese/ 2018[66]	Retro	2009-2016	39/ 30	73	36.5/ 34.0 cm	20.5%/ 36.7%	20.0/ 13.9 months	50.25 – 75 Gy	24.5
Nieuwenhuizen/ 2021[67]	Retro	2005-2011	20/ 41	63	38.0/ 44.0 cm	55.0%/ 53.7%	9.0/ 6.0 months	40 – 60 Gy	29.3

Table 6. Overview of studies comparing SABR to thermal ablation for intermediate size CRLM. TA, thermal ablation. LTPFS, local tumour progression free survival. *Of total cohort of the study

Guidelines

Full-text analysis was performed for 12 guidelines.[70-81] One guideline included recommendations for CRLM > 3 cm: the UK National Institute for Health and Care Excellence (NICE) guideline stated that "there is controversy over the indication for RFA, most operators will no longer consider lesions > 4 cm in diameter for treatment".[71] All other guidelines either did not report on RFA, MWA, SABR, or IRE at all, or they did not state recommendations for CRLM > 3 cm, or they did not state size limitations.

DISCUSSION

Currently, the preferred treatment method for unresectable intermediate-size CLRM for patients, in whom downstaging or (further) downsizing systemic therapy failed, remains unknown. This systematic review and meta-analysis aimed to collect evidence regarding local ablative therapies to treat unresectable intermediate-size CRLM and to provide a comparison of the most well-known ablative techniques. Literature to reliably assess the oncological outcome was scarce for all treatment options. A substantial shortcoming was the lack of randomized controlled trials comparing treatment methods. In addition, apart from one prospective cohort[62] and one phase II trial[35], virtually, all included studies were retrospective series, with only two of the studies making a comparison between treatment

options for intermediate-size CRLM. Furthermore, the reported oncological outcomes, the study population, and the timing of interventions with regard to periprocedural systemic chemotherapy were highly heterogeneous, making it impossible to draw any conclusion.

The majority of publications on thermal ablation concerned RFA. However, for larger-size tumours, recently, preference has started to shift towards newer generation MWA systems or tumour-bracketing multiprobe ablation techniques as potentially superior alternatives to conventional RFA.[82,83] Presumed benefits of MWA over RFA are consistently higher intratumoural temperatures, faster heating, shorter procedure time, larger ablation volumes, and less susceptibility to the "heat-sink" effect at the cost of a somewhat higher biliary tract complication rate.[84-86] Although few studies compared RFA to MWA for patients with CRLM, several retrospective cohorts reported lower local recurrence rates following MWA compared to RFA, 6% vs. 20% ($p < 0.01$)[19], 10% vs. 20% ($p = 0.02$)[55], 8.6% vs. 20.3% ($p = 0.07$)[87], respectively. In this review, LTP rate at median follow-up after the first ablation ranged 11–78% for RFA[27,43,46,48,51,53,56,58] and 14–38% for MWA.[44,52,61] Although this seems to suggest a preference of MWA for CRLM > 3 cm, the number of MWA treated tumours was low ($n = 41$). A substantial part of the included publications on thermal ablation was relatively old. Consequently, recent advances in technique and improved awareness of the necessity to expand and confirm tumour-free margins following thermal ablation are inadequately represented.[53]

For SABR, merely three articles met the inclusion criteria, and all reported different oncological outcome measures. Hence, no conclusions could be drawn regarding efficacy of SABR for intermediate-size CRLM. Many articles describing results for mixed disease and not for CRLM separately could not be included, because metastases deriving from different primary cancers or different organs containing colorectal metastases can have variable responses.[88-96] Several articles were excluded because they presented hazard ratios regarding small versus intermediate-size CRLM but did not report the actual outcomes per size-subgroup, or they reported on the size of CRLM in volumes and not diameter.[34,90,97]

Two articles met the inclusion criteria for meta-analysis after additional data collection.[66,67] No difference in local tumour progression was found between SABR and thermal ablation. Two excluded publications compared SABR to thermal ablation for hepatic metastases[98,99], without specifying outcomes for intermediate-size CRLM. Stintzing et al. compared single session robotic radiosurgery (RRS) to percutaneous RFA in 2 × 30 patients and matched them for size (mean 33–34 mm) and number of lesions.[98] They found that patients treated with RRS had a longer LTPFS compared to patients treated with RFA (34.4 vs. 6.0 months; $p < 0.001$), recurrence rates were similar (67 vs. 63%), and there was a trend towards prolonged median OS for RFA treated patients (34.4 vs 52.3 months; $p = 0.06$). A retrospective cohort by Jackson et al. compared SABR to RFA in 161 patients with liver metastases.[99] SABR demonstrated a superior FFLP compared to RFA, especially for hepatic metastases ≥ 2 cm.

There was no difference in median OS (25.9 months for RFA vs. 24.5 months for SABR). These studies, compared to the included studies in meta-analysis, imply a superior local control of SABR compared to thermal ablation for larger-size lesions. However, only comparing local control rates following one ablative procedure seems unjust when comparing a repeatable technique (RFA, MWA) with a technique that usually does not allow for retreatment (SABR). No studies reported a direct comparison of thermal ablation to SABR with regard to periprocedural complications and toxicity for intermediate-size CRLM, though both techniques are associated with an exceptionally low mortality and morbidity rate. Given the comparable overall reported mortality of 0.16% for thermal ablation[100] and 0.5% for SABR[101] (with 3/656 patients mistakenly published as 0.004%) and given the comparable serious adverse event rate of 4–5% for thermal ablation and 9% for SABR.[100,101] Because both ablative probes and ionizing radiation will potentially result in collateral morbidity by invading surrounding healthy tissue, we prefer to refrain from using the term non-invasive for SABR.

Only two studies concerning IRE were included in this review. This low number can be explained by the relative novelty of this technique and because it is generally a niche indication for CRLM unsuitable for resection and thermal ablation due to close proximity to biliary or vascular structures.[40] Interestingly, the results of the prospective phase II trial (COLDFIRE-2) did not reveal a difference in 1-year LTPFS for small-size versus intermediate-size CRLM, which may indicate that IRE, where electrodes bracket tumours, is less susceptible to differences in size.[102]

A recent multidisciplinary consensus document concerning resectability and ablatability criteria for liver only colorectal metastases did not provide strict recommendations for unresectable intermediate-size CRLM due to a lack of evidence and also stated that the exact roles of SBRT and IRE in the treatment of unresectable CRLM need to be further investigated.[103]

Although systematically acquired, the results of this systematic review and meta-analysis should be judged with restraint, as only a limited amount of studies could be included, with poor quality and heterogeneous study populations. There is a high risk of publication bias due to the inclusion of mainly retrospective observational studies.

CONCLUSION

There are no randomized controlled trials or comparative studies on local treatment for patients with intermediate-size unresectable CRLM. Heterogeneity of the reported oncological outcomes and study populations reduced the amount of obtained data suitable for pooled assessment. Although long-term disease control was described in subsets of patients in all series, there is a lack of studies directly comparing RFA to MWA or to SABR or IRE. No hard conclusions or recommendations can be drawn and further prospective research is necessary to determine what local treatment option, if any, is preferable for intermediate-size unresectable CRLM, preferably in the setting of randomized controlled trials. Therefore, we strongly support the ongoing trials, the COLLISION-XL trial *NCT04081168* (unresectable colorectal liver metastases: stereotactic body radiotherapy versus microwave ablation — a phase II randomized controlled trial for CRLM 3–5 cm), an RCT in Denmark for CRLM < 4 cm *NCT03654131* (stereotactic body radiation therapy vs microwave ablation for colorectal cancer patients with metastatic disease in the liver), and an RCT in Italy for CRLM < 4 cm *NCT02820194* (a trial on SABR versus MWA for inoperable colorectal liver metastases). Hopefully, the results of these trials will clarify and define the role of local ablative methods for the curative intent treatment of permanently unresectable intermediate-size CRLM.

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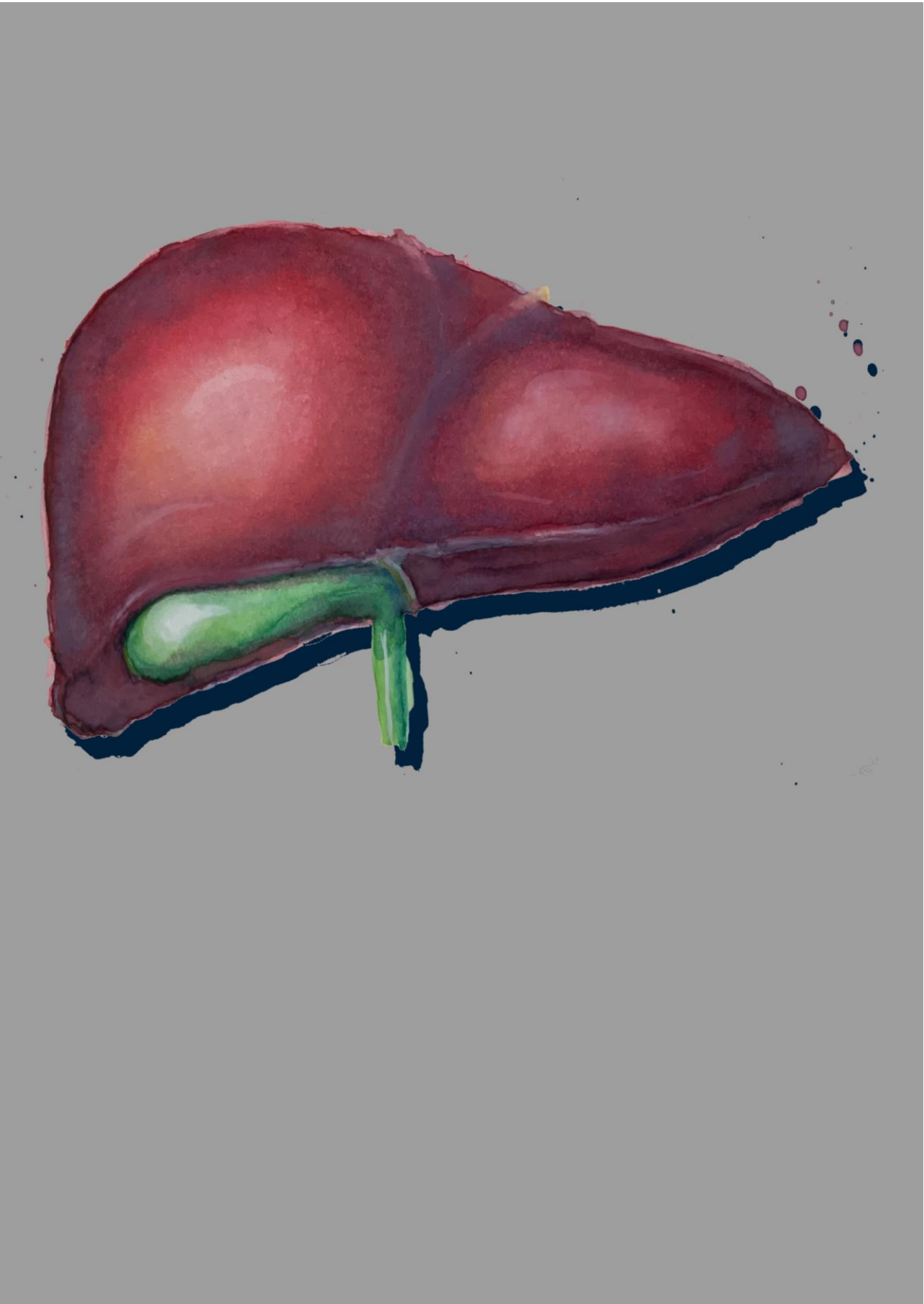

CHAPTER 4

Long-term oncological outcomes of thermal ablation

4.1

Improved outcomes of thermal ablation for colorectal liver metastases: a 10-year analysis from the prospective Amsterdam Colorectal Liver Met Registry (AmCORE).

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ABSTRACT

Background To analyze long-term oncological outcomes of open and percutaneous thermal ablation in the treatment of patients with colorectal liver metastases (CRLM).

Methods This assessment from a prospective, longitudinal tumor registry included 329 patients who underwent 541 procedures for 1350 CRLM from January 2010 to February 2021. Three cohorts were formed: 2010–2013 (129 procedures [53 percutaneous]), 2014–2017 (206 procedures [121 percutaneous]) and 2018–2021 (206 procedures [135 percutaneous]). Local tumor progression-free survival (LTPFS) and overall survival (OS) data were estimated using the Kaplan–Meier method. Potential confounding factors were analyzed with uni- and multivariable Cox regression analyses.

Results LTPFS improved significantly over time for percutaneous ablations (2-year LTPFS 37.7% vs. 69.0% vs. 86.3%, respectively, P\.0001), while LTPFS for open ablations remained reasonably stable (2-year LTPFS 87.1% [2010–2013], vs. 92.7% [2014–2017] vs. 90.2% [2018–2021], P = .12). In the latter cohort (2018–2021), the open approach was no longer superior regarding LTPFS (P = .125). No differences between the three cohorts were found regarding OS (P = .088), length of hospital stay (open approach, P = .065; percutaneous approach, P = .054), and rate and severity of complications (P = .404). The rate and severity of complications favored the percutaneous approach in all three cohorts (P = .002).

Conclusion Over the last 10 years efficacy of percutaneous ablations has improved remarkably for the treatment of CRLM. Oncological outcomes seem to have reached results following open ablation. Given its minimal invasive character and shorter length of hospital stay, whenever feasible, percutaneous procedures may be favored over an open approach.

INTRODUCTION

Colorectal liver metastases (CRLM) develop in up to 50% of patients with colorectal cancer, unfortunately only onefifth of these patients are eligible for curative local treatment.[1-6] Most consider surgical resection the golden standard in upfront resectable CRLM, however, the deep-rooted mantra that surgical resection is the only curative intent treatment option for CRLM seems no longer factual.[1,2,4,7] Radiofrequency (RFA) and microwave (MWA) ablation have proved themselves to result in cure in selected patients and consequently became routine treatment options for smaller-size hepatocellular carcinoma (≤ 2 cm) and unresectable small (≤ 3 cm) CRLM.[1,4,8-10]

Thermal ablation can be performed via an open, laparoscopic or percutaneous approach. Laparoscopic ablation is increasingly being performed due to its minimal invasive character compared to ablations via laparotomy, and local control rates are reported to be comparable between the two approaches.[11] However, laparoscopic ablation is technically more demanding and requires a fairly high level of expertise, which is presumably the reason that it is not yet widely embraced worldwide.[4,12,13] The percutaneous approach is mainly preferred in patients whose comorbid conditions preclude surgery, for centrally located tumors otherwise requiring a major resection (parenchyma-sparing), or in patients with regional or local tumor progression after prior local liver treatment.[14-18] This minimally invasive percutaneous approach is known for its favorable safety profile with low major complications rates (1.3%–2.4%).[14,19,20]

Thermal ablation procedures have developed rapidly in terms of a potential learning curve effect, extensively upgraded device specifications, optimization of anesthetic techniques, use of image guidance tools and image fusion software platforms for volumetric assessment of the ablation zone.[6,7,21-26] When it comes to analyzing the efficacy and improvement of a certain treatment modality, the technique to eradicate tumors can best be elucidated by analyzing local control and time-to-local tumor progression.[2,27] Local tumor progression (LTP) rates after thermal ablation of CRLM vary widely in the literature, ranging 7.6–22.2% for patients treated by percutaneous procedures and 2.7–9.5% for patients treated by open ablation.[7,11,28-32] Median overall survival (OS) rates after thermal ablation are reported mainly in matched cohorts or after multivariable analysis and vary from 34.3 to 53.2 months with 5- and 10-year survival rates of 20.8–60.0% and 18.0%, respectively.[9,19,20,33-39]

As oncological outcomes of thermal liver ablation differ substantially among semi-recently published papers and evidence regarding the potential improvement over time, in terms of local control and time-to-local tumor progression, is lacking, this single-center Amsterdam Colorectal Liver Met Registry (AmCORE) based study aimed to analyze local disease control and survival outcomes following thermal ablation in patients treated for hepatic metastases from colorectal cancer over the last 10 years.

MATERIAL AND METHODS

Patients

Data were sourced from a prospective, longitudinal tumor registry for patients with hepatic metastases from colorectal cancer. All patients were treated at the Amsterdam UMC, location Vrije Universiteit (Amsterdam, the Netherlands), a tertiary referral institution for hepatobiliary and gastrointestinal malignancies. Approval was granted from the affiliated Institutional Review Board (reference number 2021.0121).

Between January 2010 and February 2021, 449 consecutive patients with liver-only metastatic colorectal carcinoma underwent open or percutaneous thermal ablation with RFA or MWA (Fig. 1). One-hundred fifteen patients were excluded for having no available follow-up data at our institute. Although higher morbidity rates have never been reported after simultaneous liver ablation and bowel resection, partial hepatectomy plus colon surgery is known to be associated with a significant increased postoperative morbidity rates.[40] To overcome potential outcome interference, 15 patients were excluded having received simultaneous bowel resection. The remaining 329 patients underwent 541 procedures for 1350 liver metastases. Preprocedural treatment planning (e.g., angle of probe insertion) was performed prior to all procedures, and for percutaneous sessions, all needles/antennae were inserted under real-time computed tomography (CT) imaging. All patients had an Eastern Cooperative Oncology Group status of ≤2. The diagnosis of CRLM was based on cross-sectional imaging containing CT, magnetic resonance imaging (MRI) and [18F]-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET)–CT scans. Treatment planning was routinely discussed in a multidisciplinary tumor board. An open rather than a percutaneous approach was chosen in case of liver metastases needing concomitant partial hepatectomy or when a percutaneous approach was technically not feasible due to the position of the tumor (e.g., in close proximity to the stomach). Although induction systemic therapy is not standard of care within the Netherlands, three patient categories did often receive induction systemic therapy first, namely: (A) patients with locally advanced primary (rectal) cancer, (B) patients with unresectable but potentially downstagable CRLM or with difficultly resectable disease if systemic therapy is likely to reduce procedural risk, and (C) patients with early metachronous disease. Chemotherapy regimen consisted of either capecitabine or irinotecan monotherapy, capecitabine and oxaliplatin (CAPOX), capecitabine + irinotecan (CAPIRI), folinic acid + 5-fluorouracil + oxaliplatin (FOLFOX) or folinic acid + 5-fluorouracil + irinotecan (FOLFIRI). Additional monoclonal antibodies (bevacizumab or panitumumab) were added in case of potentially downstagable disease. Conformal to national guidelines, no patients received adjuvant systemic therapy.[41]

The baseline characteristics of all enrolled patients are summarized in Table 1. Of 541 procedures, 232 were performed intraoperatively and 309 under CT guidance. A total of 653 metastases were treated with RFA (481 by open approach; 172 percutaneous) and 697 metastases with MWA (327 open and 370 percutaneous). A total of 171 procedures (31.6%) were performed after induction chemotherapy. The median number of treated tumors per procedure was 2.0 (IQR 3.0) in the entire cohort. Of 232 open procedures for 808 metastases, 449 (55.6%) metastases were ablated in the same session as concurrent partial hepatectomy was performed. Median follow-up time after each ablation was 16.5 months (IQR 26.8) in the entire cohort.

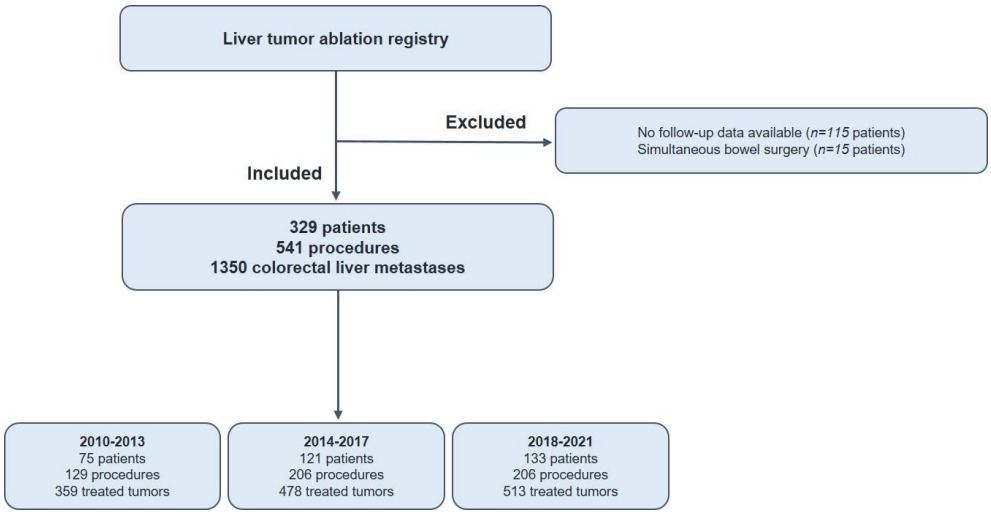


Figure 1. Flowchart of in- and excluded patients

Ablation method

The vast majority of open and percutaneous ablations were performed by three interventional radiologists (BM, JV, MM) who have performed and/or supervised >100 image-guided tumor ablations. The staff in our department has been almost stable over the last ten years. Approximately one-third of the procedures were performed by two interventional radiologists at the same time. During approximately 60% of all ablation procedures, the senior interventional radiologist (MM) was present. The procedure and other study-related details are given in supplementary materials (Appendix 1).

Efficacy evaluation and follow-up strategy

Within the first two weeks after the initial procedure, a quality control contrast-enhanced CT scan was performed when there was a potential inadequate safety margin (0–5 mm) in combination with sub-optimal tumor conspicuity and needle visibility during the procedure.[6] This allowed for an early completion ablation procedure, if indicated. Follow-up should have consisted of at least one cross-sectional imaging modality study to reliable exclude or detect LTP. Regular follow-up consisted of [18]F-FDG PET CT scans every 3 months after the initial ablation during the first year of follow-up and roughly every 6 months thereafter, according to national guidelines[41] and the standardization paper[2]. Additional MRI was only performed in case of uncertainty whether LTP was present. Follow-up imaging was reviewed by the interventional oncology team, certified diagnostic abdominal radiologists and nuclear physicians. If loco-regional disease recurrence was found on follow-up imaging, optimal retreatment was offered based on recommendations of the multidisciplinary team, depending on the extent of the disease in the liver, hepatic function, extrahepatic metastases and general condition of the patient.

Data collection and statistical analysis

For the sake of oncological outcome analyses, the entire cohort was divided into three subgroups (2010–2013, 2014–2017 and 2018–2021). Standard demographic, clinical and surveillance data were retrieved from the electronic database. Categorical variables are reported as frequencies (with or without percentage; %), whereas continuous variables are presented as median (IQR, interquartile range) or mean (± SD, standard deviation). Differences between the three subgroups in terms of baseline variables and outcomes were determined by using the Pearson Chi-square (χ^2) test for categorical variables ([a]) and the one-way ANOVA ([b]) for comparison of means between the three subgroups.

Endpoint definitions were used along the consensus guidelines for the definition of time-to-event endpoints in image-guided tumor ablation by Puijk et al.[27] To study the primary endpoint, a time-to-event superiority analysis was used to analyze local tumor progression. LTP was defined as growth of tumor tissue at the initial treated tumor site.[2,27] Patients were followed until the first recorded evidence of LTP (event) or until the last follow-up exam for those alive without LTP. Local tumor progression-free survival (LTPFS) curves, per patient and per tumor, were estimated using the Kaplan–Meier method and compared between subgroups using the log-rank test. Death without LTP was considered a competing risk. LTPFS over time was analyzed by allocating patients into one of three historical cohorts (2010–2013; 2014–2017 and 2018–2021). Baseline variables with P-values <.05 were entered in the univariable analysis. Uni- and multivariable analyses for LTPFS were performed by using the Cox proportional hazard regression model in the entire cohort.

Variables with P<.05 in the univariable analysis were included in the final multivariable model. Hazard ratios (HR) and 95 percent confidence intervals (95% CI) were calculated. Using backward selection procedure, results of step-by-step removed variables were reported. Results are from last step before removal. Secondary endpoints were overall survival (OS) and safety. OS probability was estimated using the Kaplan–Meier method (time from the first ablation until the date of death or to the last follow-up visit or exam) for the entire cohort. Death during the index hospitalization or within 30 days after treatment was considered perioperative mortality. Safety in terms of complications was evaluated and reported using the standardized Common Terminology Criteria for Adverse Events (CTCAE) grading system, version 4.0 and 5.0.[2,27,42]

Statistical analyses were performed in consultation with an independent statistician (BLW) using SPSS® software, version 24.0 (IBM®, Armonk, New York, USA)[43] and the R software package, version 3.6.3 (R Foundation, Vienna, Austria).[44] Statistical significance was established for P<.05. All results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational study data.[45]

RESULTS

Technical success and local tumor progression

A total of 329 patients (mean age, 65.3 years ± 10.8; 222 men) met the inclusion criteria (Fig. 1 and Table 1). Incomplete ablation rate was 1.0% (14/1350), identified on early follow-up imaging and retreated within ten weeks following the initial ablation. The cumulative LTP rate after 6 months, 1, 2 and 3 years follow-up was 7.4% (100/1350), 11.6% (156/1350), 13.6% (183/1350) and 13.9% (186/1350), respectively, in the entire cohort demonstrated in Table 2 and illustrated as Kaplan–Meier estimates of LTPFS in Fig. 2. For small-size metastases only (≤ 3 cm) (n = 1125), the cumulative LTP rate was 10.7% (120/1125) during a median follow-up duration of 17.5 months (IQR 27.1).

Multivariable analysis revealed four factors associated with an inferior LTPFS (Table 3): no induction chemotherapy (HR 0.480, P<.001), percutaneous approach (HR 4.265, P<.001), larger size of metastasis (HR 1.932 for intermediate size [31-50 mm] and HR 4.783 for large size [[50 mm], P<.001). Adjusted HR of ablations performed between 2014–2017 compared to 2010–2013 was 0.437 (95% CI 0.301–0.636) and 2018–2021 compared to 2010–2013 was 0.244 (95% CI 0.142–0.419) (P<.001).

LTPFS per time frame is demonstrated in Fig. 3 (P<.001). A per approach sub-analysis revealed LTP rates of 7.9% (64/808) for liver metastases treated with open ablation and

22.5% (122/542) for percutaneously ablated tumors, as shown in Fig. 4. The two-year LTPFS rate improved from 37.7% (2010–2013), to 69.0% (2014–2017) to 86.3% (2018–2021) (P<.0001) for patients treated with percutaneous ablation, while no temporal difference was found in LTPFS for patients treated with open ablation (87.1% vs 92.7% vs 90.2%, respectively; P = .12) (Fig. 4c-f; P-values in chart). Improvement in LTPFS was most remarkable after percutaneous ablation - as such, sub-analysis of all percutaneous procedures was performed to evaluate potential influencing factors. Procedure- and tumor-related characteristics of all percutaneous ablations are listed in Appendix 2a and 2b. Multivariable analysis revealed two factors associated with a superior LTPFS: Anesthetic management (HR 0.296 for propofol sedation and HR 0.978 for general anesthesia compared to midazolam + fentanyl sedation, P<.001). Adjusted HR of percutaneous ablations performed between 2014 and 2017 compared to 2010–2013 was 0.495 (95% CI (0.289–0.847) and 2018–2021 compared to 2010–2013 was 0.221 (95% CI 0.107–0.459) (P<.001).

Table 1. Clinical characteristics.

		Total	**2010-2013**	**2014-2017**	**2018-2021**	***P* value**
Patient-related characteristics		**N=329**	**N=75**	**N=121**	**N=133**	
Gender	Male	222	52	86	84	.375 [a]
	Female	107	23	35	49	
Age, years *		65.3 (10.8)	63.4 (10.5)	65.5 (9.5)	66.2 (12.0)	.196 [b]
ASA physical status	1	23	7	9	7	.493 [a]
	2	229	53	86	90	
	3	71	12	25	34	
	Unknown	6	3	1	2	
Comorbidities	None	160	34	61	65	.449 [a]
	Minimal	118	30	37	51	
	Major	45	8	21	16	
	Unknown	6	3	2	1	
BMI (kg/cm^2) *		26.0 (4.5)	25.7 (4.1)	26.2 (4.5)	25.9 (4.8)	.539 [b]
Disease-related characteristics						
Clinical Risk Score (CRS)	0-2	139	31	39	69	.201 [a]
	≥3	92	17	36	39	
	Unknown	98	27	46	25	
Diagnosis of CRLM	Synchronous	176	38	57	81	.653 [a]
	Metachronous	122	27	45	50	
	Unknown	31	10	19	2	
Primary tumor location	Right-sided	89	25	29	35	.093 [a]
	Left-sided	145	23	55	67	
	Rectum	93	25	37	31	
	Unknown	2	2	-	-	
RAS status	RAS wildtype	29	6	7	16	.773 [a]
	RAS mutation	22	3	5	14	

	Unknown	278	66	109	103	
BRAF V600 status	BRAF wildtype	46	7	11	28	.522 [a]
	BRAF mutation	3	1	-	2	
	Unknown	280	67	110	103	
MSS/MSI status	MSS	58	6	16	36	.739 [a]
	MSI	1	0	0	1	
	Unknown	270	69	105	96	
Procedure-related characteristics		**N=541**	**N=129**	**N=206**	**N=206**	
Situation	Thermal ablation alone	363	90	125	148	.006 [a]
	Simultaneous partial hepatectomy	146	38	65	43	
	Simultaneous IRE	32	1	16	15	
Induction chemotherapy	No	370	80	153	137	.048 [a]
	Yes	171	49	53	69	
No. of locally treated tumors	1-3	374	83	148	143	.349 [a]
	≥4	167	46	58	63	
Approach	Open	232	76	85	71	<.001 [a]
	Percutaneous	309	53	121	135	
Anesthesia technique	General anesthesia	317	108	106	103	NA
	Midazolam + Fentanyl sedation	68	19	49	-	
	Propofol sedation	152	-	50	102	
	Unknown	4	2	1	1	
Image-guidance technique	Conventional (Intraoperative US or CT fluoroscopy)	302	113	105	84	NA
	CT hepatic arteriography	239	16	101	122	
Ablation modality	Radiofrequency	240	113	120	7	<.001 [a]
	RF3000™, LeVeen™	210	98	112	-	
	Cool-tip™	13	5	5	3	
	Starburst® (RITA®)	10	7	8	-	
	Unknown	3	-	-	4	
	Microwave	301	16	86	199	
	Evident™	19	13	12	2	
	Solero™	9	-	5	4	
	Emprint™ with Thermosphere™	262	-	66	188	
	Unknown	6	2	2	2	
	Unknown	9	4	1	4	
Tumor-related characteristics		**N=1350**	**N=359**	**N=478**	**N=513**	
Diameter, mm *		16.2 (11.5)	17.0 (12.9)	16.0 (11.8)	15.9 (10.1)	.686 [b]
Size, mm	Small (1-30)	1125	274	399	452	.010 [a]
	Intermediate (31-50)	147	46	53	48	
	Large (>50)	22	11	8	3	
	Unknown	56	28	18	10	

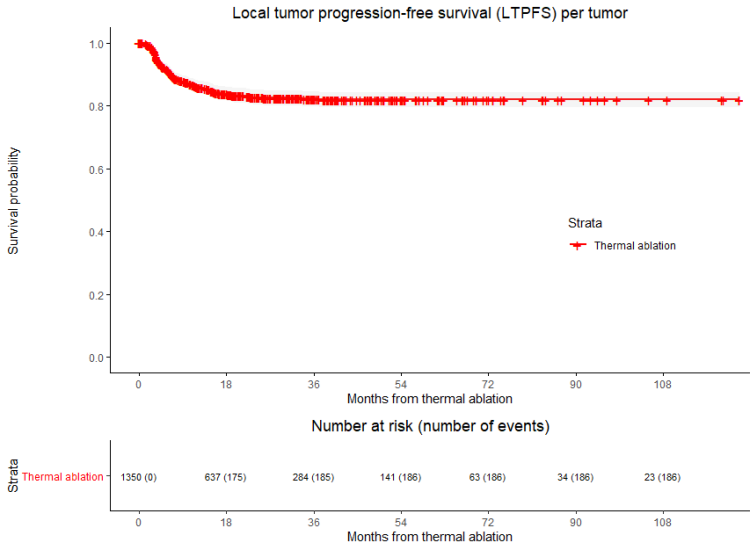
Table 1. continued

Table 2. Outcomes of all thermal ablation procedures.

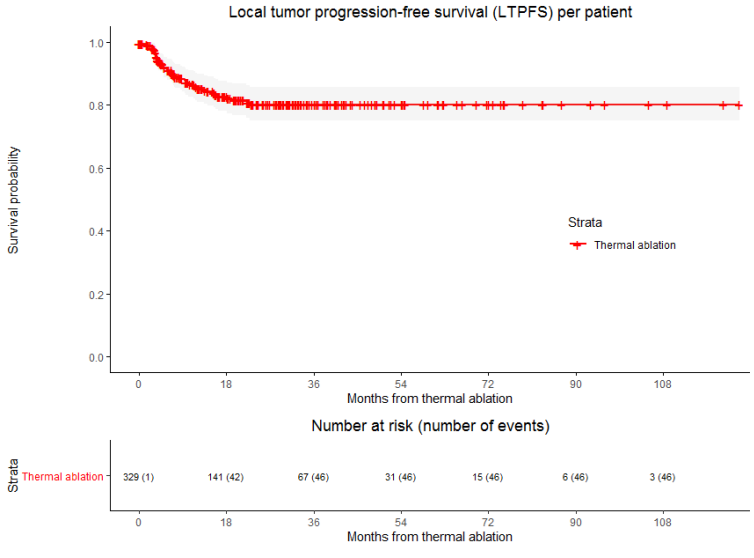
		Total	2010-2013	2014-2017	2018-2021	P value
Patient-related outcomes		**N=329**	**N=75**	**N=121**	**N=133**	
Perioperative mortality (<30 days)		1 (0.3%)	-	1	-	NA
Procedure-related outcomes		**N=541**	**N=129**	**N=206**	**N=206**	
Complications (CTCAE)	Grade 1	28 (5.2%)	8 (6.2%)	9 (4.4%)	11 (5.3%)	.404 [a]
	Grade 2	38 (7.0%)	6 (4.7%)	21 (10.2%)	11 (5.3%)	
	Grade 3	35 (6.5%)	11 (8.5%)	13 (6.3%)	11 (5.3%)	
	Grade 4	5 (0.9%)	-	4 (1.9%)	1 (0.5%)	
	Grade 5	5 (0.9%)	1 (0.8%)	2 (1.0%)	2 (1.0%)	
	Missing	13 (2.4%)	5 (3.9%)	4 (1.9%)	4 (1.9%)	
Follow-up, months, median (IQR)		13.1 (26.6)	10.6 (44.0)	18.6 (33.7)	11.5 (16.1)	<.001 [b]
Tumor-related outcomes		**N=1350**	**N=359**	**N=478**	**N=513**	
Two-year LTP rate, no. tumors		183 (13.6%)	78 (21.7%)	72 (15.1%)	36 (7.0%)	<.001 [a]
Time to detection of LTP, months, mean (SD)		7.1 (5.5)	5.8 (4.8)	8.4 (6.3)	6.9 (4.9)	.074 [b]

Table 3. Factors associated with local tumor progression-free survival identified by univariable and multivariable Cox regression analyses from the time of the first intervention to local tumor progression.

		Univariable Analysis		Multivariable Analysis	
		HR (CI)	***P*-value**	**HR (CI)**	***P*-value**
Timeframe	2010-2013	Reference	**<.001**	Reference	**<.001**
	2014-2017	0.649 (0.471-0.894)		0.437 (0.301-0.636)	
	2018-2021	0.367 (0.247-0.545)		0.244 (0.142-0.419)	
		Procedure-related factors			
Local treatment	Thermal ablation alone	Reference	**<.001**	Reference	.462
	Simultaneous partial hepatectomy	0.395 (0.272-0.574)		1.206 (0.725-2.007)	
	Simultaneous IRE	0.463 (0.217-0.989)		0.668 (0.290-1.543)	
Chemotherapy	No	Reference	**<.001**	Reference	**<.001**
	Yes	0.321 (0.228-0.453)		0.480 (0.332-0.694)	
Approach	Open	Reference	**<.001**	Reference	**<.001**
	Percutaneous	3.686 (2.722-4.990)		4.265 (2.747-6.622)	
Modality	RFA	Reference	**.026**	Reference	.855
	MWA	0.718 (0.535-0.963)		0.964 (0.648-1.434)	
		Tumor-related factors			
Size of metastasis (mm)	Small (1-30)	Reference	**<.001**	Reference	**<.001**
	Intermediate (31-50)	2.536 (1.747-3.682)		1.932 (1.321-2.825)	
	Large (>50)	8.436 (4.647-15.313)		4.783 (2.596-8.814)	

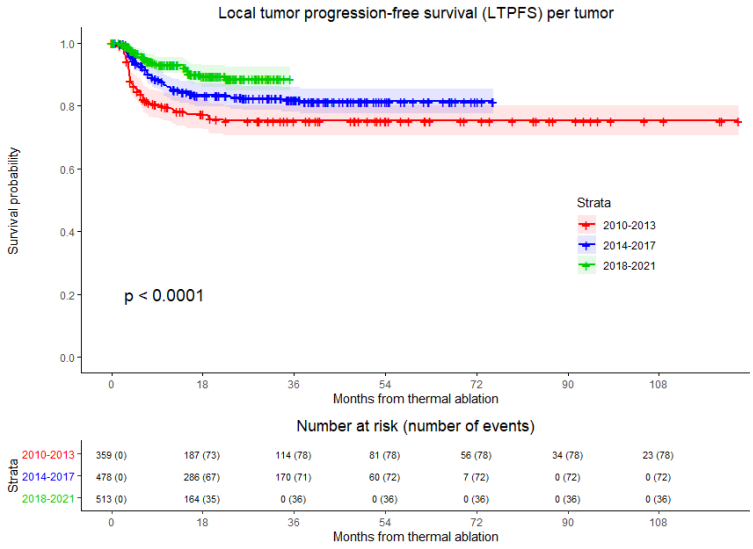


(A)



(B)

Figure 2. Kaplan–Meier survival curves indicating local tumor progression-free survival (LTPFS) per treated tumor (A) and per patient (B) after all thermal ablation sessions. Numbers at risk correspond to the amount of tumors and number of patients respectively. Death without local tumor progression (LTP) is censored (competing risk).



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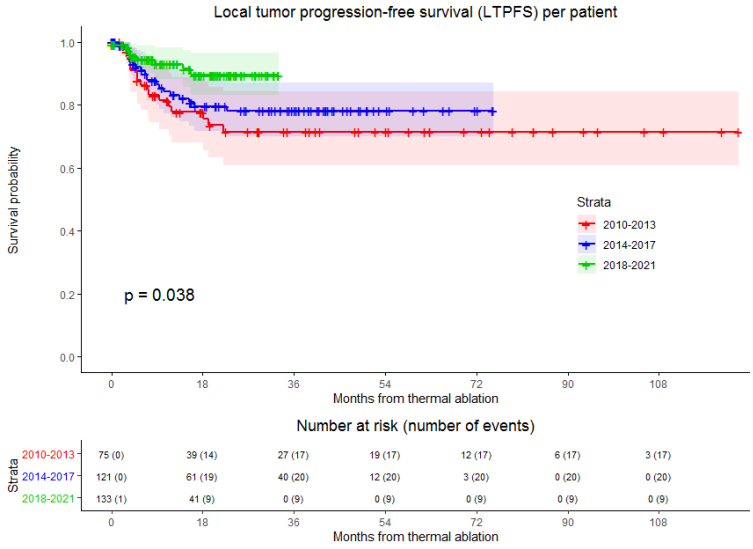
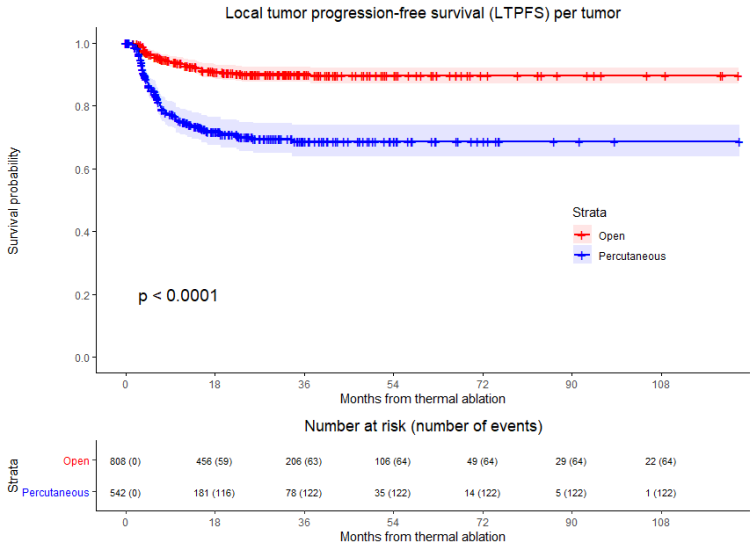
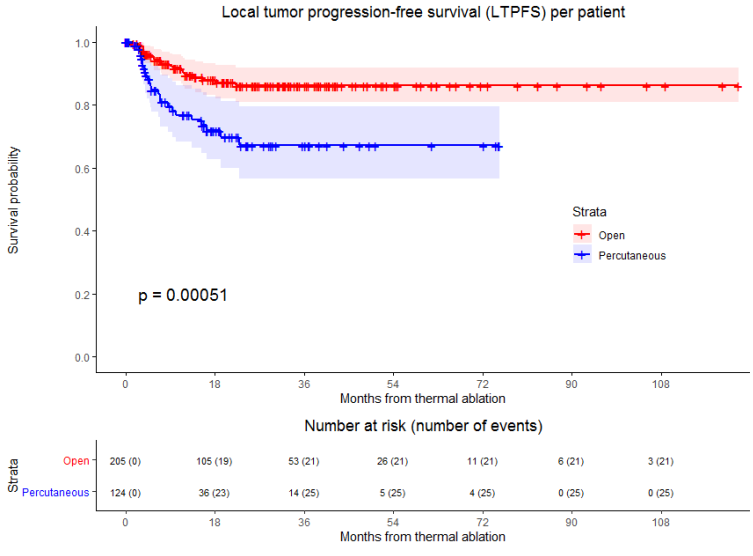


(B)

Figure 3. Kaplan–Meier survival curves indicating the local tumor progression-free survival (LTPFS) per time frame. Analysis per treated tumor (A) and per patient (B). Time frames: 2010–2013; 2014–2017 and 2018–2021. Numbers at risk correspond to the amount of tumors and number of patients respectively. Overall comparison log-rank (Mantel–Cox) test is reported per graph. Death without local tumor progression (LTP) is censored (competing risk).

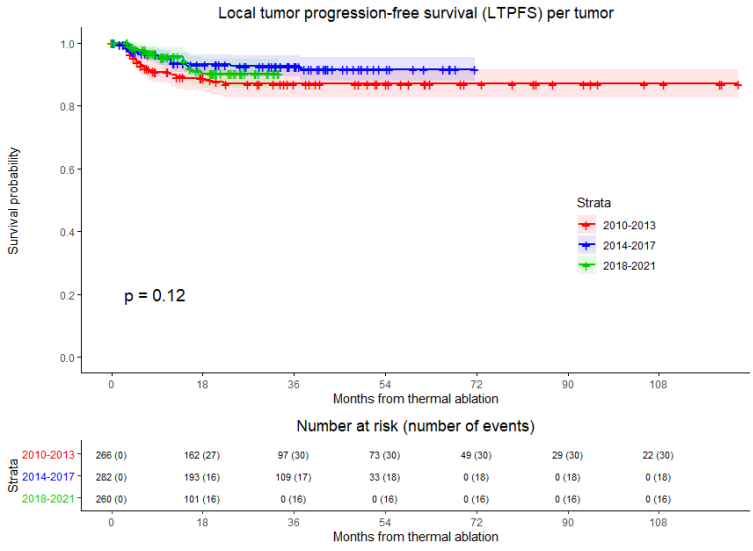


(A)



(B)

Figure 4. continued



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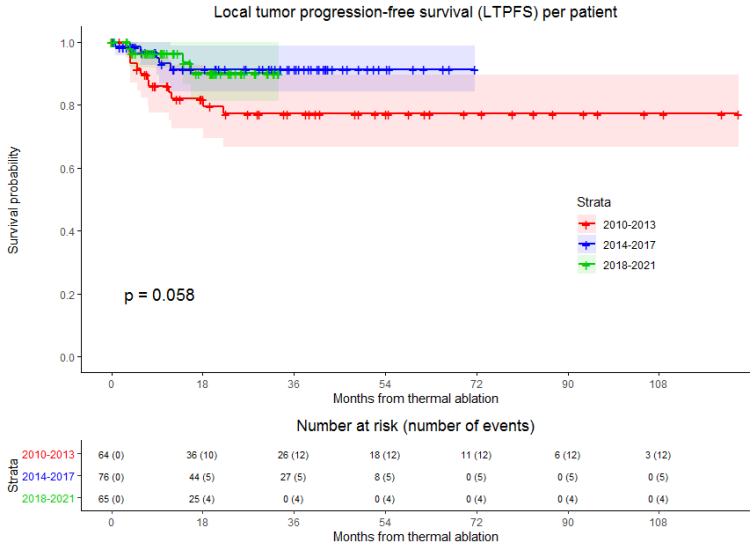

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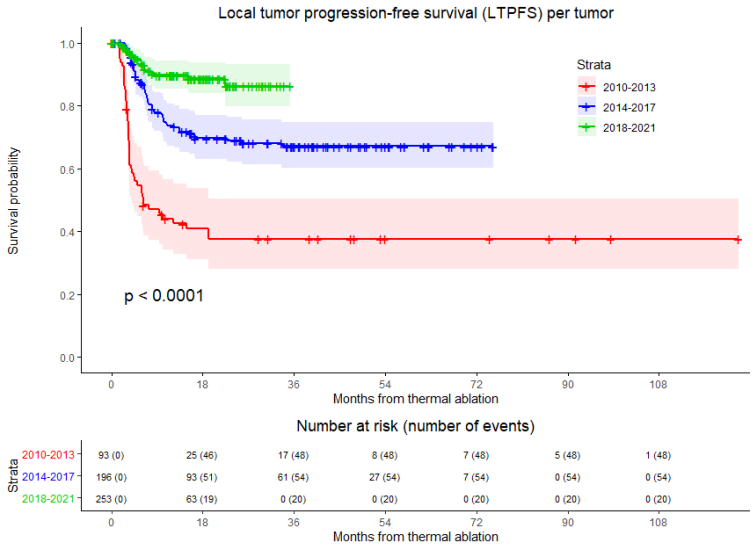

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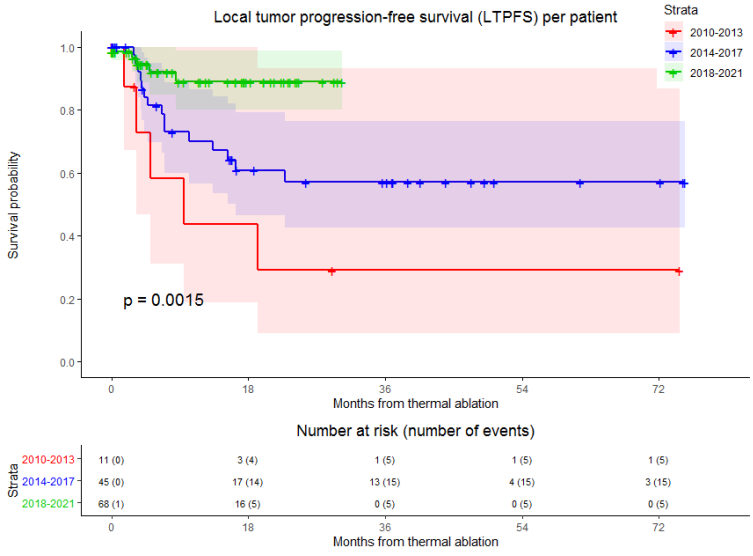

(F)

Figure 4. Kaplan–Meier survival curves indicating local tumor progresssion-free survival (LTPFS) per time frame and approach. A, B Analysis of open and percutaneous thermal ablation per treated tumor and per patient respectively, C and D patients treated with open ablation, analysis per treated tumor and per patient respectively, E and F patients treated with percutaneous ablation, analysis per treated tumor and per patient respectively. Numbers at risk correspond to either the amount of tumors or the number of patients. Overall comparison log-rank (Mantel–Cox) test is reported per graph. Death without local tumor progression (LTP) is censored (competing risk).

Complications and length of hospital stay

Grade 1–5 complication rate in the entire cohort was 20.5% (111/541 procedures; Table 2). The severity of complications did not change over time (P = .404). The rate and severity of complications favored the percutaneous approach in all three cohorts (2010–2013, P = .069; 2014–2017, P = .129; 2018–2021, P = .020). Sub-analysis of procedures were thermal ablation was used solely (in other words without simultaneous resection or irreversible electroporation in case of open procedures), revealed no difference in complication rate between the three time frames (P = .406).

Overall procedure-related mortality was 1.5% (5/329) in the entire cohort. One patient deceased 7 days after combined liver resection and ablation due to massive pulmonary embolism (30-day mortality 0.4%; n = 1/329). Five others died from postoperative complications between 30 and 90 days: one due to massive portal thrombosis and multi-organ failure 5 weeks after combined percutaneous ablation and irreversible electroporation, and three due to abdominal abscesses and cardiopulmonary failure 8–9 weeks after combined liver resection and open ablation.

For open ablations, the mean length of hospital stay did not significantly differ between the three time frames (mean 6.9 days [SD 5.9]; P = .065). Mean hospitalization after percutaneous procedures was 1.4 days (SD 2.6) with no differences between the three cohorts (P = .054).

Overall survival

A total of 99 patients (30.1%) deceased during follow-up (Table 2). Of them, 93 died from disease progression. Survival probability after the first ablative treatment was 92.0%, 78.8%, 45.9% and 26.8% at 1, 3, 5 and 10 years, respectively (Fig. 5). For the entire cohort, the median OS after the first ablation procedure was 54.2 months; 52.0 months in the 2010–2013 cohort and 66.6 months in the 2014–217 cohort. The median OS for the latter cohort was not met. The median OS did not significantly improve over the last decade (P = .088), nor differed for patients treated by open or percutaneous ablation (P = .888).

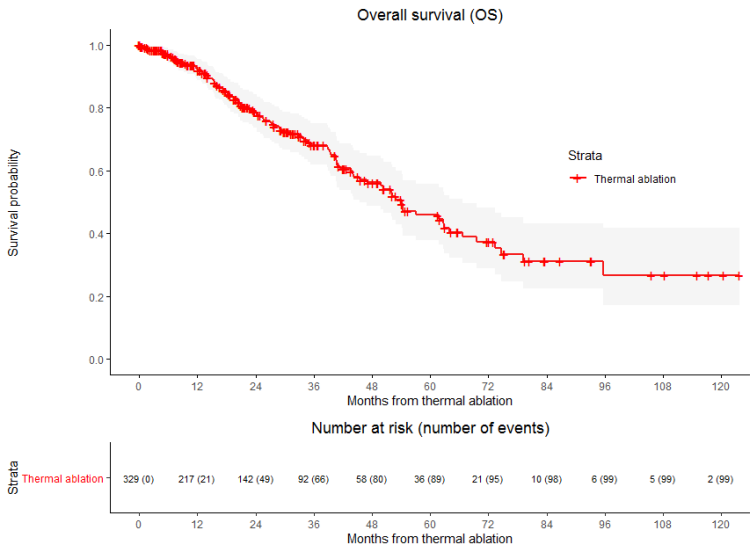

Figure 5. Kaplan–Meier survival curve of overall survival (OS) for patients treated with thermal ablation. Numbers at risk correspond to the number of patients.

DISCUSSION

Over the past decades, thermal ablation has become the standard treatment option to eradicate small unresectable CRLM (≤ 3 cm) and a fair alternative for deepseated resectable CRLM that would otherwise require major hepatectomy.[1,2,4] Though advances in energy delivery in methods for precise probe placement and in ablation confirmation techniques have, often prematurely, been introduced as alleged improvements, our results underwrite technological progresses made over time. The improvement over time, in terms of LTPFS, especially for patients being treated with CT-guided percutaneous ablations, was the most remarkable finding in our study. OS did not significantly improve over the last 10 years. Whether this reflects an absent correlation between survival and local treatment failure, especially given the relative ease to repeat ablations, or the gradual acceptance to offer curative intent ablations to more complex cases with higher disease burden, remains unknown.

Results of this study compare well with OS and LTPFS data published in other recent series regarding thermal ablation of CRLM.[1,14,35-39,46,47] We have reached the point where the local tumor progression rate after percutaneous ablation has approached results following open ablation as well as following partial hepatectomy, as the most recent surgical series report R1/R2 rates varying from 12 to 46%.[48-52] Outcomes of this current cohort study are again underlining the necessity to conduct a randomized controlled trial comparing standard partial

hepatectomy to its less invasive competitor thermal ablation for smaller-size resectable CRLM (≤ 3 cm). Although the phase III randomized LAVA trial (*ISRCTN52040363*) attempted to randomize high surgical risk CRLM patients to surgery or thermal ablation, recruitment feasibility was not established during the pilot stage, and therefore, the trial closed early without having gathered data regarding the primary endpoint two-year disease-free survival.[53] The interim results of the COLLISION trial (*NCT03088150*), presented at CIRSE 2021 and ECIO 2022, confirm thermal ablations' superior safety profile, shorter hospital stay, equal to superior local control and similar OS compared to partial hepatectomy; the final results are eagerly awaited.[54,55] Though a recent comparative analysis favored thermal ablation with regard to OS, LTPFS and eventual local control for small-size (≤ 3 cm), stereotactic body radiation therapy (SBRT) does challenge thermal ablation for intermediate-size (3-5 cm) CRLMs; the ongoing COLLISION-XL trial (*NCT04081168*) will hopefully provide clarity.[56]

Although speculative, the improvement over time, in terms of LTPFS, for patients being treated with percutaneous ablation should probably be contributed to (A) gained experience and (B) technological advancements made during the last decades. A multitude of minor improvements with regard to energy delivery spectrum, antenna and generator design (e.g., ThermosphereTM technology, multiple antennae systems or stereotactic navigation), anesthesia and breath-hold techniques, real-time image guidance (e.g., administration of intra-arterial contrast via an hepatic artery catheter) and the use of rigid and non-rigid image fusion and registration platforms allowing intraprocedural completion ablations seem to have led to this major quality improvement.[6,7,22,24-26,31,57-61]

Some limitations need to be addressed. The median follow-up period in the 2018–2021 cohort was sufficient (11.5 months), but inevitably lower compared to the earlier cohorts. This may have led to the situation where some patients in the latest cohort are still susceptible to developing LTP (immortality time bias), though this only applies to a small amount of tumors; as historically seen, the vast majority of LTPs are detected within the first 3–9 months following local treatment and a clear LTPFS plateau is reached after roughly 18 months follow-up (Fig. 2a).[9] Reported study data were analyzed from prospectively kept records, and potential confounders were excluded by uni- and multivariable analyses, which does not fully guarantee that residual confounding has been eliminated. The fact that periprocedural chemotherapy regimens and follow-up imaging protocols did not change over time decreases the likelihood for residual bias. The lack of a comparison between laparoscopic and open ablated tumors could be a potential limitation as in certain cases the laparoscopic approach might be superior to the open approach in terms of safety and length of hospital stay. Due to technological advancements in energy delivery and reduced procedure time, MWA was gradually favored over RFA, even though previously published data showed no significant difference in terms of local disease control.[6,60,61] Nonetheless, the ablation modality need to be addressed as potential confounder. In addition, the specific ablation devices used in this

study may render the comparative results as they do not necessarily represent all current day ablation systems. Although mutant RAS and BRAF status are known to be associated with LTP[47,62], these tumor characteristics were not routinely measured over the last decade, resulting in high rates of missing data. Furthermore, it should be noted that the national guideline recommendations not routinely offer neo-adjuvant or adjuvant chemotherapy for locally treatable disease, what differs from several other countries and regions, and hence, it may be challenging to compare our results with series where patients were routinely offered (neo-)adjuvant systemic therapy.[41] However, the national guideline recommendations did not change over time and were actually re-established following the recent publication of two clinical trials of which one showed no difference in OS for perioperative chemotherapy (EORTC 40983)[63] and one showed an inferior OS for adding adjuvant chemotherapy (JCOG 0603)[64].

In conclusion, the efficacy of percutaneous ablations for CRLM in terms of local tumor progression-free survival has improved remarkably over the last 10 years and seems to have approached oncological outcomes following open ablations. Over the last decade, no differences were found regarding length of hospital stay, rate and severity of complications, and overall survival. Given its minimal invasive character and shorter length of hospital stay, whenever feasible, percutaneous procedures may be favored over an open approach.

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CHAPTER 5

Periprocedural management in percutaneous liver ablation

5.1

Percutaneous liver tumour ablation: image guidance, endpoint assessment, and quality control

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M.P. van den Tol, M.R. Meijerink

Canadian Association of Radiologists Journal (CARJ) 2018

ABSTRACT

Liver tumour ablation nowadays represents a routine treatment option for patients with primary and secondary liver tumours. Radiofrequency ablation and microwave ablation are the most widely adopted methods, although novel techniques, such as irreversible electroporation, are quickly working their way up. The percutaneous approach is rapidly gaining popularity because of its minimally invasive character, low complication rate, good efficacy rate, and repeatability. However, matched to partial hepatectomy and open ablations, the issue of ablation site recurrences remains unresolved and necessitates further improvement. For percutaneous liver tumour ablation, several realtime imaging modalities are available to improve tumour visibility, detect surrounding critical structures, guide applicators, monitor treatment effect, and, if necessary, adapt or repeat energy delivery. Known predictors for success are tumour size, location, lesion conspicuity, tumourfree margin, and operator experience. The implementation of reliable endpoints to assess treatment efficacy allows for completion procedures, either within the same session or within a couple of weeks after the procedure. Although the effect on overall survival may be trivial, (local) progression-free survival will indisputably improve with the implementation of reliable endpoints. This article reviews the available needle navigation techniques, evaluates potential treatment endpoints, and proposes an algorithm for quality control after the procedure.

INTRODUCTION

With hepatocellular carcinoma (HCC) being the third leading cause of cancer deaths worldwide and colorectal cancer as the second most common cause of cancer-related mortality in developed countries, primary and secondary malignant liver tumours are very frequently encountered. About 40-76% of colorectal cancer patients develop colorectal liver metastases (CRLMs) in the course of their disease.[1,2] Although gradually shifting, surgical resection is still considered the gold standard for curative intent treatment of hepatic malignancies. However, the majority of patients (80-90%)[2,3] cannot undergo partial hepatectomy because of: 1) an impaired general health status; 2) a history of extensive abdominal surgery; 3) early or rapid disease progression; 4) the presence of lesions in an anatomical unfavorable location; or 5) an insufficient future liver remnant to resect all lesions.[1,4-6] Given the negligible ablation site recurrence rate for small (≤2 cm) HCCs, the well-known international Barcelona Clinic Liver Cancer (BCLC) staging system has replaced surgical resection with percutaneous ablation as primary treatment option.[7-15] Similarly, surgery for small (≤3 cm) CRLMs is currently being challenged in 2 large ongoing phase III trials from the Netherlands (the COLLISION [Colorectal Liver Metastases: Surgery vs Thermal Ablation] trial, low-risk patients; *NCT03088150*) and the United Kingdom (LAVA [Liver Resection Surgery vs Thermal Ablation for Colorectal Liver Metastases] trial, high-risk patients; *ISRCTN52040363*).

Over the past 2 decades thermal ablation techniques, such as radiofrequency ablation (RFA) and microwave ablation (MWA), have become auspicious treatment options for patients with hepatic malignancies due to their minimal invasiveness, good and still improving efficacy, potential for repeated ablations, and low costs.[16-23] Irreversible electroporation (IRE) is a novel, predominantly nonthermal, ablation technique that is increasingly investigated for liver tumours near major bile ducts and blood vessels.

Preprocedural staging and treatment planning is quintessential to assess treatment success. Similar to routine workup before partial hepatectomy, at minimum a contrast-enhanced computed tomography (CECT) is required. Routinely performing contrast-enhanced magnetic resonance imaging (MRI) with liver-specific contrast agents such as gadoxetate disodium (Primovist), plus high B-value MR diffusion-weighted imaging (DWI) has proven to reduce intrahepatic recurrence and, therefore, the need for repeat procedures.[24] The use of 2-[18F]-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET) CT may also be indicated for CRLM patients to exclude extrahepatic disease and to differentiate between malignant and benign lesions. However, specificity is suboptimal for mucinous tumours and poor for patients treated with neoadjuvant chemotherapy.[25]

Assessment of treatment response, during and shortly after the procedure, is crucial to determine treatment outcome and patient safety.[26] Conventional B-mode ultrasound (US) remains the gold standard for performing ablative procedures during laparotomy and, although lesion conspicuity remains a prerequisite, is still commonly used to guide percutaneous procedures.[26] CT and MRI are the most established techniques for percutaneous ablation because they enable acquisition of 3-dimensional images of the tumour in relation to the surrounding structures, the probes and the ablation zone.[26,27] Nowadays, image fusion, (electromagnetic or infrared) needle tracking, and robotics can provide even more accurate targeting.[28]

Despite technological advances, the primary technique effectiveness (90-95% for lesions ≤3 cm and <90% for lesions >3 cm in diameter) should still be considered inadequate and requires further improvements.[27] Technical success depends on several factors such as tumour size, molecular subtype (RAS wild type or mutation)[29], location, visibility, tumour-free margin, operator experience, and local availability of devoted equipment, such as (virtual) gantry tilt, computer-assisted fusion and navigation techniques, and open MR systems.[21,23,30-32] Sophisticated image-guiding techniques and parameters to evaluate treatment success directly after or within the first weeks after ablation (allowing for completion procedures) will likely improve outcome. Although the effect on overall survival may be trivial[33], local progression-free and disease-free survival will indisputably increase.

This article reviews currently available image-guiding techniques for percutaneous ablation of liver malignancies, provides an overview of methods to determine technical success, and suggests an algorithm for quality control.

Image-guiding techniques and needle navigation

In percutaneous ablation, adequate imaging is crucial for: 1) preprocedural planning; 2) intraprocedural targeting (needle guidance or catheter delivery); 3) intraprocedural monitoring (real-time imaging of tissue changes resulting from treatment); 4) intraprocedural modification (real-time ability to make adjustments); and 5) postprocedural assessment (measurement of treatment effectiveness and need for further intervention).[23,26] Different imaging techniques can be used, solitarily or in combination, to successfully perform each of these steps (Table 1).

A successful procedure can be achieved by ablation that covers the complete tumour volume plus a certain tumour-free margin without harming nearby critical structures. Therefore, optimal imaging modalities should provide anatomical 3-dimensional (3D) images to depict the target, surrounding structures, and the interventional probes, as well as physiological information indicative for the ablated volume, such as alterations in echogenicity, signal

attenuation, contrast enhancement, or metabolic activity. Although present-day imaging systems provide some of these characteristics, none provide all of them.[23]

Modality	Characteristics
US and CEUS	- Widespread availability, fast, absence of radiation exposure, inexpensive/cheap
	- Good detection of poorly visible lesions on CT or MRI
	- Repeatable in case of suspected residual tumour tissue
	- Pleural effusion: visualize liver tumours near the diaphragm
	- Poor visualization due to location, size, overlying structures, low echogenicity, gas formation in ablation zone
	- CEUS: need for repeated contrast insertion (impossible to scan the whole liver in the arterial phase)
CECT	- Widespread availability, high technical success rate
	- Fluoroscopy: precise targeting, safe, low complication rates
	- Radiation exposure
	- Limited time to differentiate between ablation zone and residual tumour
	- Limited angle of electrode insertion
MRI	- High sensitivity for small parenchymal lesions
	- Real-time monitoring of thermal effects
	- Absence of radiation exposure
	- Higher primary technique effectiveness compared with CT and fewer sessions needed for complete tumour treatment
	- Restricted availability
	- Prolonged procedure time
	- Higher costs
Fusion imaging	- Improves detectability and conspicuity of hepatic lesions with use of precise 3-dimensional targeting
	- Decreases incomplete ablations
	- Reduces procedure time
Needle tracking	- Identification of safest pathway in relation to prior pretreatment imaging with the use of 3-dimensional datasets
	- Decreases procedure time and radiation dose
	- For difficult-to-reach lesions (ie, hepatic dome)
Robotic navigation	- Use of planning software for optimal needle tracking
Catheter-guidance (CTHA, CTAP)	- High accuracy, fewer needle repositionings required
	- Accurate alternative for poorly visible tumours on (CE)US and CECT
	- Higher radiation dose, possible complications due to catheter placement

CECT = contrast-enhanced computed tomography; CEMRI = contrast-enhanced magnetic resonance imaging; CEUS = contrast-enhanced ultrasound; CT = computed tomography; CTAP = computed tomography arterial portography; CTHA = computed tomography hepatic arteriography; MRI = magnetic resonance imaging, US = conventional B-mode ultrasound.

Table 1. Real-time image-guiding techniques and needle navigation modalities in percutaneous liver tumour ablation.

Transcutaneous ultrasound

Conventional B-mode US is the most widely used real-time imaging technique, mainly because it is cheap, fast, easy to use, repeatable, and does not require ionizing radiation.[5,22,33-36] However, visualization of the target lesion can be poor (sensitivity around 55%) due to (deeper) location, small size, obscuration by overlying structures, impediment by gas formation at the ablation zone, liver cirrhosis, and low echogenicity gradient.[35-38] Interestingly, with IRE the ablation zone will become hypoechoic, as opposed to the well-known hyperechoic ablation zone following RFA and MWA (Figures 1 and 2). Contrast enhanced US (CEUS) increases lesion conspicuity and provides better real-time visibility of the target, needle placement, and safety margins.[21,36,39,40] Normally, probe placement below the costal margin increases operating difficulties due to interference of intrapulmonary gas. US combined with artificial pleural effusion provides better visibility for hepatic malignancies located near the diaphragm.[41]

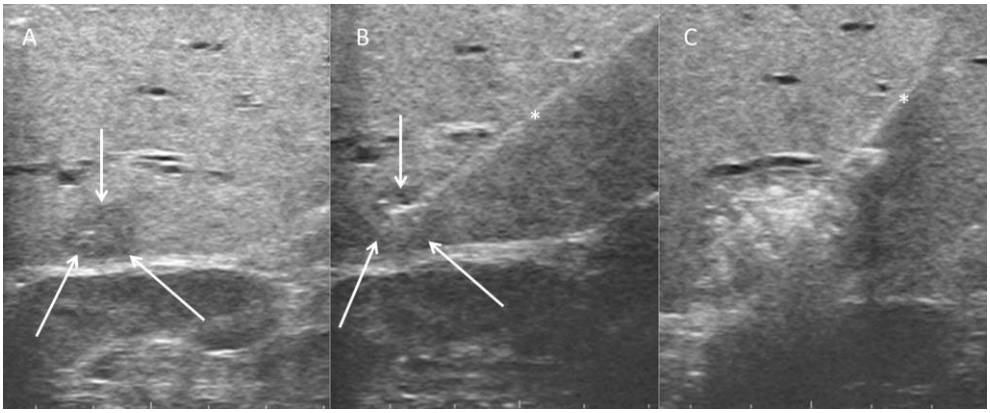

Figure 1. Ultrasound (US) of a small segment VI colorectal liver metastasis treated with radiofrequency ablation. (A) Hypoechoic lesion (white arrows) depicted on B-mode US. (B) The same hypoechoic lesion (white arrows). US during deployment of the tines with the needle electrode (asterisk) clearly visible. (C) Directly after radiofrequency ablation the ablation zone can be depicted as a hyperechoic area due to substantial vaporization and hence gas formation.

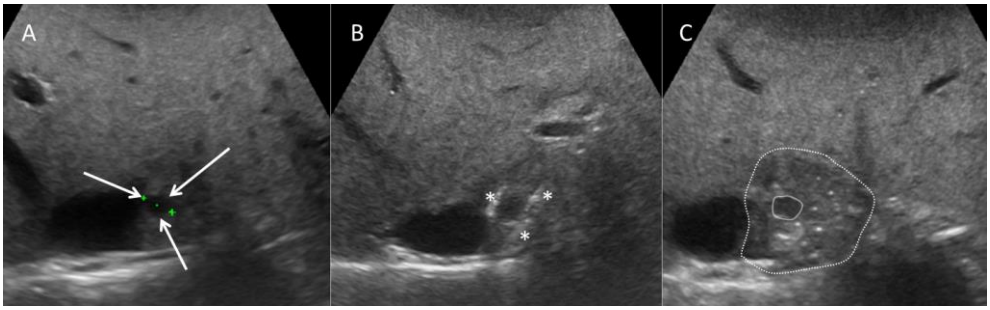

Figure 2. Real-time ultrasound during liver tumour irreversible electroporation (IRE) procedure. Patient with a small segment I colorectal liver metastasis directly adjacent to the inferior caval vein treated with IRE. (A) Hypoechoic lesion (white arrows) depicted on B-mode ultrasound. (B) During IRE the active tip of the needle electrode becomes hyperechoic (asterisk), presumably caused by electrolysis (splitting of H2O molecules in H2 and O2). (C) Contrary to thermal ablation, with IRE the ablation zone can be depicted as a hypoechoic tumour-free area (dotted line) surrounding the lesion (line).

Computed tomography

CECT guidance plus fluoroscopy enables a 3D view of the target tumour, surrounding structures, needle(s), and the ablation zone (Figure 3).[23,42] This guidance modality is associated with a high technical success rate, a fair technique efficacy, and a low complication rate.[43,44] Important disadvantages of CT fluoroscopy are high radiation exposure to patients and physicians, limited angle of needle insertion, and suboptimal visualization of intrahepatic vessels.

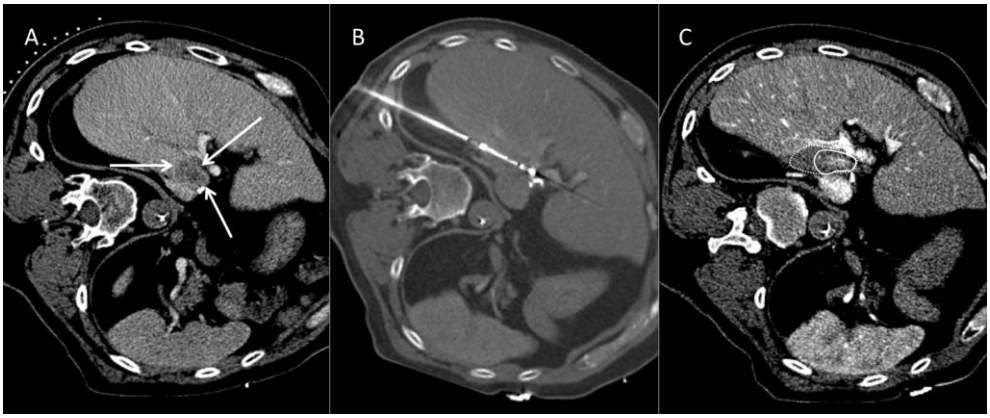

Figure 3. Contrast-enhanced computed tomography (CECT) plus CT fluoroscopy in percutaneous liver tumour microwave ablation (MWA). (A) Patient with a segment I-VI colorectal liver metastasis (white arrows) in between the inferior caval vein and main portal vein. (B) Using CT fluoroscopy the lesion was successfully targeted using an MWA antenna. (C) Post-MWA CECT shows a clear shrinkage of the metastasis (line) surrounded by a nonenhancing tumour-free ablation zone (dotted line). Naturally, there is no tumour-free margin between the ablated lesion and the directly abutting inferior caval vein and main portal vein.

Magnetic resonance imaging

MR-guided liver tumour ablation is known for its near real-time thermal monitoring and is associated with a high sensitivity for small parenchymal lesions.[21,23,38] However, some obstacles still remain, such as potentially harmful noise generated during scanning, interference of electrical noise from ablation devices with MRI, and artifacts of instrument visualization. The longer procedure time, higher costs, and restricted availability have limited the use of real-time MRI in clinical practice.[23,45] Compared with CT-guidance for HCC treatment, MR-guided ablation shows higher primary technique effectiveness which may decrease the number of required sessions for complete tumour treatment.[46]

Fusion imaging, needle tracking, and robotic navigation

Image registration refers to the colocalization of one imaging dataset to another on the basis of certain anatomical landmarks. Image fusion refers to the partially transparent overlay of one dataset over another. Rigid registration fuses fixed image datasets, while nonrigid (deformable) registration allows partial image stretching to correct for mismatch caused by target motion or tissue deformation.

In interventional oncology, PET images can be fused with interventional CT or MR images. Preprocedural CT images may be fused with real-time US. Also, preprocedural MR images may be fused with real-time CT. Nowadays, overlay of fluoroscopic images with rotational

angiographic, CT, or MR images is possible. Fusion leads to more accurate 3D targeting and improves conspicuity of smaller (<5 mm) lesions.[23,36,47-51]

In stereotactic ablation, the optimal needle trajectory is planned on a 3D imaging dataset. The dataset is transferred to a workstation where the actual target tissue coordinates are automatically coregistered with the dataset. The target tissue is traced using either an electromagnetic transmitter or infrared markers placed on the patients' skin (Figure 4). The latter is detected using a stationary infrared camera. The needle, also located using electromagnetic waves or infrared marker(s), is projected over the 3D dataset using real-time multiplanar reconstructions.[23,28,52,53] Also, physiologic images (such as 18F-FDG PET) could be merged into an intervention.[23] Stereotactic ablation reduces the number of needle readjustments and can be especially useful for difficult-to-reach areas, such as the hepatic dome.[54]

Robotic navigation can also assist with challenging ablations, especially in those that are out of the axial plane. After entering needle type and length, skin entry site, and target site, the operator moves the table to the recommended z-axis location and the optimal needle angle trajectory is automatically calculated by the planning software. The operator then manually inserts the needle through a needle guide at the end of the robotic arm.[23,28]

High-frequency jet ventilation

High-frequency jet ventilation is a mechanical ventilation method where high-flow, short-duration pulses of pressurized gas are delivered in the trachea through a small-calibre catheter.[55] It reduces the amplitude of respiratory movements, and hence liver movements. Although in theory beneficial for percutaneous liver tumour ablation, highfrequency jet ventilation carries a higher risk of barotraumatic pneumothorax.

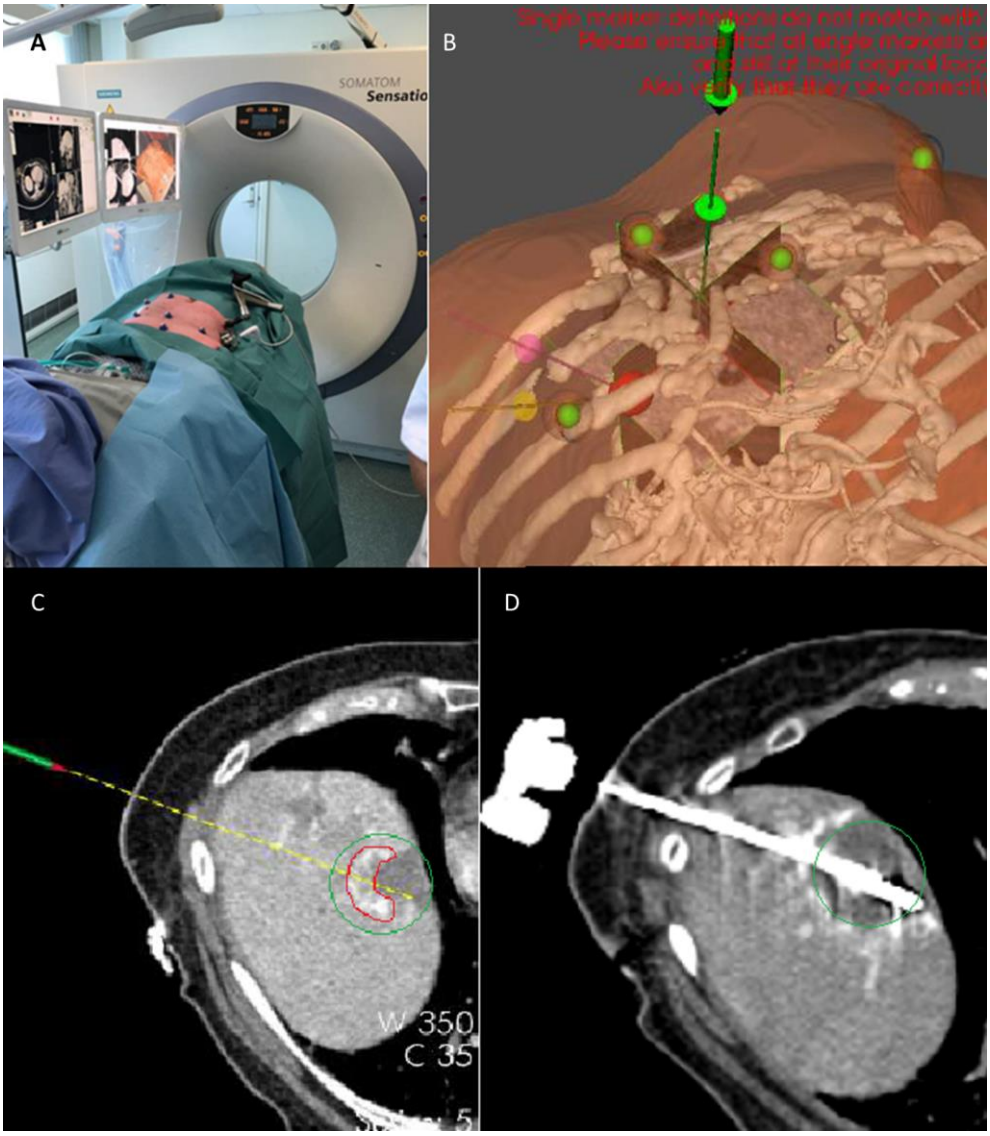

Figure 4. Three-dimensional computer assisted navigation in percutaneous liver tumour microwave ablation. Patient with a local site recurrence of a previously ablated colorectal liver metastasis in the hepatic dome. To avoid traversing the lung an angulated approach was chosen. (A) Using computer assisted navigation software (CAScination, Bern, Switzerland) with a mechanical arm and infrared markers on the patient's skin, (B) a microwave antenna was inserted using 3-dimensional computer-assisted navigation. (C) The tumour target volume (red line) and estimated ablation volume (green line) were drawn semiautomatically before advancing the probe. (D) The actual nonenhancing ablation zone, typically surrounded by a hyperemic rim, accurately matches the estimated ablation zone volume (green line). This figure is available in colour online at http://carjonline.org/.

Transarterial catheter-assisted ablation

One of the most promising new techniques to improve needle targeting is CT arterial portography or hepatic arteriography (CTHA)eguided percutaneous ablation. In CT arterial portography and CTHA an arterial catheter is placed within the superior mesenteric artery or the hepatic artery, respectively. Injecting diluted contrast medium (20 mL:20 mL saline; arterial and early portal venous phase at 7 and 22 seconds from start of injection, respectively) directly into the relevant arteries enables repeated contrastenhanced imaging and real-time CECT fluoroscopy and hence improves: 1) lesion conspicuity; 2) differentiation between ablative scar tissue and vital tumour tissue (incomplete-ring sign); and 3) treatment accuracy at the cost of an additional intervention (Figures 5 and 6).[27,56] In the study by van Tilborg et al.[27] mean needle-to-target mismatch distance was 2.4 ± 1.2 mm (range, 0-12.0 mm) and primary technique effectiveness at 3 months was 87% (33 of 38 lesions) for lesions that were undetectable on both US and unenhanced CT.

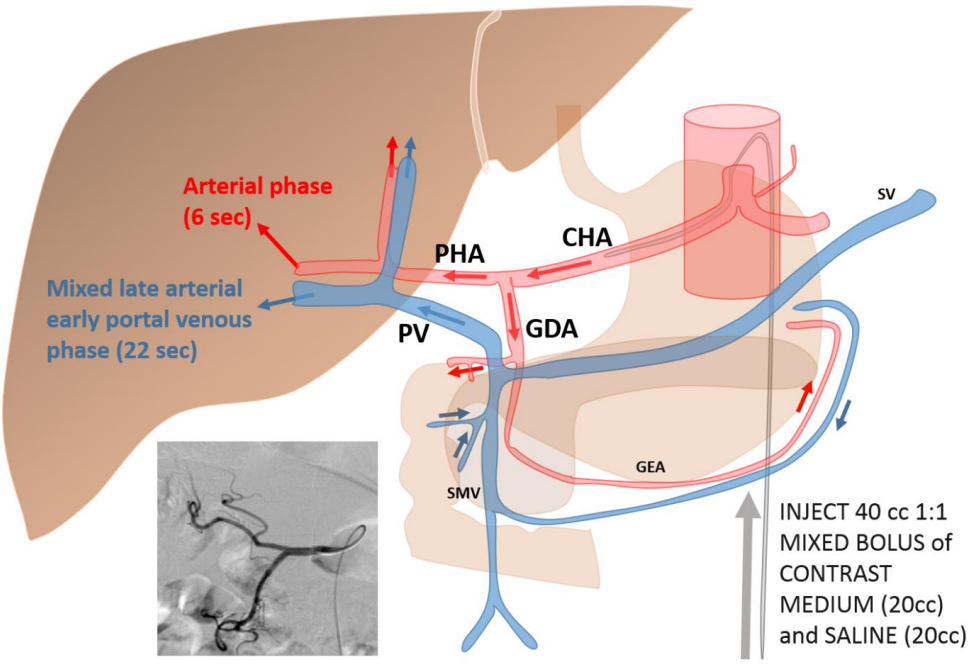

Figure 5. Schematic drawing of the transcatheter computed tomography (CT) hepatic arteriography technique. After injection of 40 cm3 of a 1:1 mixed bolus of contrast medium and saline through a catheter in the common hepatic artery (CHA) 2 CT series are acquired at 6 and 22 seconds, respectively, after start of injection (flow rate 5 cm3/s) to obtain an arterial phase CT and a mixed late arterial to early portal venous phase CT. Contrast will flow directly into the liver via the proper hepatic artery (PHA) and indirectly via the gastroduodenal artery (GDA) to the pancreatic, duodenal, and gastric circulation into the superior mesenteric vein (SMV) and hence the portal vein (PV).[27,56] GEA = gastroepiploic artery; SV = splenic vein.

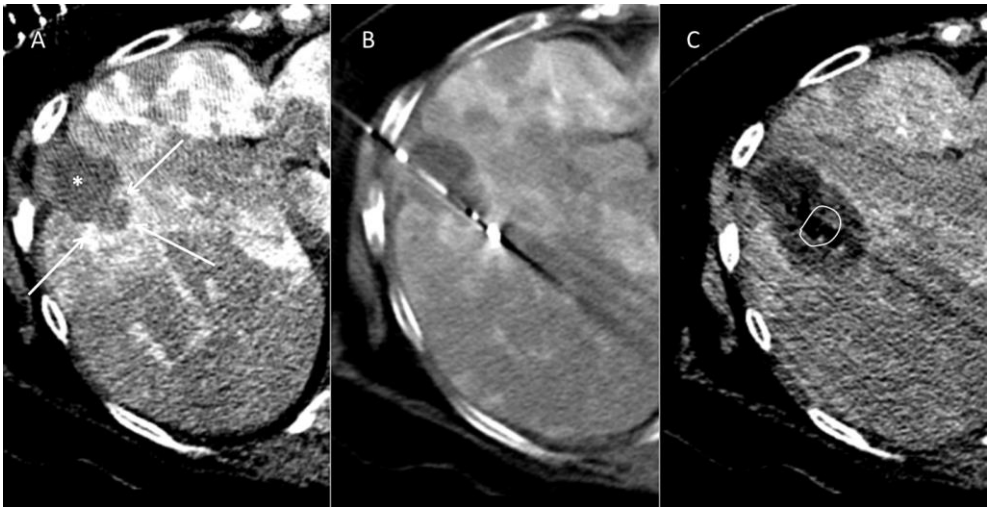

Figure 6. Computed tomography hepatic arteriography (CTHA) in percutaneous liver tumour ablation. (A) Typical incomplete-ring sign (white arrows) on CT hepatic angiography indicating ablation site recurrence. (B) Transcatheter CT fluoroscopy allows for real-time delineation of the ablation zone and the vital recurrence after injecting minimal amounts of diluted (20 cm3 contrast medium + 20 cm3 saline; 4 cm3/s) contrast. (C) The hypoattenuating ablation zone clearly encompasses the target tumour volume (white line).

Endpoints to assess technical success

With most thermal and nonthermal ablation techniques, the endpoint to determine technical success is merely defined as having successfully introduced a certain amount of energy that, according to its preclinical validation in healthy liver parenchyma in animals, is considered to create a certain spherical ablation zone.

However, several characteristics of both targeted liver parenchyma and tumour tissue, such as tissue homogeneity, calcifications, fibrosis, necrosis, cellular and vascular density, and water content, all clearly affect the expanse of tissue injury.[23] Anatomical location and proximity of certain anatomical structures, such as blood vessels, intestines, bile ducts, the diaphragm, and surrounding fatty or other tissue, also play an important role. When the hepatic lesion is located near a large (≥3 mm) abutting vessel, heat loss due to perfusion-mediated tissue cooling in the RF ablation zone can occur (heat sink), which protects vessels from bleeding.[26,27,57] This heat loss can cause a reduction of up to 50% in tumour necrosis volume and thus denotes an important risk factor for site recurrence.[58]

Tissue impedance

When tissue temperature rises, blood vessels delivering thermal energy to close regions become carbonized and impedance rapidly rises, hindering further necrosis.[59] To minimize tissue desiccation and charring in RFA, impedance can be controlled by either gradually increasing power or by a stepwise power decrease to avoid early ‘‘roll-off’’.[28]

To prevent overheating of the electrode, avoid skin injury, and permit further deposition of energy into tissue with low impedance during ablation, cooled-tip electrodes have been developed.[1] Internally cooled electrodes have an internal lumen, in which a cooling agent (saline, water, or gas) flows without direct contact with tumour tissue. In perfusion-cooled electrodes, the tip of the needle has small apertures that allow the cooling agent to be injected into the tissue before, during, or after the procedure.[21,26]

Tissue temperature

In RFA, tissue injury is considered to be achieved when the temperature reaches 60°C directly, or remains at 54°C for at least 180 seconds.[60] MWA is not limited by the conductive property of tissues, so higher temperatures can be achieved (>150°C).[31,57,58] The intention of temperature control is to ensure that the maximum energy is applied by using the standard algorithm with the system, which differs among theavailable devices, and to ensure that surrounding tissue will not be injured, especially for lesions near (<5 mm) vital structures.[1]

Temperature can be monitored indirectly by tissue impedance. The system monitors the needle tip’s temperature and delivers peak power until a fixed target temperature is reached. Liver tissue carbonizes and becomes desiccated when the temperature climbs over 100°C (roll-off). Direct monitoring is possible when a target temperature is chosen and power is automatically adjusted to maintain this temperature for a fixed time.[26,59] Additional temperature monitoring is possible by inserting an extra needle into the target area through a nonconducting trocar.[26]

One randomized controlled trial investigated the efficacy of impedance control of a radiofrequency interstitial thermal ablation system in HCC.[59] Compared with temperature control, the use of impedance control increased the ablated tissue volume and decreased the ablation time.

Imaging characteristics

Immediate (contrast-enhanced) postablation imaging should demonstrate circumferential coverage of the tumour plus a safety margin - at least 5 mm, ideally 10 mm - by the ablation zone.[26] Following thermal ablation, US shows a transient hyperechoic ablation zone that

disappears after several minutes (Figure 1C). For typical arterial phase hyper-attenuating HCCs, a nonenhancing ablation zone affirms complete ablation on CEUS.[21] A well demarcated, spherical, hypodense ablation zone with a hyperdense peripheral rim (transient periablational hyperemia) can be seen on CECT (Figures 4D and 6C).[21] MR thermometry is quantitative method of assessing technical success, which enables real-time temperature monitoring by detecting MR imaging proton resonance frequency changes that are associated with temperature change of 1°C. On MRI, the ablation zone after thermal ablation appears as a clear, hyperintense area on T1 (heterogeneous) and T2 (homogeneous) weighted images.[23]

Following IRE the ablation zone is typically hypoechoic on US (Figure 2C), hypodense on CECT, and hypointense on T1-weighted images with a hyperattenuating ring on high B-value MR DWI.

Quality control

The authors refer to quality control if the postprocedural imaging, or any alternative technique, is implemented with the intent to allow for additional overlapping ablations, either within the same procedure or in a complementary completion procedure in the days or weeks hereafter. Initial post-treatment imaging should focus on detecting procedure-related complications and primary treatment failure. Early detection of tumour residue or inadequate margins provides the opportunity to reablate the region and hereby successfully complete the procedure.[1,21,26,61] Nonetheless, differentiation between postablation scar tissue and vital tumour residue can be challenging.

Ultrasound

Reliable differentiation between coagulated and viable tumour tissue is impossible using US. In the first 30 days, the ablation zone slowly decreases in size, appearing as small transient hyperechoic areas or isoechoic areas with a hypoechoic border on US (Table 2).[1,21]

For HCCs, tumour residue can be confirmed by residual hypervascularity and a typical washout on CEUS.[36,61] Within 24 hours after the ablation, CEUS has shown a high accuracy in differentiating reactive periablation perfusion changes from residual HCC tumour tissue.[62,64] However, the hyperattenuating rim along the ablated margins should not be misinterpreted as residual tumour tissue.[65] CEUS can easily be repeated and used to target the residue.[64]

Computed tomography

Triple-phase CT (unenhanced, late arterial phase, and portal venous phase) remains the mainstay of early routine follow-up and is known for its rapid achievement of a wide range of images and clear comparison to the index tumour.[21,47,61,66] Successful ablation appears as a lower density, nonenhancing area with or without a regular, symmetric, uniform peripheral enhancing rim.[21] In the late arterial phase, peripheral, irregular areas of enhancement near the ablation area are suspect for residual tumour tissue.[61] The ablation zone gradually diminishes in volume.[47,61]

At about 1-3 weeks postablation, portal venous phase imaging allows better assessment because there is sufficient time for the ablation zone to mature and become better defined.[1,21,61]

Magnetic resonance imaging

The ablation zone will follow the same enhancement characteristics as appreciated on CECT; however, sensitivity in detection of residual disease is higher for contrast-enhanced MRI (89%) than for CECT (44%).[61] MRI therefore seems well suited for immediate postablation evaluation of technical success.[67,68]

High B-value MR DWI is increasingly used to evaluate treatment response after hepatic tumour ablation. In HCC, significant differences between pretreatment and 1-6 months post-treatment apparent diffusion coefficient (ADC) values are found, which makes the ADC of predictive value for investigating recurrent disease.[69] Usually, evidently lower ADC values in the areas of unclear hyperintense signal on T2-weighted images correlate with tumour tissue.[70]

18F-FDG PET-CT

In 18F-FDG-avid tumours, residual disease appears as an eccentric, focal, nodular area of 18F-FDG uptake against the background of low-grade homogeneous tracer distribution on 18F-FDG PET-CT imaging.[70,71] As inflammatory changes and associated 18F-FDG tracer uptake are not appreciated within the first 24-48 hours after the ablation, early 18F-FDG PET-CT accurately predicts technical success.[72,73] After 48 hours, increased 18F-FDG uptake in periablation inflammation and hyperemia tissue can mask foci of irregular 18F-FDG uptake of residual disease.[72]

Ablation zone biopsy

Relatively unknown strategy is biopsy of the margin and centre of the ablation zone immediately post-RFA.[3] It yields clinically useful information that carries prognostic significance for ablation site recurrence at the cost of an additional intervention. Ablation margins of >5 mm and a negative postprocedure biopsy predicts an ablation site recurrence risk of 3%, similar to reported marginal recurrence rates after R0 resections for CRLMs. In other words, ablation margins of <5 mm and positive postablation biopsy results will require completion procedures.

Modality	Normal signs after ablation	Signs of ablation site residue	Recommended time after treatment
US	Iso/hyperechoic area, hypoechoic border	Differentiation between ablation zone and residual tumour tissue is not possible	Immediate to confirm a hyperechoic rim that encompasses the index lesion
CEUS	Nonenhancing ablation zone; homogenous hyperenhancing rim may be present	Focal area of residual enhancement plus early washout predicts residue for hypervascular HCCs	Several minutes after the ablation (to allow for the thermally induced gas to resorb) up to 2 weeks after the ablation
CECT	Low-density area surrounded by uniform, regular, enhancing rim of hyperemia	Incomplete enhancing ring marginal to the ablation zone indicates primary treatment failure	Within 2 weeks
CEMRI and DWI	Same as on CECT plus on T1 signal heterogeneity (hemorrhagic products), on T2 hypointensity within ablation zone. With DWI: decreased ADC	Tumour protruding through the discontinuous rim with evidently lower ADC values in the areas of unclear hyperintense signal on T2-weighted images	Within 2 weeks
18F-FDG PET-CT	No residual 18F-FDG tracer uptake	Eccentric, focal, nodular area of increased, marked FDG uptake	Within 24–48 hours
Ablation zone biopsy	Absence of viable tumour cells	Viable tumour cells	Immediate, only if ablation margins <5 mm

Table 2. Quality control after percutaneous liver tumour ablation. 18F-FDG PET-CT = 2-[18F]-fluoro-2-deoxy-D-glucose (F-FDG) positron emission tomography computed tomography; ADC = apparent diffusion coefficient; CECT = contrast-enhanced computed tomography; CEMRI = contrast-enhanced magnetic resonance imaging; CEUS = contrast-enhanced ultrasound; CT = computed tomography; DWI = diffusion-weighted imaging; US = conventional B-mode ultrasound.

DISCUSSION

Ablation site recurrence rates after thermal ablation are still considered relatively high (5-10% for lesions ≤3 cm and >10% for lesions ≥3 cm in diameter).[22,27,74] Successful treatment requires complete necrosis of tumour tissue including an adequate tumour-free margin in all directions. Although not widely employed or based on high-quality research evidence yet, the reviewed technological advances seem all promising in improving the safety and outcome of liver tumour ablation.

In percutaneous liver tumour ablation there is an abundant number of real-time image-guiding modalities available, of which US and CECT are still the most commonly used. Techniques capable to improve targeting are real-time image fusion and arterial

cathetereassisted percutaneous ablation.[27,37,49-53] The potential of CTHA to differentiate scar tissue from ablation site recurrence (incomplete ring sign) will likely improve the outcome of reablations.[56]

In several clinical series, the use of needle navigation in percutaneous biopsies was associated with improved targeting and accuracy, a reduction in needle distance to the target, and off-path errors.[28] The use of a robotic assistance platform in simulated biopsies and radiofrequency ablation was investigated in 1 study.[75] Compared with a freehand single-pass needle insertion, use of robotic assistance was associated with lower mean needle tip-to-target distance for biopsies, and a lower average percentage of residual tumour tissue after ablation.[75]

Merely having exposed a tumour to a certain amount of thermal energy for a predefined period of time represents a poor endpoint to define technical success as the ablation zone size and shape are highly dependent on tissue characteristics. Especially the incorporation of immediate postprocedure or at least early follow-up imaging (quality control) is promising and offers the opportunity to re-treat patients in case of suspected site residue. A potential algorithm for quality control after percutaneous liver tumour ablation is proposed in Figure 7.

In terms of safety and efficacy, it remains difficult to compare the quality of available image-guiding modalities, needle tracking devices, and methods for quality control because of the large amount of image-guidance techniques, their local availability, and heterogeneous local expertise. For these reasons the method of choice should remain the method that works best for the physician performing the treatment.

Given the apparent difficulties in setting up high-quality prospective comparative studies in a rapidly changing environment, the interventional oncology society should focus on establishing national and international quality improvement guidelines and clinical registries to hold up a mirror and compare outcomes, with the intent to steadily improve the efficacy of percutaneous liver tumour ablation and hence the outcome for patients with liver tumours.

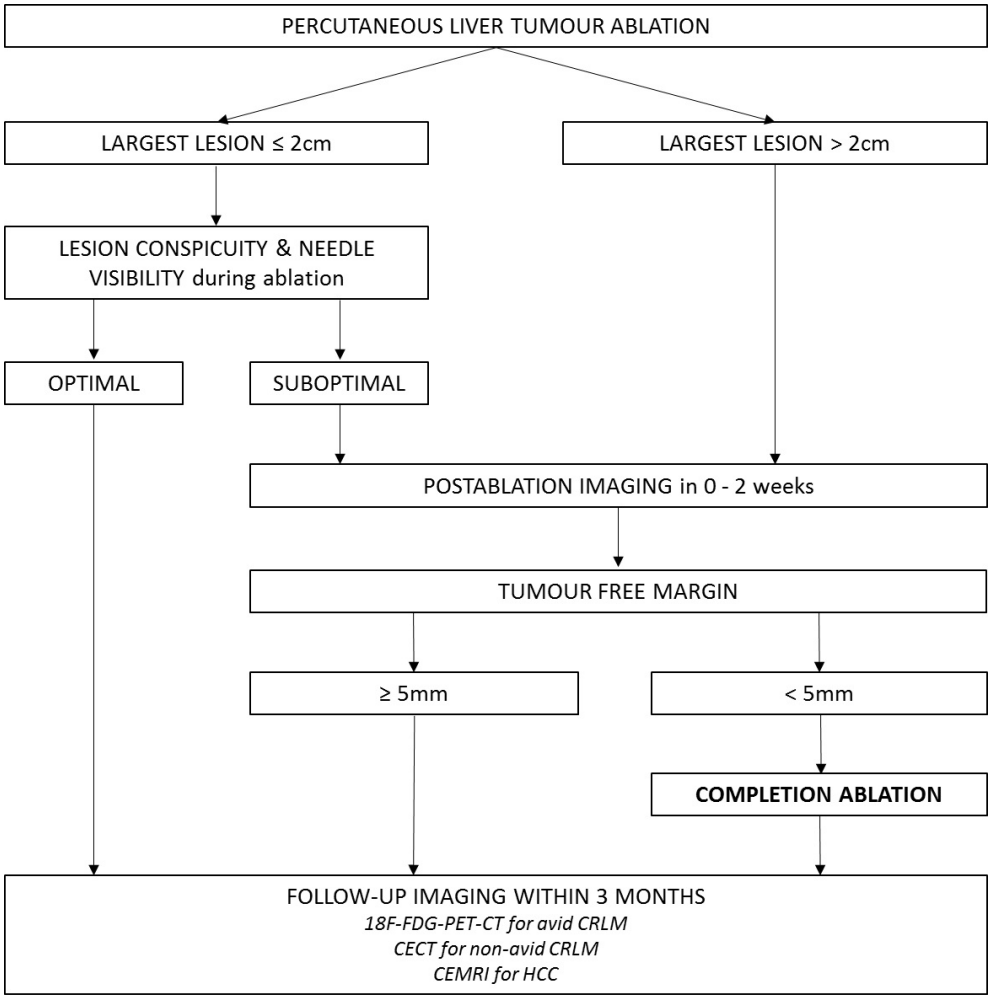

Figure 7. Algorithm for quality control after liver tumour ablation. 18F-FDG PET-CT = 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography computed tomography; CECT = contrast-enhanced computed tomography; CEMRI = contrast-enhanced magnetic resonance imaging; CRLM = colorectal liver metastasis; HCC = hepatocellular carcinoma.

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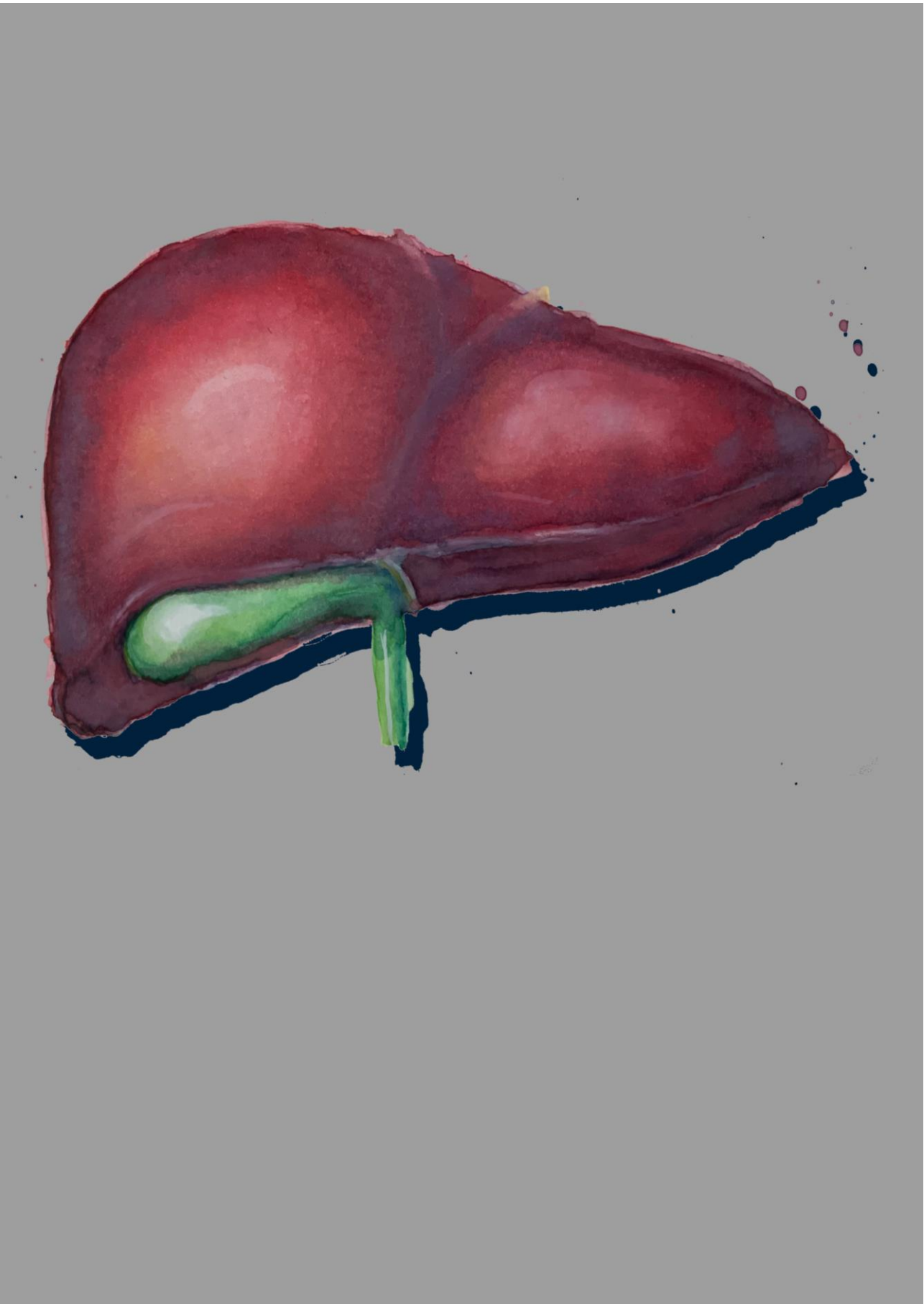

CHAPTER 6

Anesthetic management

6.1

Propofol compared to midazolam sedation and to general anesthesia for percutaneous microwave ablation in patients with hepatic malignancies: a single-center comparative analysis of three historical cohorts

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ABSTRACT

Purpose: In percutaneous ablation procedures, periprocedural pain, unrest and respiratory concerns can be detrimental to achieve a safe and efficacious ablation and impair treatment outcome. This study aimed to compare the association between anesthetic technique and local disease control in patients undergoing percutaneous microwave ablation (MWA) of colorectal liver metastases (CRLM) and hepatocellular carcinoma (HCC).

Materials and Methods: This IRB-exempted single-center comparative, retrospective analysis of three cohorts analyzed 90 patients treated for hepatic malignancies from January 2013 until September 2018. The local tumor progression- free survival (LTPFS), safety and periprocedural pain perception were assessed using univariate and multivariate Cox proportional hazard regression analyses to correct for potential confounders.

Results: In 114 procedures (22 general anesthesia; 32 midazolam; 60 propofol), 171 liver tumors (136 CRLM; 35 HCC) were treated with percutaneous MWA. Propofol and general anesthesia were superior to midazolam/fentanyl sedation regarding LTPFS (4/94 [4.3%] vs. 19/42 [45.2%] vs. 2/35 [5.7%]; P<0.001, respectively). Local tumor progression rate was 14.6% (25/171). Eighteen tumors (72.0%) were retreated by ablation. Of them, 14 (78%) were previously treated with midazolam. Propofol versus midazolam (P<0.001), general anesthesia versus midazolam (P = 0.016), direct postprocedural visual analog pain score above 5 (P = 0.050) and more than one tumor per procedure (P = 0.045) were predictors for LTPFS. Multivariate analysis revealed that propofol versus midazolam (HR 7.94 [95% CI 0.04–0.39; P<0.001]) and general anesthesia versus midazolam (HR 6.33 [95% CI 0.04–0.69; P = 0.014]) were associated with LTPFS. Pain during and directly after treatment was significantly worse in patients who received midazolam sedation (P<0.001).

Conclusions: Compared to propofol and general anesthesia, midazolam/fentanyl sedation was associated with an increased periprocedural perception of pain and lower local tumor progression-free survival. To reduce the number of repeat procedures required to eradicate hepatic malignancies, general anesthesia and propofol sedation should be favored over midazolam.

INTRODUCTION

The role of anesthetic techniques in percutaneous tumor ablation procedures is a highly debated topic worldwide since it may have impact on pain, anxiety and intraprocedural patient's movements, thereby achieving an adequate, complete ablation zone (ideally a [5 mm circumferential safety margin).[1-8] Several anesthetic methods can be used, such as general anesthesia, spinal anesthesia, and sedation using midazolam/fentanyl (hereafter: midazolam) or propofol (± intravenous analgesia).[1,3] The choice of anesthetic technique differs among institutes and is often based on the clinician's and patient's preferences and local availability. General and spinal anesthesia are invasive techniques which require specialized actions and are associated with higher systemic complication rates compared to sedation.[1,9] Midazolam and propofol sedation are known for their short time to onset of action and short time to clearance.[10,11] Moderate conscious sedation with midazolam was prospectively reported to be safe during biliary, tunneled catheter, diagnostic and vascular interventional procedures.[12] However, midazolam sedation tends to be associated with agitation, irregular breathing, respiratory depression and thoracic movement, which might lead to inadequate needle placement, needle tracking and creation of an insufficient tumor-free ablation margin.[13,14]

Over the past 15 years, propofol has become the drug of choice for many outpatient and short procedures, mainly due to its favorable pharmaceutical properties.[3] Guidelines for diagnostic and therapeutic purposes in gastrointestinal endoscopy were the first to describe clear consensus on sedation management with propofol.[15-18] Also in pediatric diagnostic imaging studies, compared to midazolam sedation, propofol is preferred in order to reduce undesired motion artifacts.[19]

However, to our knowledge, there is no consensus which anesthetic technique should be used for an image-guided percutaneous liver ablation procedure, since there are no comparative studies evaluating the impact of anesthetic technique on local disease control and oncological outcomes. The aim of this study was to retrospectively analyze safety, efficacy and periprocedural perception of pain following percutaneous microwave ablation (MWA) for hepatocellular carcinomas (HCCs) or colorectal liver metastases (CRLMs), of the three most-used techniques in current-day clinical practice: general anesthesia, midazolam and propofol sedation.

MATERIALS AND METHODS

Study design and population

This single-institution retrospective cohort study was conducted at Amsterdam University Medical Centers – location VUmc, the Netherlands, a tertiary referral center for hepatic malignancies.

Data were collected from a prospectively maintained liver tumor ablation registry. For reporting study data, the STROBE guidelines were followed [20]. Between January 2013 and September 2018, 90 consecutive patients (22 HCC; 68 CRLM) with 171 liver lesions underwent 114 percutaneous microwave ablations (Fig. 1). All patients were treated in our ambulatory interventional oncology suite, which houses a CT scanner and anesthetic facilities.

Patients were included if they were treated with computed tomography (CT)-guided percutaneous microwave ablation of either primary or secondary liver cancer. Clear documentation of anesthetic technique and medication doses were requirements for inclusion. Follow-up should have consisted of at least one imaging modality study to exclude local tumor progression (LTP). Patients treated with radiofrequency ablation were excluded, as this modality was being used less frequently over the last years as a result of clinicians' preferences.

Although general anesthesia was mostly used for patients with contraindications for sedation, the choice for midazolam or propofol sedation was based on the availability of a specialized anesthetic assistant (propofol sedation) versus an interventional radiologist certified in administering midazolam sedation.

General anesthesia

Between January 2013 and September 2018, 22 procedures were performed with general anesthesia. Intravenous propofol (Diprivan®, AstraZeneca BV, Zoetermeer, the Netherlands), rocuronium (Esmeron®, Sandoz BV, Almere, the Netherlands), remifentanyl (Ultiva®, Mylan BV, Amstelveen, the Netherlands) and sufentanil (Sufenta®, Janssen Pharmaceutica, Beerse, Belgium) doses were commissioned by an anesthesiologist. General anesthesia included intubation and controlled respiration with continual cardiopulmonary monitoring. General anesthesia was chosen for patients with contraindications for both sedation techniques.

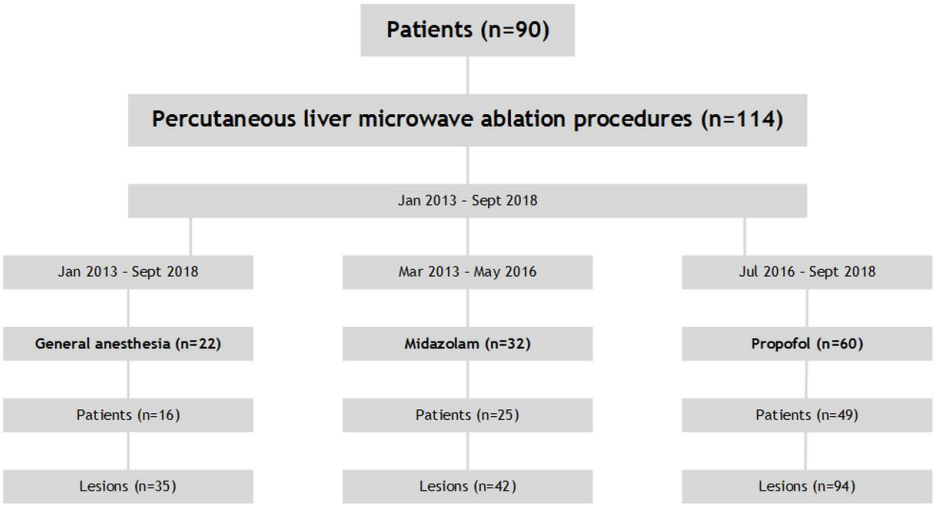

Figure 1. Flowchart for patient selection

Midazolam sedation

Between March 2013 and May 2016, all procedures were performed with midazolam/fentanyl sedation (Fig. 1). Intravenous midazolam (Dormicum®, Roche BV, Woerden, the Netherlands) sedation doses were commissioned by the primary treating interventionist and administered by an anesthetic trained technician responsible for monitoring the patient's vital functions. Starting dose of midazolam was 1–2.5 mg. Fentanyl (Durogesic®, Janssen Pharmaceutica, Beerse, Belgium) was given intravenously prior to the actual procedure (50 µg) and intraprocedurally when the patient was considered to experience pain (grimacing or body movements). Both doses were titrated and adjusted to body mass index (BMI) and clinical response. All patients received local anesthesia with an one-time bolus injection of lidocaine (B. Braun Medical B.V., Oss, the Netherlands). Respiratory depression was treated with active waking of patients, or when unsuccessful, temporary mechanical cuff breathing assistance. Flumazenil (Anexate®, Roche BV, Woerden, the Netherlands) and naloxone (Narcan®, Bristol-Myers Squibb BV, Utrecht, the Netherlands) were respectively available for potential midazolam and fentanyl overdosing.

When midazolam sedation was being performed in our institution, availability of anesthesiologists was insufficient. The first graduated group of certified anesthesia assistants (sedation specialist) following a dedicated training program to use target controlled infusion of propofol became available mid-2016.

Propofol sedation

From July 2016 until September 2018, propofol (Diprivan®, AstraZeneca BV, Zoetermeer, the Netherlands) was administered and monitored by a specialized anesthetic assistant using target controlled infusion, which automatically calculates the effective concentration of propofol in the patient's cerebrum depending on the patient's age and weight. Alfentanil (Rapifen®, Janssen Pharmaceutica, Beerse, Belgium) or remifentanil (Ultiva®, Mylan BV, Amstelveen, the Netherlands) was administered under the same circumstances as for midazolam sedation. Patients were allowed to breathe spontaneously, and the propofol infusion rate was titrated according to clinical response. Adequate sedation was considered to be reached by the absence of body movements and failure to respond to verbal commands. Although patients cannot comply to breathing instructions, propofol is known to create a tranquil, steady respiration status with minimal diaphragm movements despite the pain stimulus during probe placement dissimilar to midazolam sedation.

In case of inadequate sedation, additional propofol boluses were administered by increasing the carbon equivalent value. Some anesthesiologists preferred administration of additional esketamine (Ketanest-S®, Pfizer BV, Capelle aan den Ijssel, the Netherlands). All patients received local anesthesia with a one-time bolus injection of lidocaine (B. Braun Medical B.V., Oss, the Netherlands). During the procedure, one anesthesiologist was available on demand.

Microwave ablation details

Prior to the procedure, patients who received general anesthesia or propofol sedation were routinely checked by an anesthesiologist. All patients were fasted for at least 6 h prior to the procedure. MWA (Emprint Thermosphere; by Medtronic, Minneapolis, Minnesota, USA) was used according to its CE mark.

Real-time CT fluoroscopy was used for needle guidance and targeting of lesion(s), surrounding structures and to assess the enlarging ablation zone. Intraprocedural assessment of contrast agent (Xenetix 300; by Guerbet SA, Villepinte, France) via an arterial catheter placement in the common hepatic artery was used to improve lesion conspicuity on real-time CT imaging (CT arterial portography; CT hepatic arteriography). Just prior to the ablation, patients were admitted to the angiography suite for the arterial catheter placement. The sheath was removed directly after the procedure by placing a hemostatic closure device at the common femoral artery. This technique has been previously described in detail by van Tilborg et al.[21] Track ablation was performed to prevent potential bleeding and tumor seeding along the needle track.[1]

After the procedure, patients were directly admitted to the surgical ward in case of sedation with midazolam. After general anesthesia and propofol sedation, patients first went to the post-anesthesia care unit to monitor vital parameters before they were admitted to the surgical ward. Postprocedural analgesia protocol was identical for all three cohorts. All patients remained admitted at least one night.

All ablations were performed by two interventional radiologists (MRM and JJV) who both have a master degree in image-guided tumor ablation (having performed and/or supervised >100 thermal ablation procedures).

Follow-up

All patients underwent contrast-enhanced (ce) CT immediately after ablation to assess technical success and complications. In case of an incomplete ablation, additional MWA was performed to treat the residual unablated tumor tissue. Follow-up consisted of [18F]-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET)—CT scans 3 monthly during the first year and every 6 months thereafter, according to national guidelines[22] and the reporting criteria for image-guided tumor ablation.[23]

Data collection and analysis

Patient's general (health) status, characteristics per lesion and characteristics per procedure were retrieved from the electronic patient database (Table 1). Total procedure time (from induction of sedation until needle removal), periprocedural pain perception, complications and local tumor progression and survival data are reported in Tables 2 and 3.

Intraprocedural pain was subjectively rated (present/absent) and reported by the anesthesiologist and/or interventional radiologist by signs of discomfort (e.g., [non-]verbal expression of agitation, grimacing, body movements). Postprocedural pain was measured by the nursing staff and documented as a written description or a pain perception score (visual analog scale; VAS) from 0 (no pain), 1–2 (mild pain), 3–5 (moderate pain) and 5–10 (severe pain), according to the adopted guidelines.[23,24] The first pain perception score was noted directly after the procedure when patients were able to communicate. Within six hours afterwards, the second score was routinely noted. Separately, VAS scores of 5 and higher were analyzed since these scores are associated with severe pain.[24] If there was only a written description of postprocedural pain available, these data were first interpreted and translated into an interchangeable numeric score (VAS) by an independent researcher (VZP) and reviewed by a second author (RSP) to assess for interobserver variability.

A thermal ablation procedure was considered technically successful after having delivered the energy as planned and showing no residual enhancement around the ablation zone on

immediately obtained ce-CT imaging.[23] Technical effectiveness was defined as complete ablation of the hepatic lesion as shown on first follow-up imaging after the ablation. LTP was defined as the ‘‘appearance of tumor foci at the edge of the ablation zone, after at least one contrast-enhanced follow-up study has documented adequate ablation and the absence of viable tissue in the target tumor and surrounding ablation margin’’.[23] Local tumor progression-free survival (LTPFS) was calculated from the time of treatment to LTP per lesion treated, with death being censored.

Statistical analysis

Statistics are reported as number (with or without percentage; %), median (interquartile range, IQR) or mean (standard deviation, ± SD). Continuous measures were compared using the Kruskal–Wallis test (§). Non-continuous variables were compared using the Pearson v2 test (‡).

Survival rates were estimated using the Kaplan–Meier method, with comparisons made using the log-rank test. The proportional hazards assumption was tested graphically in order to evaluate parallelism of the survival curves. Factors associated with LTPFS were analyzed using univariate and multivariate Cox proportional hazard regression models. Factors (e.g., tumor diameter) which are known having an association with LTPFS and factors with $P < 0.20$ in univariate analysis were entered into the multivariate analysis model to simultaneously adjust for other potential predictors. Hazard ratios (HR) and 95 percent confidence intervals (95% CI) were calculated. The significance level for all parameters was set at $P < 0.05$. Statistical analyses were performed in consultation with an independent, blinded epidemiologist (MCJ) using SPSS® Version 22.0 (IBM®, Armonk, New York,USA).[25]

RESULTS

Baseline characteristics

Between January 2013 and September 2018, 90 patients (68 CRLM; 22 HCC) underwent 114 percutaneous MWA procedures for liver tumors that were not previously ablated. Forty-eight patients had a history of liver surgery for CRLM or HCCs distant from the ablation site. Of all procedures, 22 were performed under general anesthesia, 32 with midazolam/fentanyl and 60 with propofol sedation. The average number of ablated lesions per procedure was 1.50 ± 0.88 (range 1–5), and the average size of the largest diameter was 17.2 mm ± 10.6 (range 3–48 mm). Mediation dosages are listed in Table 1. There were no cases of medication

overdosing where reversal of the administered medication was required. There were no significant P values found.

Median follow-up time after each procedure for the general anesthesia group was 8.4 months (IQR 17.6), 23.3 months (IQR 26.8) for the midazolam group and 6.5 months (IQR 6.6) for the propofol group (Table 3). Of all 90 patients, 12 (13.3%) deceased during follow-up (general anesthesia, n = 6; midazolam, n = 5; propofol, n = 1). All patients died from progression of disease. In case of death, median time from last ablative therapy to death was 15.8 months (IQR 29.2).

Complications

There were slightly more complications reported in the propofol group compared to the midazolam group (4 vs. 1, respectively; [P = 0.392]; Table 2). In both groups, one minor iatrogenic pneumothorax occurred due to the ablation devices. Those resolved spontaneously. Two procedures with propofol sedation were complicated by hepatic hemorrhages along the needle track. These patients were admitted for an emergency coiling procedure. In both cases, there was no lack of breathing control reported. The last complication, respiratory insufficiency, occurred due to postprocedural aspiration which required emergency intubation and recovery at the intensive care unit.

Pain perception

Intraprocedural pain occurred significantly more often in the midazolam group (11 out of 32 procedures, [34.4%]) compared to the general anesthesia (0%) and propofol groups (1.7%) (Table 2; [P<0.001]). Pain scores after the procedures were significantly higher in the midazolam group (P<0.001).

	Entire cohort	General anesthesia	Midazolam	Propofol	*P*-value
Number of patients	90	16	25	49	
Patient characteristics					
Gender (M : F)	69 : 21	11 : 5	18 : 7	40 : 9	0.463‡
Mean age ± SD †, in years	66.9 ± 11.0	69.4 ± 11.3	64.4 ± 12.3	67.4 ± 10.2	0.521§
Body mass index *, in kg/m^2	25.9 (5.3)	26.9 (8.5)	26.6 (6.3)	25.3 (4.4)	0.094§
ASA physical status, ≥3	23	5	4	14	0.426‡
Primary tumor type					0.560‡
CRLM	68	13	17	38	
HCC	22	3	8	11	
Location colorectal cancer, right-sided	12 (17.6%)	4 (30.8%)	2 (11.8%)	6 (15.8%)	0.361‡
Characteristics per lesion					
Number of lesions	171	35	42	94	
Primary tumor type, no. of lesions					0.821‡
CRLM	136 (79.5%)	28 (80.0%)	32 (76.2%)	76 (80.9%)	
HCC	35 (20.5%)	7 (20.0%)	10 (23.8%)	18 (19.1%)	
Mean diameter ± SD †, in mm	17.2 ± 10.6	18.1 ± 11.1	17.6 ± 11.8	16.6 ± 9.9	0.791§
Largest diameter (mm), >30	21 (12.3%)	5 (14.3%)	11 (26.2%)	5 (5.3%)	0.921‡
Tumor-free margin size (mm), 0-5	26 (15.2%)	5 (14.3%)	12 (28.6%)	9 (9.6%)	0.423‡
Perivascular location	12 (7.0%)	5 (14.3%)	5 (11.9%)	2 (2.1%)	0.167‡
Characteristics per procedure					
Number of procedures	114	22	32	60	
Tumor number, >1	37 (32.5%)	7 (31.8%)	8 (25.0%)	22 (36.7%)	0.397§
Synchronous CRLM	33 (28.9%)	5 (22.7%)	9 (28.1%)	19 (31.7%)	0.718‡
Catheter-guidance	98 (86.0%)	20 (90.9%)	26 (81.3%)	52 (86.7%)	0.589‡
General anesthesia					
Mean propofol dose (mg), ± SD		1160 ± 637			
Mean rocuronium dose (mg), ± SD		78 ± 46			
Mean remifentanil dose (µg), ± SD		2235 ± 1338 *(n=12)*			
Mean sufentanil dose (µg), ± SD		20 ± 12 *(n=10)*			
Midazolam sedation					
Mean midazolam dose (mg), ± SD			4.5 ± 2.1		
Mean fentanyl dose (µg), ± SD			205 ± 102		
Propofol sedation					
Mean propofol dose (mg), ± SD				706 ± 344	
Mean alfentanil dose (µg), ± SD				372 ± 197 *(n=54)*	
Mean remifentanil dose (µg), ± SD				248 ± 84 *(n=6)*	
Mean esketamine dose (mg), ± SD				18.6 ± 10.3	

Table 1. Baseline characteristics. Values are reported as number (with or without percentage; %) or dose ASA American Society of Anesthesiologists score, CRLM colorectal liver metastases, F female, HCC hepatocellular carcinoma, kg kilogram, M male, mg milligram, mm millimeter, lg microgram, min minutes, VAS visual analog scale, y year. * median (interquartile range, IQR) or † mean (standard deviation, ± SD). ‡ Pearson $\chi 2$ test between groups; § Kruskal–Wallis test.

	Entire cohort	General anesthesia	Midazolam group	Propofol group	*P*-value
Procedures	114	22	32	60	
Mean procedure time (min), ± SD	101 ± 50	108 ± 69	105 ± 63	97 ± 36	0.956§
Intraprocedural pain	12	-	11	1	<0.001‡
First measured postprocedural pain (VAS)*	1 (0-8)	0 (0-5)	3 (0-8)	1 (0-5)	<0.001§
Second measured postprocedural pain (VAS)*	1 (0-7)	0 (0-2)	2 (0-7)	0 (0-5)	<0.001§
No. of procedures after which the *first* measured postprocedural pain (VAS) score was ≥5-10	12	1	10	1	<0.001‡
No. of procedures after which the *second* measured postprocedural pain (VAS) score was ≥5-10	4	-	3	1	0.101‡
Intraprocedural complication(s)	5	-	1	4	0.392‡
- pneumothorax		-	1	1	
- bleeding			-	2	
- respiratory insufficiency			-	1	

Table 2. Outcomes of all percutaneous liver tumor microwave ablation procedures. Statistics are reported as number (with or without percentage; %). Min minutes, VAS visual analog scale. * Median (interquartile range, IQR) or † mean (standard deviation, ± SD). ‡ Pearson $\chi 2$ test between groups; § Kruskal–Wallis test.

Local disease control, local tumor progression and local tumor progression-free survival

Technical success was achieved in all 171 hepatic lesions (primary technique effectiveness of 100%), showing no residual enhancement around the ablation zone on immediately assessed ce-CT imaging.

Twenty-five out of 171 hepatic lesions (entire cohort 14.6%; general anesthesia, n = 2 [5.7%]; midazolam, n = 19 [45.2%]; propofol, n = 4 [4.3%]) showed LTP on follow-up imaging. Eighteen lesions (18/25 [72.0%]) in 10 patients were retreated by ablation (general anesthesia, n = 1 [5.6%]; midazolam, n = 14 [77.8%]; propofol, n = 3 [16.7%]). In six patients (7/25 [28.0%] locally progressed tumors), local reintervention was considered biologically futile because of concomitant distant progression (Table 3). For CRLM versus HCC, LTP was respectively detected in 22 out of 136 lesions (16.2%) versus 3 out of 35 lesions (8.6%) (P = 0.420). In case of local tumor progression, the mean time to detection of LTP was 5.7 ± 4.3 months (general anesthesia), 6.1 ± 4.8 months (midazolam) and 3.6 ± 0.7 months (propofol) (P = 0.230).

LTPFS (analyzed per tumor) significantly differed between the three groups (P<0.001) (Fig. 2). Univariate and multivariate associations with LTPFS are shown in Table 4. For LTPFS, the HR after multivariate analysis was 7.94 (95% CI 0.04–0.39; [P<0.001]) in favor of propofol versus midazolam sedation and 6.33 (95% CI 0.04–0.69; [P = 0.014]) in favor of general anesthesia versus midazolam sedation. Per-patient LTPFS results significantly differed between the cohorts (P<0.019) (Fig. 3).

	Entire cohort	General anesthesia group	Midazolam Group	Propofol Group	*P*-value
Number of patients	90	16	25	49	
Number of lesions	171	35	42	94	
Number of procedures	114	22	32	60	
Median follow-up after each procedure (months)*	8.9 (14.1)	8.4 (17.6)	23.3 (26.8)	6.5 (6.6)	<0.001§
Local tumor progression (LTP; no. of lesions)	25 (14.6%)	2 (5.7%)	19 (45.2%)	4 (4.3%)	<0.001‡
Time-to-local tumor progression (TTLTP) median for all lesions (months; 95% CI)*	Not reached	Not reached	Not reached	Not reached	NA
Mean time to detection of LTP†	5.6 ± 4.3	5.7 ± 3.1	6.1 ± 4.8	3.6 ± 0.7	0.230§
Repeat sessions (no. of re-ablated lesions)	18 (72.0%)	1 (5.6%)	14 (77.8%)	3 (16.7%)	0.769‡

Table 3. Outcomes of all treated liver lesions. Statistics are reported as number (with or without percentage; %). NA, not applicable. * Median (interquartile range, IQR) or † mean (standard deviation, ± SD). ‡ Pearson $\chi 2$ test between groups; § Kruskal–Wallis test.

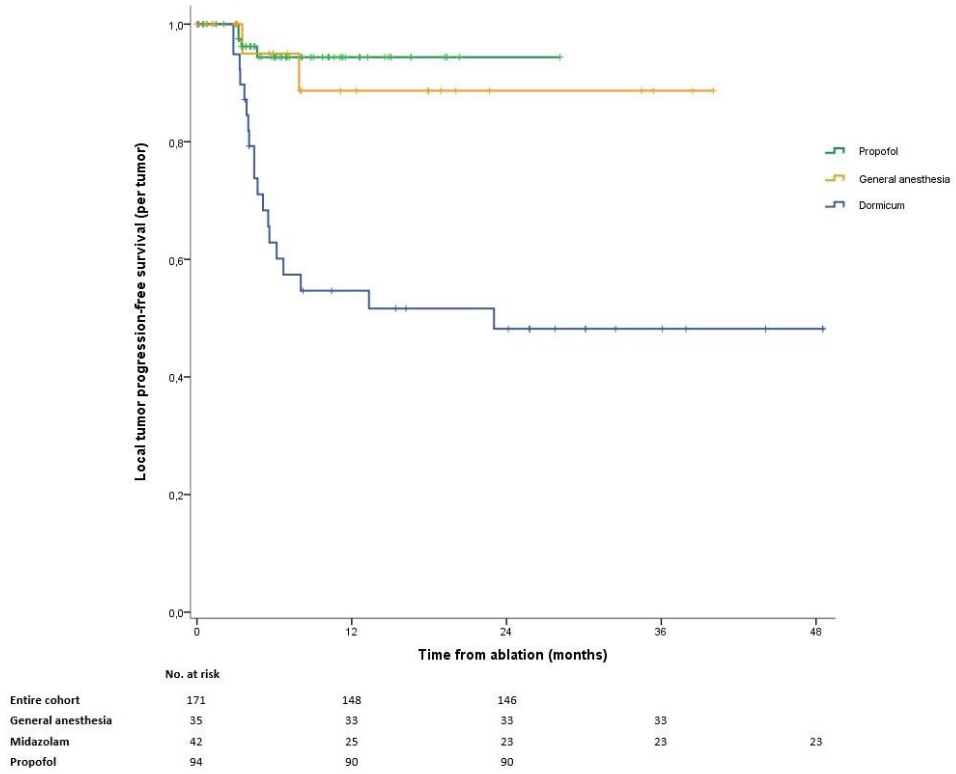

Figure 2. Kaplan–Meier curves indicating the survival time without local tumor progression (local tumor progression-free survival) per MWA-treated tumor. Kaplan–Meier curves showing freedom from local tumor progression (per-lesion) for patients with hepatic malignancies treated by percutaneous microwave ablation with either propofol sedation (green line), general anesthesia (orange line) or moderate conscious sedation with midazolam (purple line). Numbers at risk are MWA-treated tumors. Overall comparison log-rank (Mantel–Cox) P<0.001. Death without local tumor progression is censored.

	Univariate analysis			Multivariate analysis		
	Hazard ratio	**95% CI**	***P*-value**	**Hazard ratio**	**95% CI**	***P*-value**
Patient characteristics						
Age	1.00	0.97-1.03	0.979			
BMI	1.01	0.94-1.09	0.743			
ASA, ≥3	0.96	0.40-2.30	0.928			
Primary tumor type	2.08	0.62-6.95	0.237			
Location colorectal cancer, right-sided	0.50	0.12-2.16	0.356			
Characteristics per lesion						
Mean diameter (mm)	1.02	0.99-1.06	0.266			
Largest diameter (mm), >30	1.19	0.41-3.47	0.753			
Tumor-free margin size (mm), 0-5	1.23	0.46-3.29	0.679			
Perivascular location	1.86	0.56-6.23	0.313			
Characteristics per procedure						
Tumor number, >1	2.45	1.02-5.87	0.045	2.03	0.20-1.19	0.117
Catheter-guidance	0.59	0.22-1.58	0.293			
Outcomes						
Intraprocedural pain	1.85	0.65-5.26	0.246			
Intraprocedural complications (other)	1.35	0.18-10.06	0.771			
First measured postprocedural pain, VAS ≥5-10	2.52	0.99-6.35	0.050	1.24	0.34-2.32	0.809
Anesthetic technique						
Propofol versus midazolam	8.70	0.04-0.34	<0.001	7.94	0.04-0.39	<0.001
General anesthesia versus midazolam sedation	5.99	0.04-0.72	0.016	6.33	0.04-0.69	0.014

Table 4. Factors associated with local tumor progression-free survival identified by univariate and multivariate Cox regression analyses from the time of the ablation to local tumor progression.

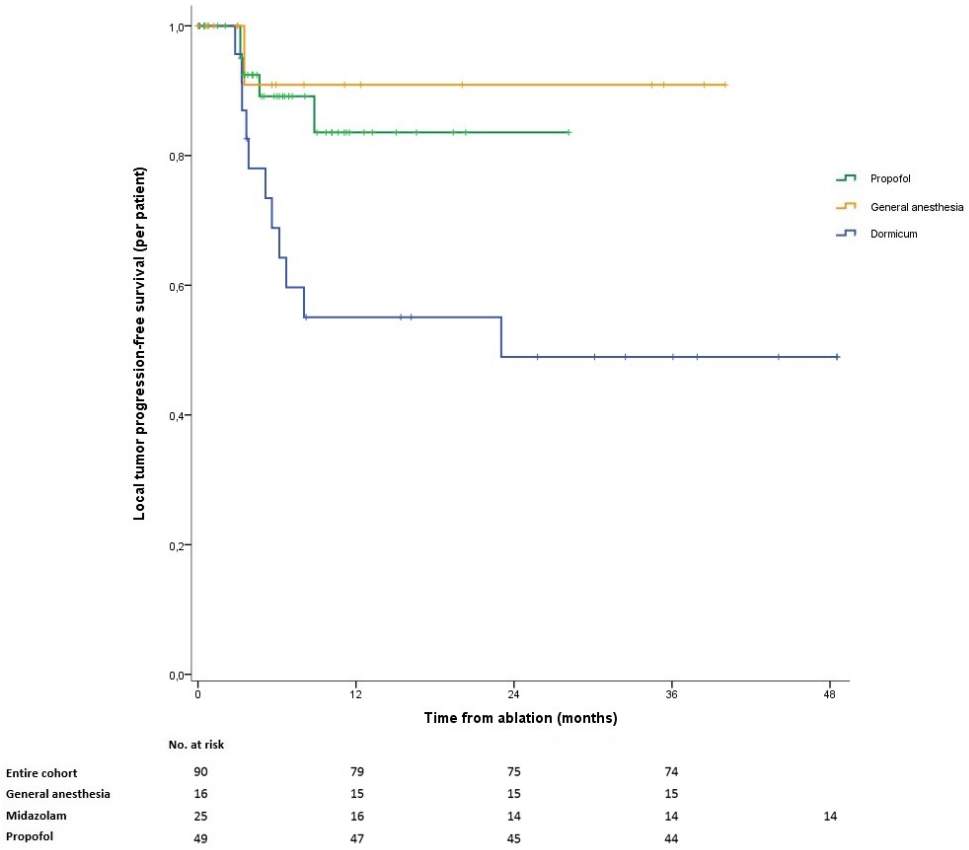

Figure 3. Kaplan–Meier curves indicating the survival time without local tumor progression (local tumor progression-free survival) per patient. Kaplan–Meier curves showing freedom from local tumor progression (per-patient) for patients with hepatic malignancies treated by percutaneous microwave ablation with either propofol sedation (green line), general anesthesia (orange line) or moderate conscious sedation with midazolam (purple line). Numbers at risk are patients. Overall comparison log-rank (Mantel–Cox) P<0.019. Death without local tumor progression is censored.

DISCUSSION

Due to the expanding role of interventional radiology in liver cancer treatment, the amount and complexity of thermal ablation procedures have raised the demand for safe anesthetic management in the ambulatory interventional oncology suite.[3] This comparative analysis of three historical cohorts described the outcomes of patients undergoing percutaneous liver

tumor MWA for CRLM or HCC to identify potential differences between general anesthesia, midazolam and propofol sedation.

Anesthetic technique was the most significant predictor of LTPFS in the Cox regression model in favor of propofol versus midazolam sedation (HR 7.94; P<0.001) and in favor of general anesthesia versus midazolam sedation (HR 6.33; P = 0.014). This result suggests that patients who underwent a percutaneous procedure under general anesthesia or propofol sedation had an equally reduced risk of developing LTP compared to patients treated under midazolam sedation. These outcomes imply that propofol sedation results in fewer patient movements, better control of breathing and less pain compared to midazolam sedation. General anesthesia and deep sedation with propofol apparently lead to more controlled ablative procedures with superior precision in needle placement and needle tracking, presumably creating wider and more accurate ablation zones. General anesthesia is the ideal technique due to the fact that one can request apnea at any time with completely controllable respiration. Propofol appears to be equivalent regarding local control, although it is theoretically possible that the continued respiration during probe placement contributed to the two cases of probe-induced hepatic hemorrhage.

The efficacy following percutaneous MWA under propofol sedation and general anesthesia in this series is comparable to the per-lesion LTPFS reported in the most recent surgical series following open MWA for similar sized liver tumors.[26] This may indicate equipoise has been reached between the open and percutaneous approach.

Although the CIRSE quality improvement guidelines mention that thermal liver ablation can be performed under intravenous sedation and general anesthesia, to the best of our knowledge, this is the first study that has compared anesthesia techniques for liver tumor ablation.[1] Kim et al. retrospectively compared general anesthesia to midazolam/fentanyl sedation in a small number of renal cell carcinoma patients treated with percutaneous radiofrequency ablation.[27] The authors also reported a significantly higher LTP rate in the midazolam group, mainly caused by insufficient pain control and breath holding during the procedure leading to incomplete ablations.

Midazolam sedation is traditionally being used for interventional procedures because of its reported safety.[12] From a pharmacodynamics point of view, midazolam differs widely from propofol, which is known to achieve a more profound sedation level and shorter recovery time.[28] Several series compared midazolam sedation to propofol in interventional procedures. One outdated trial included 40 patients with intracranial vascular disease and randomized between the two.[29] No differences were found with regard to complications (pain, inappropriate movements and respiratory changes) and both patient's and physician's satisfaction score. However, another randomized study concluded that propofol sedation was associated with superior physician satisfaction (P<0.05) and less respiratory depression and

anxiety compared to midazolam for equivalent sedation levels in patients undergoing a percutaneous transluminal angioplasty (P<0.05).[14]

In other medical fields, propofol is being used extensively for various procedures. In gastro-intestinal endoscopy, one meta-analysis of 22 studies reported that propofol sedation was associated with shorter recovery and discharge time and that patients were more likely to cooperate compared to traditional sedative agents.[28] One recently published, double-blind, randomized trial revealed that significantly fewer patients who received propofol remembered being awake during outpatient colonoscopy compared to midazolam sedation (respectively 2% vs. 17%, P<0.001).[30] More patients who received propofol were ''very satisfied'' with their level of consciousness compared to midazolam (86.3% vs. 74%, P = 0.0005). Twenty-six percent of midazolam procedures were rated as ''difficult'' by the treating physician compared to 4.3% for propofol (P<0.001). Anesthesia related complications were fewer in the propofol group (2.7% vs. 11.7%, P<0.001). Another randomized trial also reported less pain perception (P<0.001) and greater patient and endoscopist satisfaction during colonoscopy in case of propofol-based sedation (n = 126) compared with midazolam/fentanyl (n = 136).[31]

Interestingly, several in vitro studies describe another potential advantage of propofol—that it may contribute to immune modulation, anti-inflammation and inhibition of cancer cell proliferation and invasion.[32,33]

This study has several limitations. First, the three groups are retrospectively analyzed; in other words, the anesthetic technique was not randomly allocated. As such, the possibility of selection bias is not negligible. Though all procedures were analyzed consecutively from a prospective registry database and even though univariate and multivariate analysis was performed to correct for potential biases, there are no guarantees that exclude residual confounding. Because general anesthesia was often chosen for patients with contraindications for both sedation techniques, assessing patient-based oncological endpoints such as overall or cancer-specific survival was considered untrustworthy. Intraprocedural pain perception contains subjective measurements which may have introduced recall bias. Whenever possible, data were reviewed separately by two researchers (RSP and VZP). Since periprocedural parameters, such as pain, were digitally reported by the anesthesiologist and nurse anesthetist, these factors were presumably being more extensively documented in the general anesthesia and propofol groups. In addition, monitoring and administration of midazolam/fentanyl were performed by the interventional radiologist, who, even though specifically trained and certified for this procedure, had limited knowledge of the systemic effects, while general anesthesia and propofol sedation were always administered by a specialized anesthetic assistant under direct supervision of an anesthesiologist.

Despite the fact that propofol administration should be reserved for anesthesia providers, a recently published survey showed that anesthesia providers are not uniformly available

during interventional procedures.[3] This could result in situations where interventional radiologists are increasingly being involved in administering sedative drugs and managing complications, as was the case in our institution. Another limitation was the unequal median follow-up duration between the groups ($P<0.001$); however, since the majority of LTPs appeared within the first 6 months post-treatment (Fig. 2, numbers at risk), the likelihood of developing LTP decreases over time (plateau curve). Although overall survival is generally considered the most relevant oncological endpoint, the efficacy of closely related ablation techniques to eradicate tumors can best be elucidated by comparing the time to LTP. Although multiple lesions in one patient cannot be considered independent, the per-patient analysis (counting LTP of one of the ablated lesions in a single patient as an event) showed equal differences between the three groups.

To conclude, propofol sedation represents a valid alternative to general anesthesia for percutaneous liver tumor ablation, and midazolam sedation does not. Midazolam sedation was inferior to both general anesthesia and to propofol with regard to local tumor control. Compared to midazolam sedation, propofol reduced the periprocedural perception of anxiety and pain, decreased patient movements and resulted in better control of breathing. This probably contributed to more precise needle placements and tracking with higher ablation accuracy, which is reflected by the superior LTPFS. Propofol-based sedation reduces the number of repeat procedures and should be favored over midazolam sedation in percutaneous liver tumor ablation. Future research should focus on the added value of innovative techniques such as one lung and highfrequency jet ventilation.

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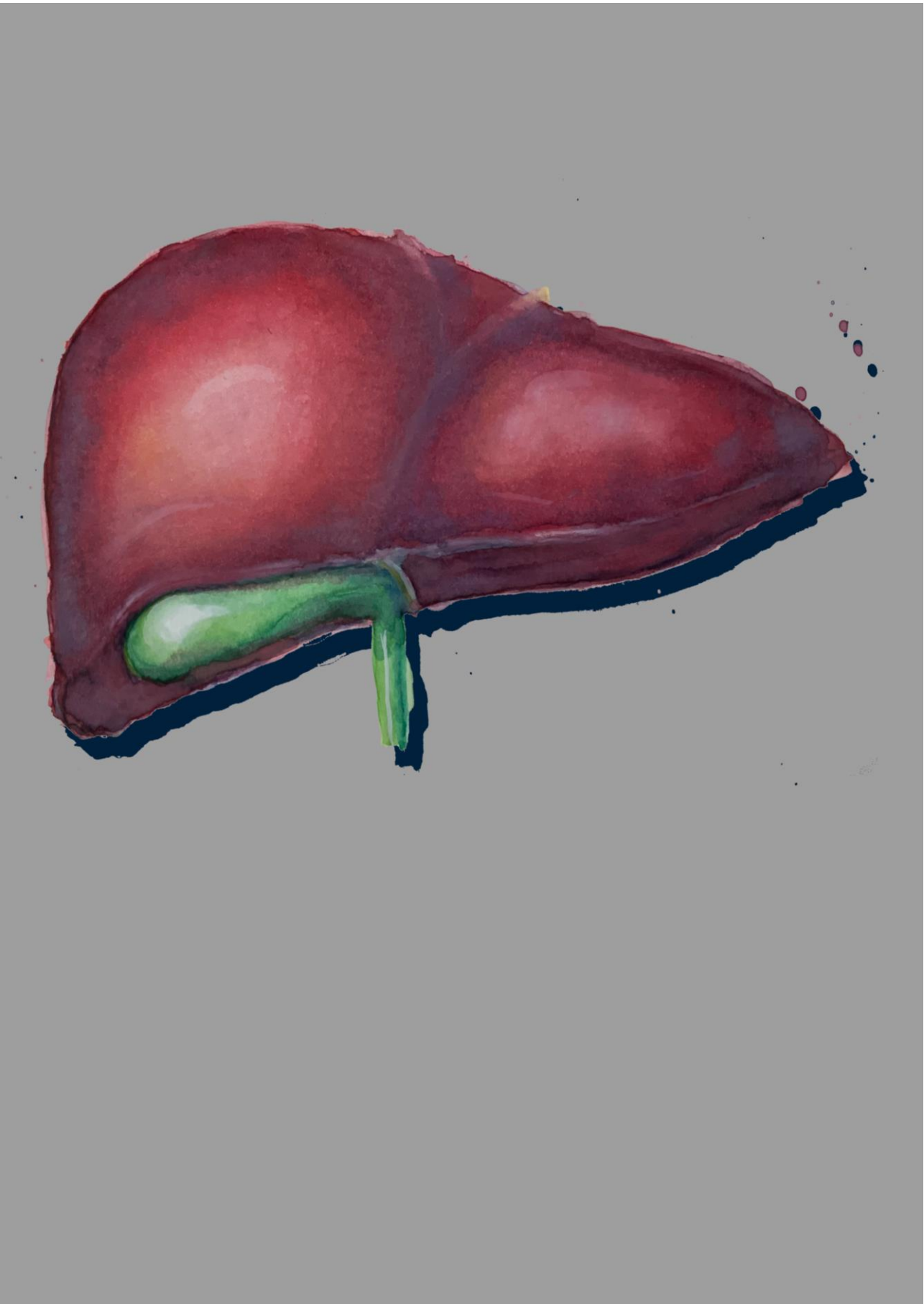

Chapter 7

Real-time image guidance

7.1

Transcatheter CT hepatic arteriography compared with conventional CT fluoroscopy guidance in percutaneous thermal ablation to treat colorectal liver metastases: a single-center comparative analysis of 2 historical cohorts

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ABSTRACT

Purpose: To evaluate safety and efficacy of CT hepatic arteriography compared with conventional CT fluoroscopy guidance in percutaneous radiofrequency (RF) and microwave (MW) ablation to treat colorectal liver metastases (CRLM).

Materials and Methods: This single-center comparative, retrospective study analyzed data of 108 patients treated with 156 percutaneous ablation procedures (42 CT fluoroscopy guidance [25 RF ablation, 17 MW ablation]; 114 CT hepatic arteriography guidance [18 RF ablation, 96 MW ablation]) for 260 CRLM between January 2009 and May 2019. Local tumor progression-free survival (LTPFS) was assessed using univariate and multivariate Cox proportional hazard regression analyses. LTPFS and overall survival (OS) were estimated using the Kaplan-Meier method.

Results: There were no complications related to the transarterial catheter procedure. CT hepatic arteriography proved superior to CT fluoroscopy regarding 2-year LTPFS (18/202 [8.9%] vs 19/58 [32.8%]; $P < .001$, respectively). CT hepatic arteriography versus CT fluoroscopy (hazard ratio = 0.28; 95% confidence interval, 0.15–0.54; $P < .001$) and MW ablation versus RF ablation (hazard ratio = 0.52; 95% confidence interval, 0.24–1.12; $P = .094$) were positive predictors for longer LTPFS. Multivariate analysis revealed that CT hepatic arteriography versus CT fluoroscopy (hazard ratio = 0.41; 95% confidence interval, 0.19–0.90; $P = .025$) was associated with a significantly superior LTPFS. OS was similar between the 2 cohorts ($P = .3$).

Conclusions: While adding procedure time and marginal patient burden, transcatheter CT hepatic arteriography guided ablation was associated with increased local disease control and superior LTPFS compared with conventional CT fluoroscopy. CT hepatic arteriography represents a safe and valid alternative to CT fluoroscopy, as it reduces the number of repeat ablations required without adding risk or detrimental effect on survival.

INTRODUCTION

Imaging guidance for percutaneous liver tumor ablation should ensure precise tumor targeting and needle tracking and enable real-time monitoring of tissue changes, which are independently required for achieving a complete ablation (circumferential tumor-free margin > 5 mm).[1-8] Numerous image guidance techniques can be used, such as conventional B-mode ultrasound, computed tomography (CT) fluoroscopy, and CT fluoroscopy assisted by hepatic arteriography (CT hepatic arteriography) or arterial portography (CT arterial portography).[1,4] The choice of guidance system is often based on tumor visibility, clinician preferences, and local availability of dedicated equipment.[2] Ultrasound is still the most widely used technique; however, it is also known for its poor tumor visualization, which is mainly due to overlying structures, low tumor echogenicity gradient, and gas formation around the ablation zone.[9,10] Conventional CT fluoroscopy enables a three-dimensional view of the target tumor, surrounding structures, electrodes, and tissue changes.[11,12] Important disadvantages are high radiation exposure, limited angulation possibilities during electrode insertion, short contrast-enhanced imaging time frame, and suboptimal visualization of intrahepatic vessels and bile ducts owing to limited administration of intravenous contrast agent (nephrotoxicity).[12,13]

In recent decades, transarterial catheter-assisted ablation (CT hepatic arteriography or CT arterial portography) has become a promising technique that enables the repeated admission of small doses of intra-arterial intrahepatic contrast to improve tumor conspicuity, needle targeting, and ablation zone visualization.[5,6,14,15] CT hepatic arteriography is generally preferred because it provides more homogeneous contrast distribution throughout the liver and has the ability to improve differentiation between vital tumor tissue and ablative scar tissue (incomplete ring sign).[6] As a consequence, it improves treatment accuracy and reduces the number of required additional ablations.[4-6]

In hepatic metastases, diagnostic CT arterial portography performed before surgical resection is known to have a significantly higher detection rate compared with contrastenhanced CT.[16] When used to guide percutaneous ablations, combined CT arterial portography/CT hepatic arteriography have shown a significantly higher detection rate of hepatic malignancies compared with conventional unenhanced CT and contrast-enhanced CT (5). In hepatocellular carcinoma (HCC), CT hepatic arteriography/CT arterial portography may also detect local tumor progression (LTP) earlier; however when used preoperatively, it does not improve cumulative recurrence-free and overall survival (OS).[14] The higher detection rate of hepatic tumors and ablation site residual disease led to the presumption that hepatic tumors would be ablated more effectively with the use of CT hepatic arteriography guidance.[6]

The primary aim of this study was to retrospectively analyze safety and efficacy of real-time image guidance by CT hepatic arteriography compared with conventional CT fluoroscopy

during percutaneous radiofrequency (RF) and microwave (MW) ablation in patients with colorectal liver metastases (CRLM).

MATERIALS AND METHODS

Study design and population

This single-center retrospective cohort study was conducted at the Amsterdam University Medical Center (location VUmc), a tertiary referral institution for hepatobiliary and gastrointestinal malignancies. The Medical Ethics Review Committee of Amsterdam University Medical Center confirmed that the Medical Research Involving Human Subjects Act does not apply to this study, and thus an official approval of this study was not required (reference number 2019.701).

Data were obtained from a prospectively maintained registry. The STrengthening the Reporting of OBervational studies in Epidemiology (STROBE) guidelines for reporting study data were followed.[17] All cases and their treatment strategy were discussed in a multidisciplinary liver tumor board. Between January 2009 and May 2019, 134 patients were treated in the interventional oncology suite, which houses an angiography system (Philips Azurion; Philips Healthcare, Best, The Netherlands), CT scanner (SOMATOM Sensation or Drive, Siemens Healthineers AG, Erlangen, Germany), and anesthetic facilities. Only patients with CRLM treated by percutaneous RF or MW ablation were included (Fig 1). Diagnosis was made with contrastenhanced CT and magnetic resonance (MR) imaging with liver-specific contrast agent (gadoxetate disodium [Primovist; Bayer AG, Leverkusen, Germany]) plus high B-value MR diffusion weighted imaging according to national guidelines.[18] Imaging was evaluated using the Response Evaluation Criteria in Solid Tumours.[1] Although neo-adjuvant or adjuvant systemic therapy is not standard of care in The Netherlands, the following patients often received induction systemic therapy first: patients with locally advanced primary rectal cancer, patients with unresectable but potentially downstageable CRLM or with difficult-to-resect disease if systemic therapy is likely to reduce procedural risk, and patients with early metachronous disease. No patients received adjuvant systemic therapy. All included procedures were guided by either conventional CT fluoroscopy or transcatheter CT hepatic arteriography. Conventional CT fluoroscopy was chosen for patients with contraindications (obstructing arterial stenosis or arteriosclerosis) for catheter placement and for tumors that were visualized well on nonenhanced or enhanced diagnostic CT. Follow-up consisted of at least 1 cross-sectional imaging study to reliably exclude or detect LTP. Patients without available follow-up imaging and patients with procedures guided with ultrasound alone were excluded.

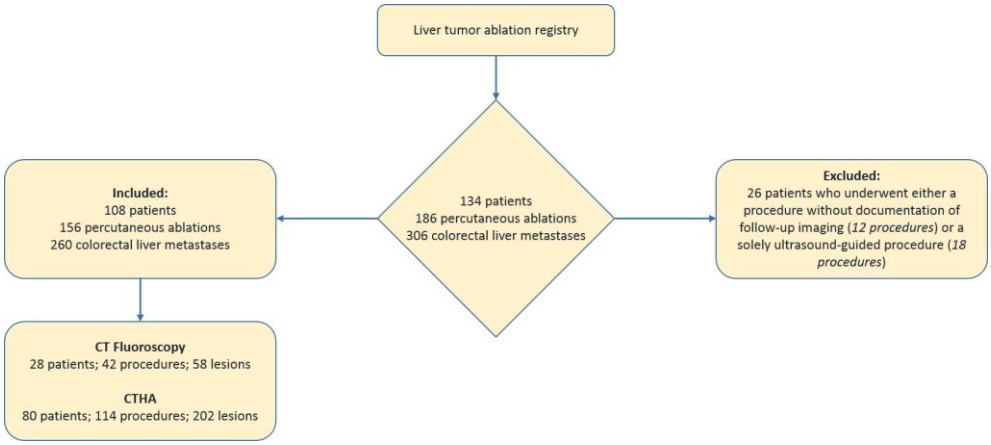

Figure 1. Flowchart for patient selection

CT Fluoroscopy

Between January 2009 and April 2019, 42 procedures (25 RF ablation; 17 MW ablation) were performed with realtime conventional CT guidance plus fluoroscopy. Baseline abdominal contrast-enhanced CT imaging was obtained by administering 100 mL of contrast agent (Xenetix 300; Guerbet SA, Villepinte, France) via a peripheral intravenous injection. This baseline scan was performed just before needle advancement. The table was placed in a stable position so that the needle remained in the appropriate plane. At the end of each procedure, a repeat injection of 100 mL of contrast agent was administered to evaluate the ablation zone.

CT hepatic arteriography

Between July 2012 and May 2019, 114 thermal ablation procedures (18 RF ablation; 96 MW ablation) were performed with transarterial catheter guidance. Before the procedure, patients were admitted to the angiography suite. The sheath was introduced in the right common femoral artery. A 4-F Cobra (Cordis Corp, Bridgewater, New Jersey) or 5-F Cobra (Cook, Inc, Bloomington, Indiana) catheter was placed with the tip preferably in the common hepatic artery, but in cases of unstable positioning the tip was advanced in the proper hepatic artery or in the left or right hepatic artery (depending on the location of the tumor). In the angiography suite, 10 mL of contrast agent was injected to verify the catheter position.

A baseline CT hepatic arteriography scan was performed first for treatment planning. To obtain the arterial phase, 2 series of mixed late arterial and early-to-portal venous phase CT images were acquired at 6 and 22 seconds, respectively, after start of injection (flow rate 5

mL/s) of 40 mL of 1:1 mixed bolus of 20 mL contrast medium (Xenetix 300) and 20 mL saline into the arterial catheter. Tumors were identified as having a hypoattenuating core surrounded by an enhancing ring or an incomplete ring in cases of LTP (Fig 2). When considered necessary, or in cases of multiple (additional) tumors, repetitive small amounts of contrast agent (20 mL per tumor) were injected to obtain a series of CT hepatic arteriography scans to verify and adjust the needle position allowing for overlapping (completion) ablations. For ablation confirmation, another 20 mL of contrast agent was injected at the end of each procedure. If the catheter tip dislocated during movement of the patient from table to bed, the tip was placed in the abdominal aorta to obtain an arteriogram. This did not compromise the images. In this case, a double amount of contrast agent (40 mL) was injected per tumor. The arterial sheath was removed directly after the ablation procedure by placing a hemostatic closure device at the insertion in the common femoral artery. The entire protocol has been previously described in detail by van Tilborg et al.[5,6]

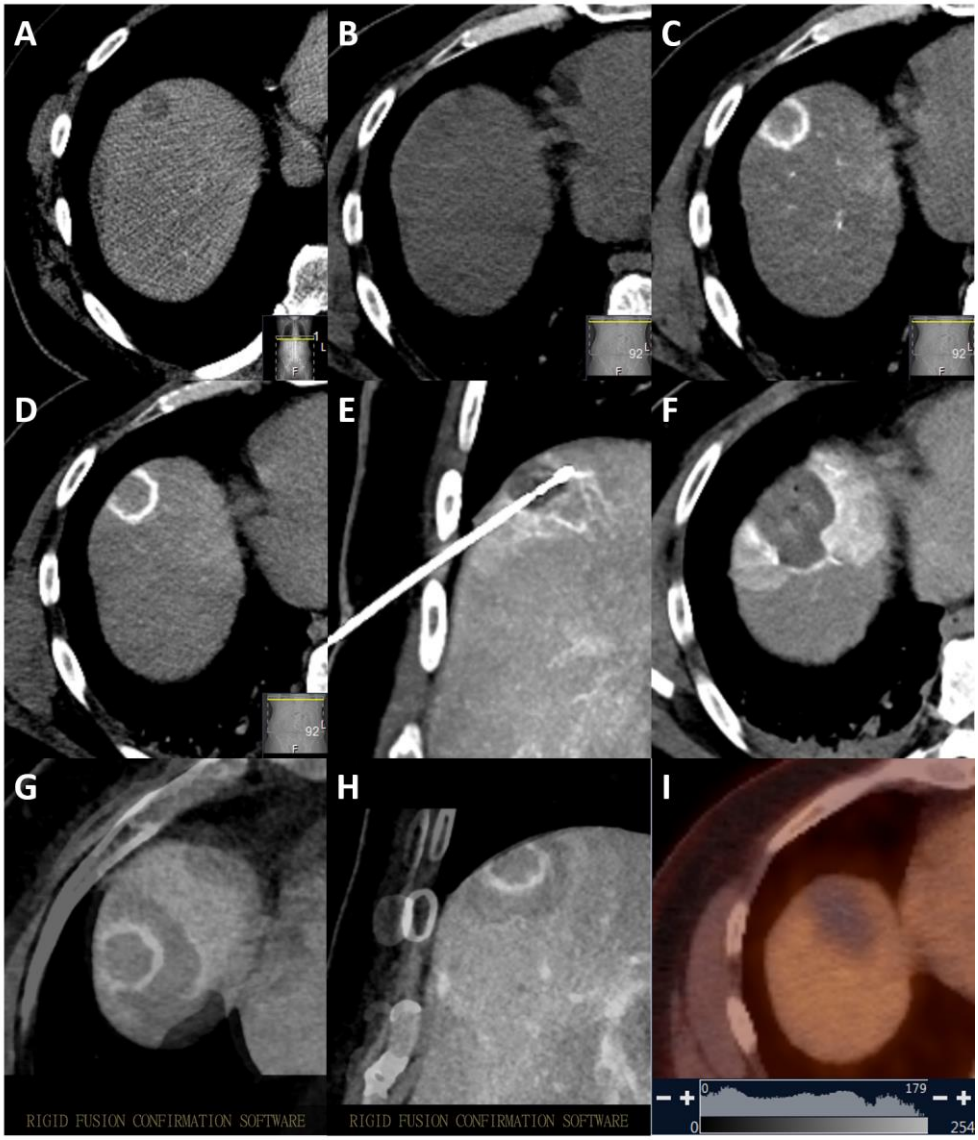

Figure 2. (A + B) Diagnostic CT. Superficially located CRLM (23 mm, segment 8), hypoattenuating on routine diagnostic contrast-enhanced CT. **(C - H)** Intraprocedural CT. After introduction of the transarterial catheter within the common hepatic artery (CT hepatic arteriography), real-time CT image shows a clearly visible tumor characterized by a hypoattenuating core that is surrounded by a typical enhancing ring (ring sign) on arterial phase **(C)**. Mixed late-arterial to early-portal venous phase images shown on **(D)**. **(E + F)** Ablation procedure. **(G + H)** CT after ablation. The metastasis was treated with MW ablation (Emprint) with adequate circumferential tumor-free margins. Pre-posed MW ablation image shows overlay image before the procedure of hypoattenuating core with enhancing ring (tumor) (asterisk) and the ablation zone (pound sign), perpendicular to the needle.

Thermal Ablation Procedure

Before the procedure, all patients underwent a routine examination by the anesthesiologist and were fasted for at least 6 hours. The procedures were performed with either general anesthesia (propofol [Diprivan; AstraZeneca BV, Zoetermeer, The Netherlands], rocuronium [Esmeron; Sandoz, Almere, The Netherlands], remifentanil [Ultiva; Mylan BV, Amstelveen, The Netherlands], and sufentanil [Sufenta; Janssen Pharmaceutica NV, Beerse, Belgium]) or propofol sedation with alfentanil (Rapifen; Janssen Pharmaceutica NV) or remifentanil. Patients were positioned in a supine position with their head and spine aligned. Both arms are fixed above the head and tucked to the table to prevent brachial neuropathy. In cases of dorsally located tumors (segment 6 or 7), patients were positioned in an oblique and lateral decubitus position.

The RF ablation device (RF3000 with LeVeen electrodes [Boston Scientific, Marlborough, Massachusetts] and MW ablation devices (Emprint with Thermosphere Technology [Medtronic, Minneapolis, Minnesota] and Solero [Angio-Dynamics, Amsterdam, The Netherlands]) were used according to their CE marking. RF ablation and MW ablation were not simultaneously used during a procedure. In this institution, MW ablation is generally the preferred modality for perivascular located tumors. For both CT fluoroscopy and CT hepatic arteriography guidance, baseline images were obtained just before the ablation procedure. The RF ablation device was set to automatically increase power to control impedance and avoid early roll-off. The MW ablation device was manually set to deliver 100 W for 10 minutes. After ablation, cauterization of the needle tract during retraction of the electrode (track ablation) was routinely performed to diminish bleeding and tumor seeding along the needle tract.[2] Immediately after the procedure, conventional contrast-enhanced CT images were acquired in the CT fluoroscopy group, and additional CT hepatic arteriography images were acquired in the CT hepatic arteriography group. Rigid fusion confirmation software (syngo Fusion; Siemens Healthineers AG) was used to overlay the CT images obtained before and after the procedure to ensure circumferential coverage of the tumor plus a specific tumorfree margin by the ablation zone (Fig. 2G + H). The images obtained after the procedure were also used to assess for complications and technical success. Additional, overlapping ablation was performed to treat residual unablated tumor tissue in cases of an incomplete procedure. Patients were admitted to the postanesthesia care unit to monitor vital signs. All patients remained in the surgical ward for at least 1 night. All catheter placements and percutaneous ablations were performed by 2 interventional radiologists (J.J.J.d.V., M.R.M.) with a master degree in image-guided tumor ablation (ie, have performed and/or supervised > 100 thermal ablation procedures).

Follow-up

Within the first 2 weeks after the initial procedure, a completion ablation was performed when there was a potentially inadequate safety margin (0–5 mm) in combination with suboptimal tumor conspicuity and needle visibility during the procedure.[4] Combined fluorodeoxyglucose positron emission tomography/CT scans were performed every 3 months after the initial ablation during the first year of follow-up and every 6 months thereafter, according to national guidelines[18] and reporting criteria[1]. Imaging was reviewed by the interventional oncology team, certified diagnostic abdominal radiologists, and nuclear medicine physicians.

Data collection and analysis

Baseline characteristics per patient, per procedure, and per tumor were retrieved from the electronic patient database. Catheter- and ablation-related complications were evaluated using the unified standardized Society of Interventional Radiology (SIR) grading system.[1,19] LTP and survival data were analyzed and reported.

According to the reporting criteria for image-guided tumor ablation by Ahmed et al.[1], the following definitions were used: (a) technical success (ie, having delivered the energy as planned and showing no residual enhancement around the ablation zone on immediately obtained contrastenhanced CT imaging and (b) LTP (ie, appearance of tumor foci at the edge of the ablation zone, after at least 1 contrastenhanced follow-up study has documented adequate ablation and the absence of viable tissue in the target tumor and surrounding ablation margin).[1] Evaluation of technical success after all ablations was supported by the use of rigid fusion software, as described previously. Local tumor progression-free survival (LTPFS) was calculated from the time of treatment to LTP (event) for the per tumor and per patient assessment. Death without LTP is considered a competing risk. OS was calculated from the time of the first ablative therapy to death. A perivascular tumor was defined as a tumor with nearest margin ≤ 5 mm from a vessel at least 4 mm in diameter.[1,19,20]

Statistics

Statistics were reported as number (with or without percentage), median (interquartile range) or mean (SD). Continuous measures were compared using the Mann-Whitney U test. Categorical variables were compared using the Pearson χ^2 test between cohorts. The survival rates for time without LTP (LTPFS) were estimated using the Kaplan-Meier method, with comparisons made using the log-rank test. To evaluate parallelism of the survival curves, the

proportional hazards assumption was tested graphically. Factors with a known association with LTPFS (eg, tumor diameter) and factors with $P \leq .15$ in the baseline characteristics were entered into the univariate Cox proportional hazard regression model. Survival estimates for OS were analyzed separately using the Kaplan-Meier method. Factors with $P \leq .15$ in the univariate analysis were entered into the multivariate analysis model. Hazard ratio and 95% confidence interval were calculated. The significance level for all parameters was set at $P \leq .05$. Statistical analyses were performed in consultation with an independent epidemiologist using IBM SPSS Version 24.0 (IBM Corp, Armonk, New York)[21] and R for Windows version 3.6.3. (R Foundation for Statistical Computing, Vienna, Austria).[22]

RESULTS

The medical records of 134 patients with CRLM were reviewed (Fig 1). After excluding 26 patients, 108 patients who underwent 156 image-guided liver tumor ablation procedures were included (42 procedures with CT fluoroscopy guidance [25 RF ablation; 17 MW ablation] and 114 procedures with CT hepatic arteriography guidance [18 RF ablation; 96 MW ablation]). Overall, 260 metastatic liver tumors were treated. Of these, 46 tumors were treated for LTP after previous ablation (RF ablation and CT fluoroscopy [n = 12], RF ablation and CT hepatic arteriography [n = 10], MW ablation and CT fluoroscopy [n = 8], MW ablation and CT hepatic arteriography [n = 9], or RF ablation and ultrasound [n = 7]).

For the entire cohort, the average number of ablated tumors per procedure was 1.8 ± 1.2 (range, 1–7). The average diameter per tumor treated was 18.2 mm ± 10.3 (range, 2–57). The mean (SD) amount of contrast per procedure was 131.0 (46.8) mL in the CT fluoroscopy group compared with 88.4 (26.1) mL in the CT hepatic arteriography group ($P < .001$). Baseline characteristics are shown in Table 1. Median follow-up time after each procedure was 17.6 months in the CT fluoroscopy group and 9.3 months in the CT hepatic arteriography group (Table 2). In 6 procedures, the tip dislocated from the common hepatic artery during movement of the patient from table to bed. The catheter was placed in the abdominal aorta to obtain an arteriogram, which did not compromise the CT images.

Per Patient	CT Fluoroscopy	CT Hepatic Arteriography	*P* Value
	n = 28	**n = 80**	
Age, y, mean (SD)	65.4 (8.6)	66.9 (10.6)	.501*
Sex, M:F	19:9	57:23	.735†
BMI, mean (SD)	26.1 (4.3)	25.9 (5.1)	.691*
ASA score ≥ 3	10	15	.067†
Right-sided primary	4	17	.423†
Rectal primary	7	22	.797†
Per Procedure	**n = 42**	**n = 114**	
Tumor number, > 1	13	56	.043†
Synchronous	17	41	.605†
Anesthesia technique			< .001†
General anesthesia	30	36	
Propofol sedation	12	78	
Ablation technique			< .001†
RF ablation	25	18	
MW ablation	17	96	
Contrast, mL, mean (SD)	131.0 (46.8)	88.4 (26.1)	< .001*
Per Tumor	**n = 58**	**n = 202**	
Neoadjuvant chemotherapy	15	62	.478†
Diameter, mm, mean (SD)	19.3 (8.5)	17.8 (10.8)	.079*
Diameter, > 30 mm	6 (10.3%)	31 (15.3%)	.337†
Tumor-free margin, < 5 mm	9	14	.042†
Perivascular location	9	17	.112†

Table 1. Baseline characteristics. Baseline results are shown per patient, per procedure, and per tumor for the 2 analyzed cohorts. Statistics are reported as number (with or without percentage) or mean (SD). ASA = American Society of Anesthesiologists; BMI = body mass index; F = female; M = male; MW = microwave; RF = radiofrequency. *Mann-Whitney U test. † Pearson $\chi 2$ test between groups.

No. Procedures	CT Fluoroscopy	CT Hepatic Arteriography	*P* Value
	n = 42	**n = 114**	
Intraprocedural complications	5	11	.680*
Allergic reaction to contrast	—	—	
Contrast nephropathy	—	—	
Catheter-related	NA	—	
Pneumothorax	5	7	
Probe-induced hepatic hemorrhage	—	4	
FU after procedure, months, median (IQR)	17.6 (28.3)	9.3 (18.7)	.001†
No. Tumors	**n = 58**	**n = 202**	
LTP rate, no. tumors	19 (32.8%)	18 (8.9%)	< .001*
TTLTP, months, median (IQR)	NR	NR	NA
Time to detection of LTP, months, mean (SD)	5.0 (3.5)	6.2 (4.9)	.461†

Table 2. Outcomes of all percutaneous thermal ablation procedures. Outcomes are shown per procedure and per tumor for the 2 analyzed cohorts. Statistics are reported as number (with or without percentage), mean (SD), or median (IQR). FU = follow-up; IQR = interquartile range; LTP = local tumor progression; NA = not applicable; NR = not reached; TTLTP = time to local tumor progression. *Pearson χ 2 test between groups. †Mann-Whitney U test.

Complications

No contrast- or catheter-related complications were reported, and the overall complication rate between the 2 groups did not differ (P = .680) (Table 2). In the CT hepatic arteriography group, 4 active contrast extravasations were detected along the needle tract on the CT scan performed immediately after the procedure. Two patients were admitted for an emergency coiling procedure (SIR classification D), and 2 patients were treated conservatively (SIR classification B). Although likely detected owing to the presence of an arterial sheath in the common hepatic artery, the probe-induced hemorrhages had no etiologic relationship with the catheter. Pneumothoraces were diagnosed after 5 procedures under CT fluoroscopy guidance (SIR classification B [n = 3] and C [n = 2]) and after 7 procedures with CT hepatic arteriography (SIR classification B [n = 4] and C [n = 3]).

Mortality and OS

Of 108 patients, 21 (19.4%) died during follow-up (CT fluoroscopy [n = 11]; CT hepatic arteriography [n = 10]). Twenty patients (95%) died of progression of disease. One patient died of progressive cardiopulmonary failure 6 months after ablation that was complicated by a probeinduced hemorrhage (from which the patient recovered) and several episodes of respiratory insufficiency and cardiac decompensation. No patients died within 30 days of the last ablation. OS estimates are shown in Figure 3 (log-rank P = .300).

	Univariate analysis			Multivariate analysis		
	Hazard ratio	**95% CI**	***P*-value**	**Hazard ratio**	**95% CI**	***P*-value**
Per patient						
ASA ≥3	0.42	0.12-1.40	0.156			
Per procedure						
Tumor number, >1	0.21	0.07-0.59	0.003	0.33	0.16-0.68	0.002
Anesthesia technique, propofol sedation	0.39	0.17-0.87	0.021	0.37	0.15-0.90	0.028
Ablation technique, microwave ablation	0.52	0.24-1.12	0.094	1.35	0.57-3.22	0.498
Per tumor						
Diameter, >30mm	2.36	1.11-5.00	0.025	1.98	0.91-4.32	0.087
Tumor-free margin, <5mm	1.73	0.68-4.45	0.253			
Perivascular location	1.76	0.69-4.53	0.241			
Image guidance						
CTHA	0.28	0.15-0.54	<0.001	**0.41**	0.19-0.90	0.025

Table 3. Death without LTP is censored. Variables with P value ≤ .15 were entered into the multivariate analysis. ASA = American Society of Anesthesiologists; CI = confidence interval; HR = hazard ratio; LTP = local tumor progression; LTPFS = local tumor progression-free survival; MW = microwave; RF = radiofrequency.

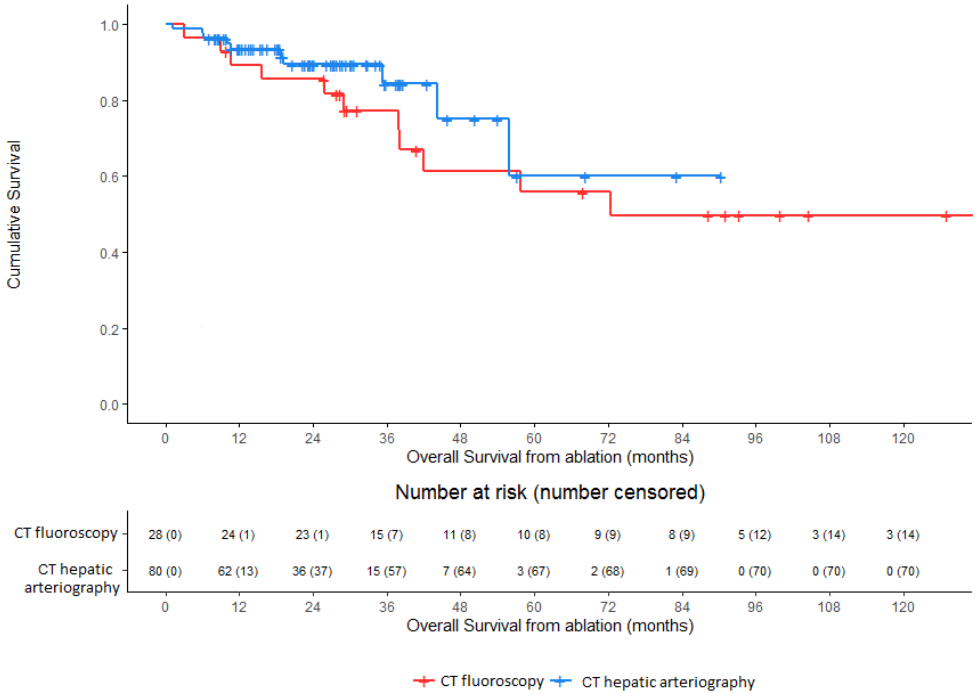

Figure 3. Kaplan-Meier curves indicating OS time per treated patient. Kaplan-Meier curves indicating OS after ablation for patients with CRLM treated with conventional CT fluoroscopy guidance (red line) and CT hepatic arteriography guidance (blue line). Numbers at risk are per patient. Overall comparison log-rank (Mantel-Cox) test, P = .3.

Local Disease Control

The rate of incomplete ablations identified on early follow-up imaging with repeat ablations within 2 weeks following the initial ablation was 1.5% (4/260). The cumulative overall LTP rate was 14.2% (37/260 tumors) for the entire cohort (12.7% at 1 year. Of the tumors with LTP, 23 tumors (23/37 [62.2%]) received repeat ablation. Univariate and multivariate associations with LTPFS are shown in Table 3. After multivariate analysis, the hazard ratio was 0.41 (95% confidence interval, 0.19–0.90; P = 0.025) in favor of CT hepatic arteriography versus CT fluoroscopy.

CT hepatic arteriography proved superior to CT fluoroscopy regarding per-tumor analyzed LTPFS (18/202 [8.9%] vs 19/58 [32.8%]; P < .001) (Fig 4). Per-patient LTPFS showed similar-shaped curves between the 2 groups (P = .010) (Fig 5). Figure 6 shows freedom from LTP per tumor after sensitivity analysis for ablation technique (RF ablation and MW ablation) with CT fluoroscopy and CT hepatic arteriography.

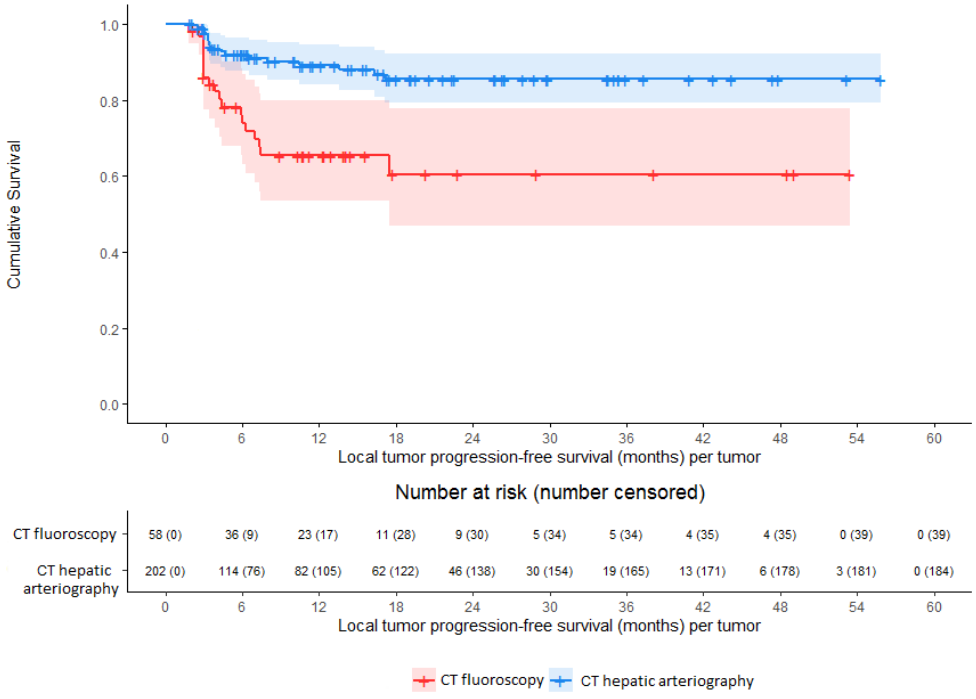

Figure 4. Kaplan-Meier curves indicating survival time without LTP (LTPFS) per treated tumor. Kaplan-Meier curves indicating freedom from LTP (per tumor) for patients with CRLM treated with conventional CT fluoroscopy guidance (red line) and CT hepatic arteriography guidance (blue line). Numbers at risk are per tumor. Overall comparison log-rank (Mantel-Cox) test, P < .001. Death without LTP is censored.

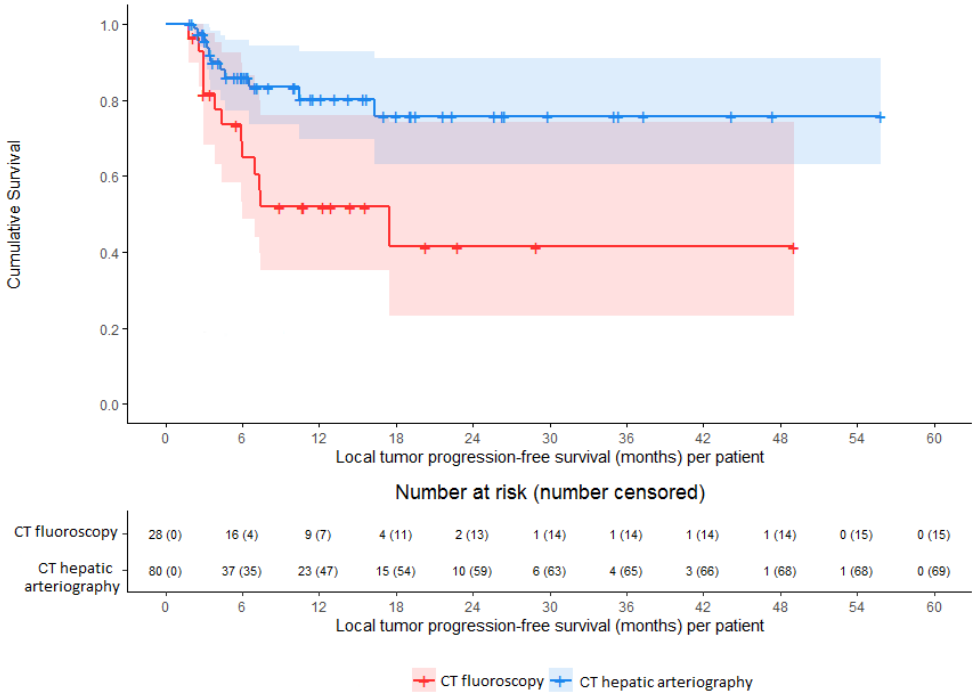

Figure 5. Kaplan-Meier curves indicating survival time without LTP (LTPFS) per patient. Kaplan-Meier curves indicating freedom from LTP (per patient) for patients with CRLM treated with conventional CT fluoroscopy guidance (red line) and CT hepatic arteriography guidance (blue line). Numbers at risk are per patient. Overall comparison log-rank (Mantel-Cox) test, P ¼ .004. Death without LTP is censored.

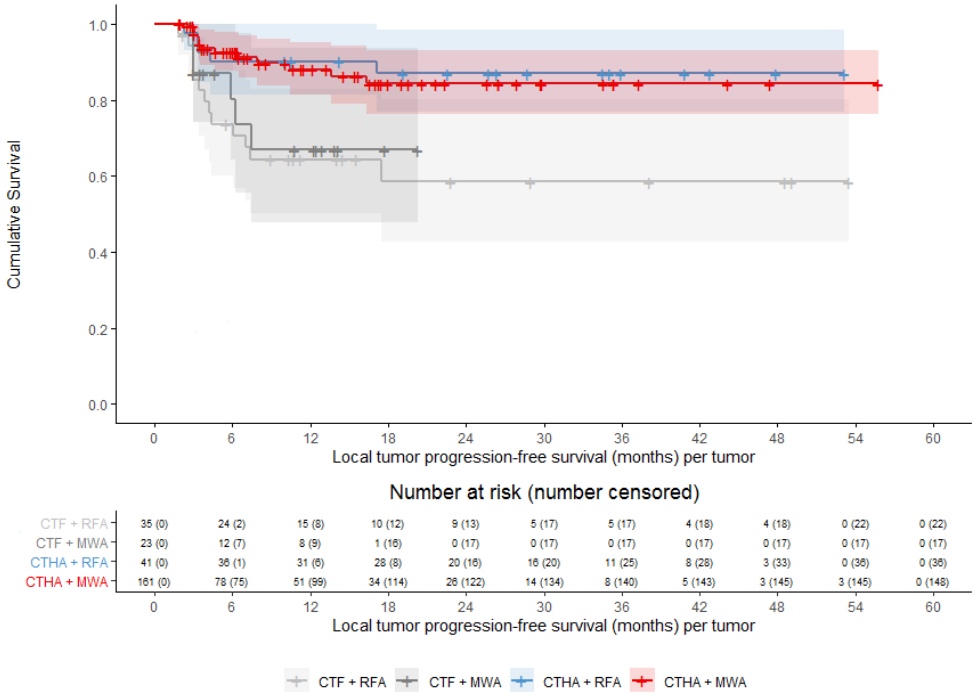

Figure 6. Kaplan-Meier curves indicating survival time without LTP (LTPFS) per ablation technique and per tumor. Kaplan-Meier curves indicating freedom from LTP (per tumor) for patients with CRLM treated by percutaneous MW ablation with CT fluoroscopy guidance (dark gray line), MW ablation with CT hepatic arteriography guidance (red line), RF ablation with CT fluoroscopy guidance (light gray line), and RF ablation with CT hepatic arteriography guidance (blue line) CT hepatic arteriography. Numbers at risk are per tumor. Overall comparison log-rank (Mantel-Cox) test, $P < .001$. Death without LTP is censored.

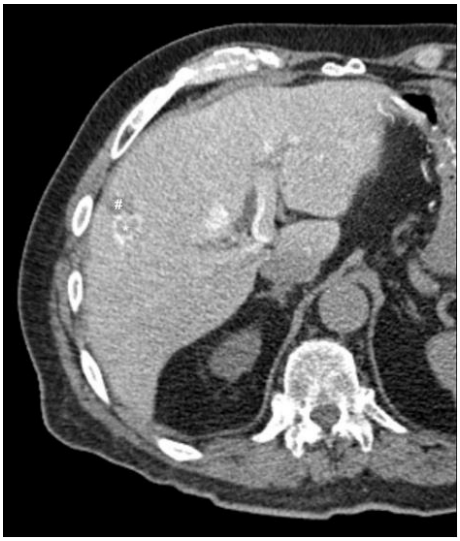

Figure 7. Incomplete ring sign. A 70-year-old patient with suspected LTP on fluorodeoxyglucose positron emission tomography imaging. Intraprocedural CT hepatic arteriography image shows a typical incomplete enhancing ring (asterisk) adjacent to the ablation zone (pound sign) (mixed late-arterial to early-portal venous phase).

DISCUSSION

Real-time image guidance was the most significant predictor of LTPFS in the Cox regression model in favor of CT hepatic arteriography versus CT fluoroscopy guidance (hazard ratio = 0.41; P = .025). In other words, patients who underwent a percutaneous liver ablation with CT hepatic arteriography guidance had a significantly reduced risk of developing LTP compared with patients treated with CT fluoroscopy. CT hepatic arteriography leads to better tumor conspicuity and thus more accurate needle placement. This leads in turn to superior coagulation necrosis visualization, allowing more precise ablation zones. As a result, the number of repeat procedures could be further reduced. The use of CT hepatic arteriography guidance was found to be safe with similar OS rates compared with conventional CT fluoroscopy. For CT hepatic arteriography–guided procedures, the amount of injected contrast agent was significantly reduced by an average total of 42.6 mL per procedure.

Neither the SIR Reporting Standards nor the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) quality improvement guidelines mentions the use of CT hepatic arteriography as a real-time image guidance technique.[1,2,23] Ohki et al.[14] randomly assigned 280 patients in whom HCC was diagnosed on conventional multiphase dynamic CT and who were eligible for RF ablation to a group with CT hepatic arteriography/CT arterial

portography performed before ablation or to a control group without additional imaging. In 45 patients, 75 additional definite HCC tumors were found in the CT hepatic arteriography/CT arterial portography group. Although CT hepatic arteriography/CT arterial portography performed before the procedure did not improve cumulative recurrence-free survival or OS, CT hepatic arteriography/CT arterial portography was found to detect recurrent tumors earlier. van Tilborg et al.[5] prospectively included 20 patients with unresectable CRLM (29 tumors), HCC (7 tumors), or intrahepatic cholangiocarcinoma (2 tumors), all suitable for percutaneous ablation, that were difficult to delineate on both ultrasound and unenhanced CT. The authors concluded that the operator's confidence in delineating tumors during the procedure significantly increased with the use of CT hepatic arteriography/CT arterial portography compared to conventional CT. Elaborating on their previous results, 9 patients with LTP after ablation of CRLM underwent repeat ablation with the CT hepatic arteriography technique resulting in optimal differentiation between (vital) residual or recurring tumor tissue and nonenhancing scar tissue (incomplete ring sign).[6] All previously mentioned advantages come at the cost of an additional procedure, including higher costs and higher radiation dose.[5,14] Possible complications related to catheter placement, which were not seen in the present study results, are additional risks.[5] Compared with conventional CT, diagnostic CT hepatic arteriography/CT arterial portography was found to have a higher false-positive detection rate owing to nontumorous perfusion abnormalities and subsequent formation of pseudotumors.[24]

The study's nonrandomized, retrospective design, which allows potential selection bias, was a limitation. As patients with obstructing arterial stenosis or arteriosclerosis were not eligible for catheter placement, this might have contributed to potential selection bias. Owing to technologic improvements, scientific support, and shortened procedure time, MW ablation has been gradually favored over RF ablation in the last decade, even though nonsignificantly different recurrence rates between the 2 techniques have been previously published.[20] Nonetheless, together with the associated experience gained in multiple additional procedures over time, both are potential confounders. Albeit all study data were analyzed consecutively from a prospective registry and even though univariate and multivariate analyses were performed, there are no guarantees that exclude residual confounding. However, after multivariate analysis, the ablation technique was omitted as a potential confounder. In addition, the per-tumor analysis per ablation technique with or without catheter guidance showed equal differences between the use of CT hepatic arteriography compared with CT fluoroscopy (Fig 8). Technical success was based on CT hepatic arteriography criteria in 1 group and on CT fluoroscopy in the other group. To address the different image guidance techniques, all ablations were evaluated with rigid fusion software. Although follow-up management is standardized and homogeneous in terms of imaging modality and frequency, the median follow-up period for the CT hepatic arteriography group was shorter because patients were treated more recently (P = .001). Notwithstanding, the

likelihood of developing LTP decreases over time (plateau curve) because the majority of ablation site tumor progression appeared within the first 9 months after the initial treatment (Fig. 7). The specific RF and MWablation systems used in this study may render the comparative outcomes as they do not necessarily represent all thermal ablation devices (eg, use of multiple antennae[25] or stereotactic navigation[26]). Another limitation would be the accessibility to both an angiography suite and a CT suite in actual daily practice. Although this study did not reveal any catheter-related complications, adding a minimally invasive procedure to the actual ablative procedure is more time-consuming with marginal additional patient burden.

The efficacy of real-time image guidance techniques to eradicate malignancies can best be illustrated by comparing the time to LTP. Although multiple tumors in 1 patient cannot be considered independent, the per-patient analysis (counting LTP of 1 of the ablated tumors in a single patient as an event) showed equal differences between the 2 cohorts. The last limitations are related to the patient's oncologic status. In compliance with national guidelines, patients did not receive adjuvant chemotherapy. Patients' mutational status (ie, microsatellite instability or K-Ras) was not routinely determined, as assessing the mutational status is reimbursed only before third-line systemic therapy and not before surgery and/or ablation.[18]

In conclusion, real-time image guidance with intraarterial contrast delivery directly into the hepatic arteries (CT hepatic arteriography) represents a safe and valid alternative to CT fluoroscopy guidance in percutaneous liver tumor ablation. CT fluoroscopy was inferior to CT hepatic arteriography with regard to local tumor control. Compared with CT fluoroscopy, CT hepatic arteriography increased tumor, needle, and ablation zone visualization. This probably contributed to more precise needle targeting, less needle repositioning, and higher ablation accuracy. This is reflected by the superior LTPFS per tumor and per patient, without compromising OS. As a result, CT hepatic arteriography reduces the number of repeat ablations and should be favored over CT fluoroscopy as a real-time image guidance tool. Likewise, visualization of the needle, tumor, surrounding structures, and ablation zone will always be superior with use of continuous, real-time three-dimensional imaging modalities compared with two-dimensional fused imaging software modalities. Future research should focus on the added value of innovative real-time image guidance techniques and artificial intelligence instruments.

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7.2

The added value of transcatheter CT hepatic angiography (CTHA) in percutaneous thermal liver ablation – a pictorial essay

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ABSTRACT

With the rapidly evolving field of image-guided tumor ablation, there is an increasing demand and need for tools to optimize treatment success. Known factors affecting the success of (non-)thermal liver ablation procedures are the ability to optimize tumor and surrounding critical structure visualization, needle targeting and ablation zone confirmation. A recent study showed superior local tumor progression-free survival and local control outcomes when using transcatheter computed tomography hepatic angiography (CTHA) guidance in percutaneous liver ablation procedures. This pictorial review provides eight clinical cases from four institutions, MD Anderson (Houston, Texas, United States), Gustav Roussy (Paris, France), UMC Utrecht (Utrecht, the Netherlands), and Amsterdam UMC (Amsterdam, the Netherlands), with the intent to demonstrate the added value of real-time CTHA guided tumor ablation for primary liver tumors and liver-only metastatic disease. The clinical illustrations highlight the ability to (1) improve detectability of the initial liver tumor, (2) detect additional tumors intraprocedurally, (3) identify surrounding critical vascular structures, (4) detect vanished tumors after induction chemotherapy, (5) differentiate local tumor progression from non-enhancing scar tissue, and (6) promptly detect and respond to iatrogenic hemorrhagic events. Although at the cost of adding a minor but safe intervention, CTHA-guided liver tumor ablation minimizes complications of the actual ablation procedure, reduces the number of repeat ablations and improves the oncological outcome of patients with liver malignancies. Therefore we recommend to adopt CTHA as a potential quality-improving guiding method within the (inter)national standards of practice.

INTRODUCTION

As thermal ablation, and especially the percutaneous approach, becomes more popular and available in the treatment of primary and secondary liver malignancies over the last years, optimizing treatment efficacy is one of the main goals ahead of us.[1-8] An adequate safety (or 'peri-ablational') margin, reflecting the distance from the initial lesion boundaries to the border of the post-treatment ablation zone, is one of the most determining factors influencing local tumor control of thermal ablation.[9,10] Circumferential safety margins of at least 5mm, and preferably >10mm, are known to improve local control, respectively with around 15% and 5% local tumor progression (LTP) rates during follow-up.[9,11,12] Complete ablation, commonly expressed as technical success rates or local tumor progression-free survival (LTPFS), should be pursued in all patients, and confirmed by rigid or non-rigid image-fusion and registration software.[13,14]

As such, multiple periprocedural tools, i.e. (stereotactic) navigation and real-time image fusion, have found their way to clinical daily practice.[15,16] One of those helpful tools is the administration of small doses of intra-arterial intrahepatic contrast agent (40 mL 1:1 mixed bolus of contrast and saline) via a catheter placed via the groin into the hepatic artery, known as CT hepatic arteriography (CTHA).[17] Although this procedure has previously been described for diagnostic purposes, it has recently demonstrated to be a promising technique that improves tumor and surrounding vascular structure(s) conspicuity, needle targeting, and real-time ablation zone visualization.[18-20] These findings resulted in an increased local disease control and superior LTPFS compared to conventional CT fluoroscopy guidance. By using CTHA-guidance as an alternative guidance tool, more patients, for example those with poorly visible lesions on ultrasound or conventional CT fluoroscopy, could become eligible for percutaneous thermal ablation.[17,21] For the detection of additional tumors or local tumor progression at the edge of the prior ablation zone ('incomplete ring-sign'), CTHA was also found to be supportive.[21]

In this pictorial essay, eight clinical cases from four institutions will be illustrated and discussed demonstrating the added value of CTHA-guidance in percutaneous liver tumor ablation.

Cases

This pictorial review was conducted at the interventional radiology departments of the Amsterdam University Medical Center location VUmc (Amsterdam, the Netherlands), the University of Texas MD Anderson Cancer Center (Houston, Texas, United States) and the Institut de Cancérologie Gustave Roussy (Villejuif, France), all tertiary referral institutions for hepatobiliary and gastrointestinal malignancies. Disease specific parameters and imaging data were collected and reported anonymously, not requiring ethical approval. The CTHA technique protocol has previously been described in detail by Van Tilborg et al. and Puijk et al.[17,21,22]

The local CTHA procedure guidelines were similar between the Amsterdam UMC, Gustave Roussy Cancer Center and MD Anderson Cancer Center. In the Utrecht UMC the ablation is performed using the C-arm CT within the angiography system. Each case is accompanied by diagnostic imaging and intraprocedural CTHA images. The cases are presented in Figures 1-8.

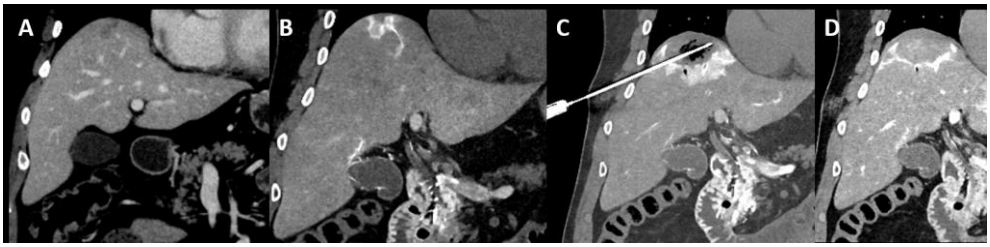

Figure 1. Identification of colorectal liver metastasis. Solitary colorectal liver metastasis in the hepatic dome, hardly visible on diagnostic CT-imaging in portal venous phase (A). The lesion became clearly visible as an enhancing ring after injection of 10 mL 1:1 mixed bolus of Xenetix 300® and saline just prior to the probe placement (B). After the microwave ablation (C) another 10 mL 1:1 mixed bolus was injected to assess the created ablation zone (D). *Courtesy of BC Odisio.*

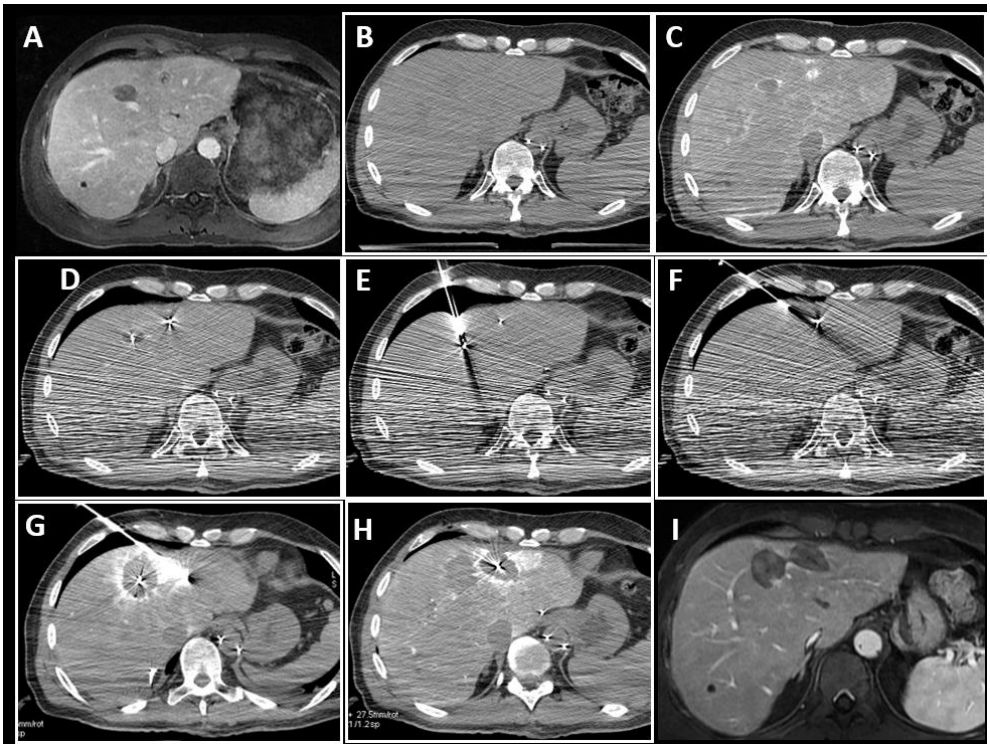

Figure 2. Identification of colorectal liver metastases. Two colorectal liver metastases visible on diagnostic contrast-enhanced MRI (A). During the procedure the lesions were not seen on non-enhanced CT (B). The lesions became clearly visible as enhancing rings after the injection of 4 mL Xenetix 300® contrast (C). Additionally, in this case, 0.018 coils have been inserted via a 22G needle into the lesions as a fiducial marker (D). A carboxypneumothorax was being created prior to the actual RFA procedure (E + F). Another 4 mL contrast was injected after each ablation to assess the created ablation zone (G + H). Follow-up MRI after two months showed no signs of local tumor progression (I). *Courtesy of F Deschamps.*

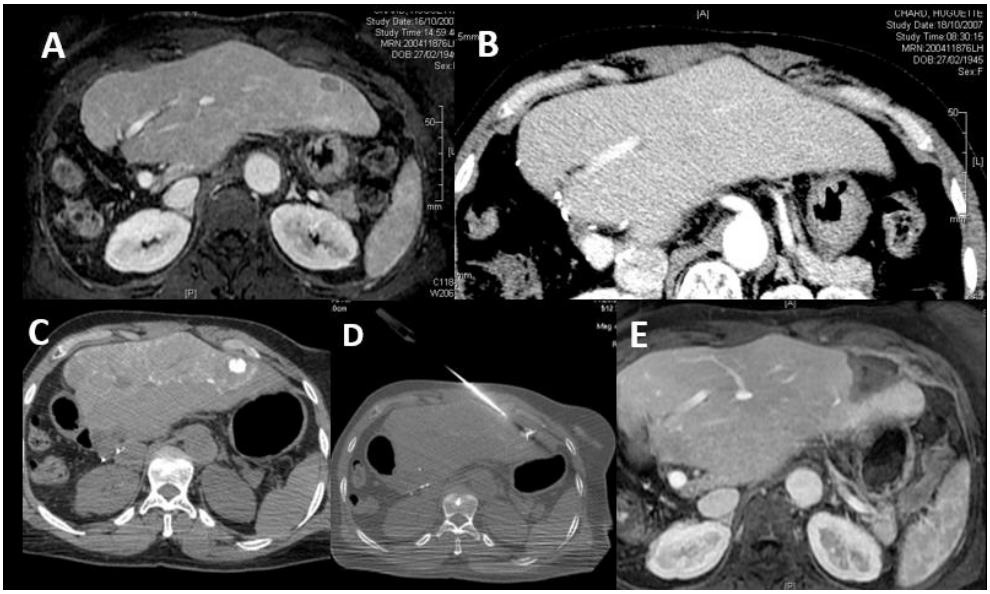

Figure 3. Visualization of the lesion by Lipiodol® Ultra Fluid contrast agent. Solitary colorectal liver metastasis in the left liver lobe visible on diagnostic MRI (A), but not on the intraprocedural CT in late arterial to early portal venous phase (B). After administration of intra-arterial intrahepatic Lipiodol® Ultra Fluid contrast agent (Guerbet, Villepinte, France), the lesion became clearly visible as an enhancing nodule on non-enhanced CT imaging (C). Percutaneous RFA was performed successfully (D). Follow-up imaging showed no signs of local tumor progression (E). *Courtesy of T de Baere.*

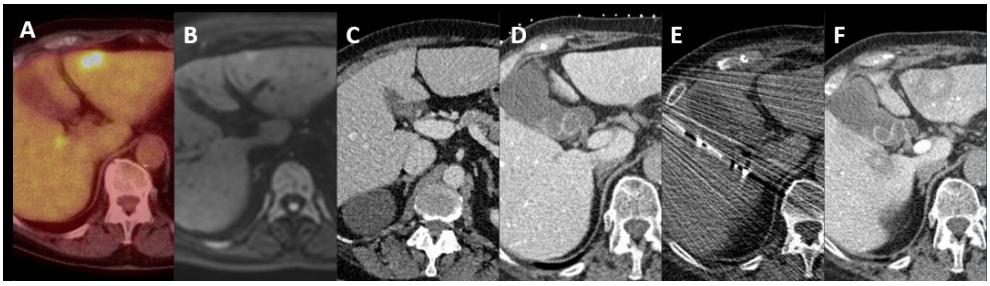

Figure 4. Visualization of a 'vanished' lesion after downstaging chemotherapy. Diagnostic 18F-FDG PET-CT showed two colorectal liver metastases (A, segment III and V). Chemoradiation was given to pretreat the rectum tumor. The tumor in segment V 'vanished' on post-chemoradiation MRI (B, Diffusion-weight imaging, b-800) and CE-CT (C). The patient qualified for local ablative treatment as the tumor in segment III was still visible. With the administration of intra-arterial contrast (20 mL 1:1 mixed bolus of Xenetix 300® and saline), the lesion became clearly visible as an hypodense lesion of 9 mm in the portal venous phase (D). Percutaneous microwave ablation was successfully performed (E) and the tumor was circumferentially covered by the ablation zone (F). *Courtesy of MR Meijerink.*

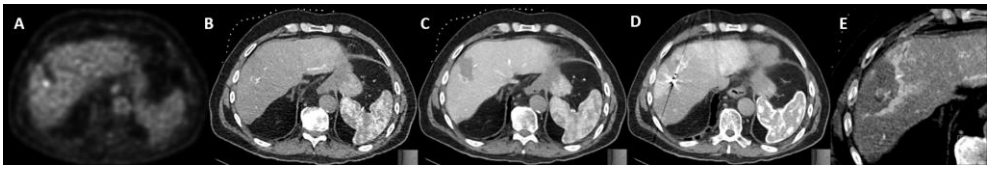

Figure 5. Differentiation between residual or recurring tumor tissue and non-enhancing scar tissue. Follow-up 18F-FDG PET-CT showed focal FDG-uptake at the edge of the ablation zone in segment VIII (A). Intra-procedural CT hepatic arteriography showed a typical incomplete enhancing ring, identified at the interface with the post ablation scar tissue (B, arterial phase; C, portal venous phase). After the percutaneous procedure (D), postprocedural image fusion showed complete coverage of the tumor by the ablation zone (E). *Courtesy of MR Meijerink.*

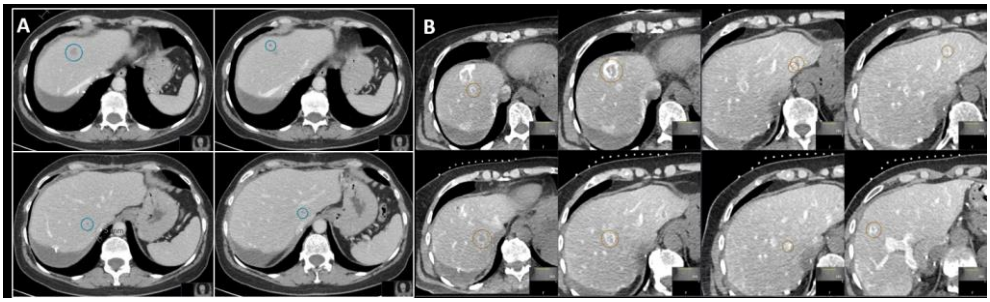

Figure 6. Detection of additional lesions during the procedure. Progressive disease after partial right-sided hepatectomy manifesting in four tumors seen on follow-up contrast-enhanced CT (A). The percutaneous procedure was planned within three weeks after the follow-up scan. During the procedure, after administration of intra-arterial intrahepatic 1:1 mixed bolus of 20 mL Iodine-based contrast agent (Xenetix 300®) and 20 mL saline, at least five additional ring-enhancing lesions were found (B). Due to the extensiveness of disease, the procedure was terminated. One day after the procedure, the additional lesions were confirmed to be metastases showing diffusion restriction on MRI. *Courtesy of MR Meijerink.*

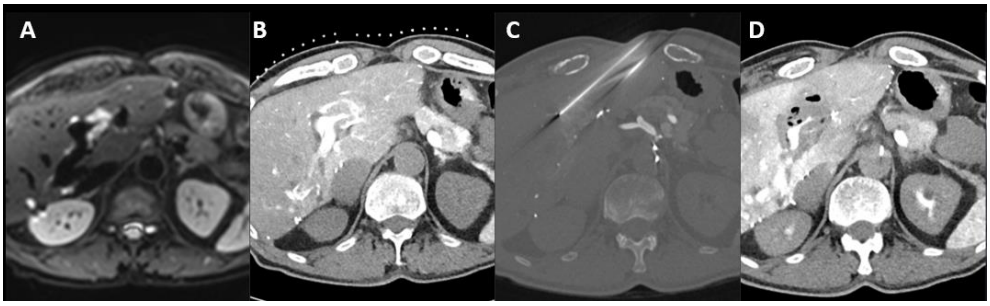

Figure 7. Identification of surrounding vascular structures for safety reasons. Progressive disease with five colorectal liver metastases, of which one was located in segment II/III surrounding a branch of the portal vein (A, diffusion restriction on MRI). After administration of intra-arterial contrast (20mL, 1:1 mixed bolus Xenetix 300® and saline), the tumor became clearly visible (B). In order to preserve the vascular structure, irreversible electroporation was performed by using 4 electrodes (20 mm exposure length, sequential pulses 10-90) (C).

Postprocedural image fusion showed no complications and sufficient ablation margins with tailoring of the portal vein branch' (D). *Courtesy of MR Meijerink.*

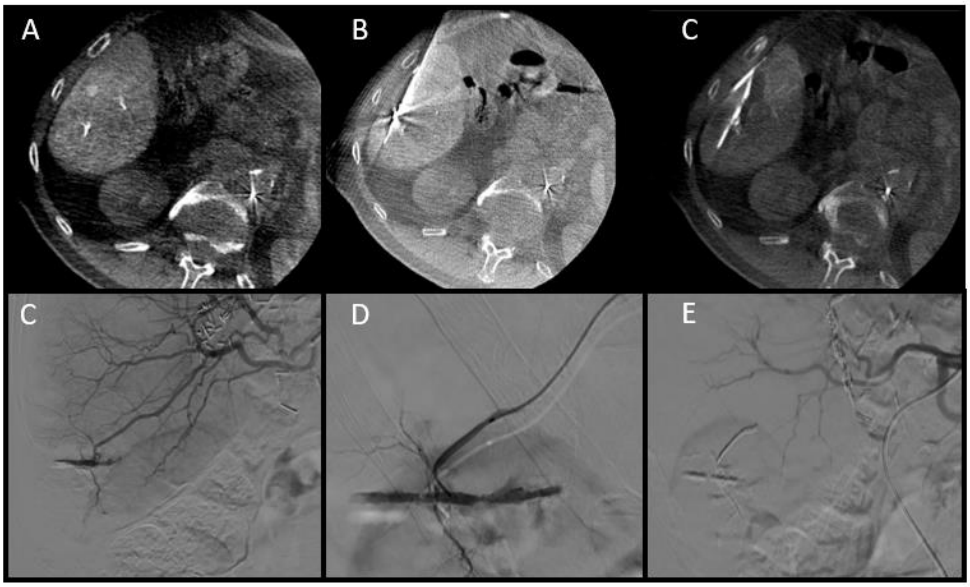

Figure 8. Critical care management: Direct embolization of post-ablation hemorrhage. Probe-induced hepatic hemorrhage is seen in 0.7% of the patients (30). This patient has a superficial hepatocellular carcinoma, which is illustrated prior to ablation (A, CTHA with C-arm CT in the angiography suite) and after ablation (B). Postablation, there is a linear contrast configuration at the former position of the antenna and contrast extravasate along the liver surface. Since the ablation took place in the angiography suite, a DSA could instantly be performed confirming the active hemorrhage (C and D). No signs of ongoing hemorrhage after selective glue embolization (E). *Courtesy of MLJ Smits*

DISCUSSION

As supported by the provided clinical cases, the use of CT hepatic angiography contributes to increased delineation of liver lesions, more accurate needle placement and superior coagulation necrosis visualization – all allowing for more precise ablation zones and wider circumferential safety margins (Figures 1 and 2).

CTHA-guidance has recently been compared with conventional CT fluoroscopy guidance in liver tumor ablation and was found to be safe with superior LTPFS.[17] As supported by Figure 5, previously reported results by Van Tilborg et al. underline that CTHA-guidance might also contribute to superior differentiation between (vital) residual or recurring tumor tissue and non-enhancing scar tissue ('incomplete ring sign'), indicating LTP.[21] Another potential

advantage has been published previously by Ohki et al., highlighting the ability to detect additional lesions during diagnostic work-up.[18] Translating that to a therapeutic setting, additional lesions may be found during the ablation procedure after injecting intra-arterial contrast, as shown in Figure 6. Shrinkage of the tumor(s) after downstaging chemotherapy has previously been reported as a significant therapeutic dilemma as the lesion might 'disappear' on diagnostic imaging (Figure 4).[23] Lipiodol® has been used in transarterial chemoembolization where it has shown to be more densely retained within liver tumors than alternative water-in-oil emulsions when paired with selected drug(s).[24] These oily features of Lipiodol® seem to facilitate in transarterial catheter assisted ablation as well (Figure 3). The latter advantage of CTHA-guidance encompasses the total amount of contrast needed per procedure, where CTHA-guidance was found to be associated with a significant smaller amount of contrast (88.4 mL) compared to conventional CT fluoroscopy guidance (131.0 mL; $p < .001$).[17]

Possible complications related to catheter placement are iatrogenic damage to the arterial vasculature or a pseudo-aneurysm at the access site in the common femoral artery. Although these complications were not seen in the recently published study by Puijk et al.[17], active bleeding can be treated instantly (Figure 8). The catheter placement is an additional procedure performed in the angio-suite which entails marginal additional costs, which, in our opinion, is endurable when it comes to optimize patient care. The additional costs and time required compared to ablation without CTHA can be reduced by performing the entire procedure (both catheterization and ablation) in the angio-suite. Although the catheter placement itself provides an extra negligible radiation dose to the patient, a dose comparing study between a CTHA-guided and conventional CT fluoroscopy guided procedure has never been executed. Theoretically, better lesion conspicuity with CTHA might allow fewer needle repositioning's with fewer single shot CT-images, leading to lower radiation exposure. The catheter placement does increase the number of bed-to bed-movements. In case of tip dislocation, the tip could be placed in the abdominal aorta to obtain an arteriogram (with 40cc mixed contrast). This is not compromising the images. Extra bed-to-bed movements can be prevented by using the C-arm of the angiography system.

In addition to the transcatheter CT hepatic angiography technique, multiple other advances have been developed and investigated over the years in order to positively affect the success of thermal ablation procedures. Segmentation, rigid and non-rigid co-registration in three dimensions increase lesion detection, improves needle targeting and thereby decrease incomplete ablation rates and may shorten procedural time.[13] Ablation-fit™ is one of the latest developments, offering the possibility to predict peri-ablational safety margins and relative risk of developing LTP[16,25] in the liver by using three dimensional (3D) targeting image fusion software.[15] Technical success can be assessed by volumetric assessment of the peri-ablational safety margin in stereotactic RFA and may be valuable in RFA and MWA as well.[16] Image fusion and navigation systems that combine multiple modalities have also been

developed and are used with ever increasing frequency for tumor targeting by real-time fusion guidance of US combined with preplanned CT images.[26] This fusion system allows to visualize the tumor and your needle position for target tumors undetectable with US alone. Furthermore, a novel technique, where the tip of the RFA electrode includes electromagnetic tip tracking, shows the exact tip location by electromagnetic position sensor in US-guided radiofrequency ablation.[27] Unfortunately, no difference in technical thermal ablation success was found and the proposed benefit of the electromagnetic tip tracking was not realized. Additionally, Taghavi and colleagues proposed a CT-based Radiomics analysis before thermal ablation and are, to our knowledge, the first to enable a machine learning-based Radiomics analysis to predict LTP in thermal ablation in patients with CRLM.[28] This preprocedural predictive model could guide treatment decisions to reduce LTP, as well as the detection of high risk lesions for LTP. Augmented reality is the newest development, with systems combining tumor tracking and navigation software with a goggle which shows your needle and the landmarks on the patients skin.[29] Ultimately leading to systems where the real-time ultrasound images are displayed in the goggles as well. These novel techniques, all focused on advanced imaging and innovative real-time image guidance techniques and artificial intelligence instruments, are not yet able to substitute our currently available techniques and should be further explored in future studies.

This pictorial review encompasses illustrative cases of CT hepatic angiography guidance in percutaneous thermal ablation of primary or secondary liver cancer. This technique offers the ability of vital tumor tissue visualization, more precise targeting and less needle repositioning allowing for the ability to: (a) create an adequate circumferential safety margin around the initial lesion, (b) detect additional lesions during the procedure, (c) visualize surrounding vascular structures for safety reasons, (d) differentiate residual or recurring tumor tissue of non-enhancing scar tissue (‘incomplete ring sign’, indicating LTP), (e) identify vanishing lesions after downstaging chemotherapy, and (f) promptly deal with a potential probe-induced hemorrhage in the liver. Although at the cost of adding a minor intervention, CTHA-guided liver tumor ablation minimizes complications, combining both CTHA ablation and software-aided ablation margin assessment, which will undoubtedly improve local disease control and reduce the number of re-interventions needed. Future developments on real-time fusion imaging, volumetric assessment of the peri-ablational safety margin with biomechanical ablation software, needle and electromagnetic tracking devices, machine learning Radiomics and augmented reality tools could be of immense value for intraprocedural decision-making and could potentially positively impact on the LTP rates. We recommend to adopt CTHA as a quality-improving guiding method within the (inter)national standards of practice.

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7.3

The added diagnostic value of transcatheter CT-hepatic arteriography for intraprocedural detection of previously unknown colorectal liver metastases during percutaneous ablation and impact on the definitive treatment plan

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ABSTRACT

Purpose: This study assessed the diagnostic value of CT hepatic arteriography (CTHA) for the intraprocedural detection of previously unknown colorectal liver metastases (CRLM) and the impact on the definitive treatment plan.

Materials and Methods: All patients treated with CTHAguided percutaneous ablation for CRLM between January 2012 and March 2022 were identified from the Amsterdam Colorectal Liver Met Registry (AmCORE). Radiology reports of the ablative procedure and follow-up imaging were reviewed to see if (a) previously unknown CRLM were detected intra-procedurally and if (b) new CRLM, potentially missed on CTHA, appeared within 6 months following the procedure; three abdominal radiologists re-reviewed the baseline CTHA scans of these patients with early recurrence. To ratify immediate ablations of concomitantly detected CRLM, the upper limit of false positives was predefined at 10%.

Results: One hundred and fifty-two patients were included. With CTHA, a total of 17 additional tumours in 15 patients were diagnosed and treated immediately, two representing disappeared tumours following systemic chemotherapy. Compared to the conventional contrast-enhanced (ce)CT, ceMRI and 18F-FDG PET-CT, adding CTHA was superior for the detection of CRLM ($P < .001$). Within 12 months of follow-up 121, new CRLM appeared in 49/152 patients (32.2%); retrospective blinded assessment revealed 56 to already be visible on the baseline CTHA scan (46%); four lesions without substrate on follow-up scans were considered false positives (n = 4/60; 7%). Arterial ring enhancement was the most frequently reported imaging characteristic (n = 45/60; 75%).

Conclusion: The subsequent use of CTHA has added value for the detection of previously unknown and vanished CRLM. Taking into account the low number of false positives (7%) and the favourable safety profile of percutaneous ablation, we believe that immediate ablation of typical ring-enhancing supplementary tumours is justified and sufficiently validated.

INTRODUCTION

Colorectal cancer (CRC) is a frequently diagnosed malignancy and the second leading cause of cancer-related mortality in the world. Approximately half of the patients with CRC develop colorectal liver metastases (CRLM).[1-5] Currently, multiple curative-intent local treatment options are available for patients with liver only or liver dominant disease. Over the past decades, thermal ablation has acquired an important role, either as an adjunct or as a less invasive alternative to partial hepatectomy.[4-8]

In conventional computed tomography (CT)-guided liver tumour ablation, a baseline intravenous contrast-enhanced (ce)CT, often including the arterial and portal venous phase, is acquired for treatment planning. Probe placement is usually performed under unenhanced CT fluoroscopy while focusing on unsteady anatomical landmarks or using stereotactic navigation. To timely detect complications and assess technical success, a second ceCT with intravenous contrast is used after the ablation. Confirmation of the ablation zone, if performed at all, is either based on so-called 'eye-balling' to subjectively estimate if the tumour-free margin around the initial tumour was achieved or using image registration and confirmation software.[9-12]

The transcatheter CT hepatic arteriography (CTHA) technique[9,12,13] is a relatively new technique to assist percutaneous thermal ablation procedures in the treatment of hepatocellular carcinoma (HCC), colorectal and non-colorectal liver metastases. This technique entails the selective placement of a catheter in the common or proper hepatic artery, to enable the repeated admission of small doses of intra-arterial intrahepatic iodine-based contrast agent. Compared to conventional ceCT fluoroscopy guidance, CTHA is hypothesized to optimize (a) pre-procedural planning, by (repeatedly) clearly depicting most liver tumours and surrounding blood vessels, (b) intraprocedural targeting by improving tumour conspicuity and (c) image registration and ablation confirmation.[11-14] In case of insufficient tumour coverage by the ablation zone, the needle can be directly repositioned to allow for additional overlapping ablations. CTHA is also known for its ability to differentiate between viable residual tumour tissue and ablative scar tissue ('incomplete ring sign'), thereby improving intraprocedural monitoring.[10-12,15] Besides leading to a decrease in the number of patients with local tumour progression (LTP), potentially reducing the number of repeat procedures, CTHA is also thought to visualize metastases at an earlier stage, hence potentially contributing as a diagnostic tool.[9-12] However, the detection of concomitant, previously unknown liver tumours, does not automatically justify immediate local treatment in the same session, as the rate of lesions representing benign liver tumours or heterogeneous perfusion deficits is unknown.

The primary aim of this study was to determine the added diagnostic value of CTHA for the intraprocedural detection of previously unknown CRLM during percutaneous ablation and the impact on the treatment plan. By defining specific imaging characteristics, we intend to validate criteria that help decide whether to ablate immediately or a wait-and-see.

MATERIALS AND METHODS

Study design and patient selection

This study is a retrospective cohort study from a prospectively maintained database (Amsterdam Colorectal Liver Met Registry—AmCORE) and was conducted at a tertiary referral institution for hepatobiliary and gastrointestinal malignancies. The AmCORE database consists of patients with CRLM and contains specific patient-, disease-, tumour- and procedure-related characteristics at baseline and during follow-up. The Institutional Review Board pre-approved the AmCORE registry (reference number 2021.0121) and waived the need for additional medical ethical approval for this specific project. All patients consented to the registration and the catheter-guided percutaneous tumour ablation.

Patients treated with CTHA-guided percutaneous ablation for new CRLM between January 2012 and March 2022 were identified from the prospective database. Supplementary descriptive data were collected from an electronic patient database. Included patients were treated with thermal ablation according to national guidelines, e.g. at least one small unresectable CRLM <3 cm. A maximum of 6 weeks between the last pre-procedural diagnostic scan(s) and the CTHA-guided procedure was allowed. Routine pre-operative imaging consisted of guideline protocolled ceCT plus ceMRI including diffusion-weighted imaging; the use of 18F-FDG PET-CT was not standardized.

Exclusion criteria were patients aged under 18 years, missing follow-up or follow-up less than 6 months. Patients in whom the catheter was not selectively located in the hepatic artery (because selective placement was not possible or because the catheter was displaced during transport) were noted but excluded from the assessment. The CTHA technique has been described more extensively in the previous publications.[9,12]

All procedure and radiology reports were reviewed by two researchers (MD, 1st year PhD candidate and MD, 4th year resident interventional radiology) to assess whether concomitant, previously unknown, CRLM were found intra-procedurally and if so, whether this impacted the original treatment plan. Patients with rapid disease progression, defined as >20% growth in the longest diameter of the known CRLM, were noted but excluded from further analysis, assuming that potentially detected concomitant lesions could also be explained by growth

over the detection-threshold in between the pre-procedural imaging and the CTHA-guided ablation.

In addition to the analysis of the intraprocedural detected tumours, CTHA was compared to each individual diagnostic modality for the detected of the pre-procedural known tumours.

Patients in whom new CRLM were detected within 12 months on follow-up ceCT, 18F-FDG PET-CT and/or ceMRI were extracted from the database for retrospective review. Routine follow-up imaging post-ablation was 3–4 monthly CEA and 18F-FDG PET-CT and/or ceMRI scans in the first 2 years. Patients with diffuse scattered new CRLM, which makes it impossible to correlate with the initial CTHA, were excluded. The CTHA series were assessed independently, by three academic abdominal radiologists with, respectively, 3, 10 and 14 years of experience, to determine whether the 'new' CRLM diagnosed on follow-up imaging were retrospectively visible on CTHA, before (blinded inspection) and after revealing (targeted inspection) the segment and location where the CRLM would later appear. For tumours detected on baseline CTHA, specific characteristics such as overall attenuation compared to surrounding liver parenchyma, conspicuity, delineation and ring enhancement were reported. All radiologists were simultaneously instructed on how to assess the scans in order to minimize interobserver variability.

Outcome measure

The primary purpose of this study was to determine the diagnostic value of CTHA (for the intraprocedural detection of previously unknown CRLM) and thereby validating (or rebutting) the immediate ablation of concomitantly detected tumours on CTHA (change of treatment plan). The added diagnostic value of CTHA over conventional ceCT, ceMRI (routine pre-procedural imaging) and, whenever available, 18F-FDG PET-CT (mostly used as problem solver) was defined as the proportion of supplementary detected CRLM. To determine whether immediate ablation for a previously unknown tumour should be preferred over a watch-and-wait approach, the upper limit of false-positive lesions, defined as retrospectively detected on CTHA by radiology review, but without substrate on follow-up imaging, was predefined at 10%. Secondary endpoints were overall technical success and specifically for the concomitantly treated CRLM, overall complications and complications surely or potentially related to the ablation of concomitantly detected CRLM and, for the retrospective analysis, specific imaging characteristics of newly detected tumours and interobserver variation.

Statistical analyses

All statistical analyses were performed using SPSS v. 28 (IBM Corp., Armonk, NY). On account of the dichotomous variables, McNemar tests were used to determine the accuracy in diagnosing new CRLM amongst the different diagnostic tests. Only descriptive statistics such as reporting numbers (with or without percentage), median (interquartile range) or mean (standard deviation) were used. $P < 0.05$ was considered statistically significant. Interobserver agreement for the retrospective detection of CRLM was assessed using kappa statistics (agreement was considered fair, substantial and excellent for kappa values 0.41–0.6, 0.61–0.8 and 0.81–1, respectively).

RESULTS

Between January 2012 and March 2022, 191 patients treated with 273 transcatheter CTHA-guided percutaneous ablation procedures were assessed. Twenty-seven patients were excluded due to intended non-selective placement (n = 15) or luxation of the catheter during transport (n = 12). After reviewing all procedure records, 155 patients treated with 194 CTHA-guided ablations met the inclusion criteria (Fig. 1, Table 1). In eighteen procedures (in 18 distinct patients) concomitant, previously unknown, CRLM were detected (n = 18/194; 9.3%). Three procedures were discontinued (n = 3/194; 1.5%), because multiple new CRLM were detected alongside rapid tumour growth of the known CRLM (increase in longest diameter of the known CRLM > 20%), excluding the procedure from further analysis in this study. Eventually, 152 patients underwent 191 CTHA-guided percutaneous thermal ablations (Fig. 1, Table 1). Forty-six patients were treated with induction chemotherapy prior to the procedure (30.3%).

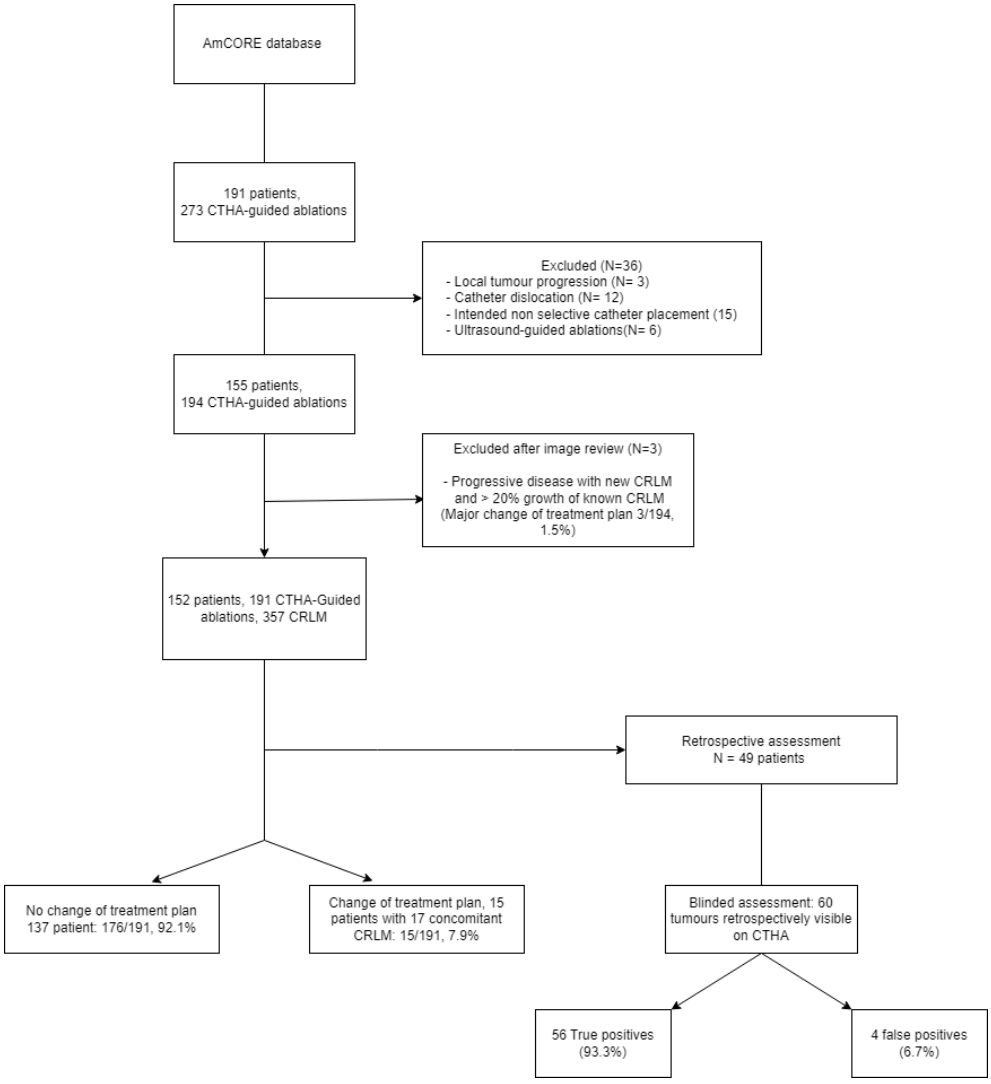

Figure 1. Flowchart of the included patients

Previously unknown tumours

A total of 17 CRLM (n = 17/357; 4.8%) were not detected on any pre-procedural diagnostic scan and visualized for the first time with CTHA (Fig. 2). The detection led to a change in treatment plan as all tumours were ablated within the same session (n = 15/191; 7.9%). The rate of additionally detected CRLM did not differ between the subgroup of patients treated with versus without induction chemotherapy prior to the procedure (p = 0.534). The rate of pre-treated patients with additionally detected CRLM was 6/46 (13.0%) versus 9/106 (8.5%)

in the group without pre-treatment. In two patients, the detected CRLM actually represented CRLM initially disappeared after induction systemic chemotherapy (Fig. 3).

CTHA failed to visualize six CRLM (overall accuracy 98.3%), all also not detected with ceCT, but detected with ceMRI. In these cases, the area was successfully ablated using ultrasound, real-time fusion imaging with MRI or 18F-FDG PET or using anatomical landmarks.

Patient characteristics	**Overall**	**Concomitant CRLM immediately ablated**	**Tumours retrospectively detected**
Patients (N)	N = 152	N = 15	N = 49
Age, Y, mean (SD)*	65.0 (12.8)	64.7 (16.4)	63.4 (13.0)
Sex, M:F	66% : 34%	67% : 33%	75% : 25%
BMI, mean (SD)*	26.4 (5.0)	26.0 (5.0)	26.6 (0.8)
ASA, mean	2.2	2.2	2.1
Disease characteristics			
Primary tumour location, N (%)			
Rectum	34 (22.4)	3 (20.0)	5 (10.2)
Colon left-sided	80 (52.6)	7 (46.7)	31 (63.3)
Colon right-sided	37 (24.3)	5 (33.3)	13 (26.5)
Tumour characteristics			
Size, mm, Mean (SD)*	17.03 (10.47)	11.12 (6.6)	17.47 (10.6)
Location (Couinaud segment), N (%)			
I	8 (2.2)	1 (5.9)	2 (3.2)
II	30 (8.4)	1 (5.9)	7 (11.3)
III	14 (3.9)	0	1 (1.6)
IVa	38 (10.6)	0	7 (11.3)
IVb	5 (1.4)	1 (5.9)	2 (3.2)
V	43 (12.0)	1 (5.9)	6 (9.7)
VI	50 (14.0)	3 (17.6)	7 (11.3)
VII	82 (23.0)	5 (29.4)	17 (27.4)
VIII	87 (24.4)	5 (29.4)	12 (19.4)
Procedure characteristics			
Induction chemotherapy, $N_{patients}$ (%)	46 (30.3%)	6 (40%)	-
Procedures (N)	191	15	62
Anesthesia Technique			
General Anesthesia, N (%)	41 (22%)	3 (20%)	12 (19%)
Sedation (Midazolam) , N (%)	27 (14%)	3 (20%)	8 (13%)
Sedation (Propofol), N (%)	117 (61%)	9 (60%)	40 (65%)
Ablation Technique			
RF Ablation	35 (18%)	2(13%)	37 (19%)
MW Ablation	156 (82%)	13 (87%)	159 (80%)

Table 1. Patient-, tumor-, and procedure-related characteristics. * = continuous variables reported as mean (standard deviation; SD), BMI = Body Mass Index, ASA = American Society of Anesthesiologists score, RF = Radiofrequency and MW = Microwave

Accuracy of ceCT, ceMRI and 18F-FDG PET-CT without versus with CTHA

In this study, accuracy of ceCT alone in detecting preprocedurally known CRLM (diagnosed with ceMRI and/or 18F-FDG PET-CT) was 76.5%. Compared to ceCT alone, CTHA detected 69 additional lesions. The McNemar test showed a statistically significant difference in detecting CRLM, favouring ceCT plus CTHA over ceCT alone ($P < 0.001$).

Accuracy of ceMRI alone was 88.8%. By adding CTHA, an additional 28 pre-procedural diagnosed CRLM (with CT and/or 18F-FDG PET-CT) were found over ceMRI alone ($P < 0.001$) (Table 2). As mentioned above, six pre-procedurally diagnosed CRLM visible on ceMRI were not identified on CTHA.

Accuracy of 18F-FDG PET-CT alone proved to be 85.8%. By adding CTHA, an additional 33 pre-procedural diagnosed (with ceCT and/or ceMRI) CRLM were found. Again, the McNemar analysis showed a statistically significant difference in detecting CRLM, favouring CTHA over 18F-FDG PET-CT alone ($P < 0.001$).

No complications related to the catheter placement were reported. Technical success overall and for concomitantly detected CRLM was 100%. The overall complication rate for the ablative procedures was 15.2% (Common Terminology Criteria for Adverse Events (CTCAE) grades I–II: $n_s = 25/191$; 13.1%; CTCAE grade III: $n_s = 4/191$; 2.1%). No major and one minor complication (CTCAE grade I: $n_s = 1/17$; 5.9%), a small hematoma of the hepatic capsule, was likely related to the ablation of the concomitant CRLM. Median hospital stay was 1 day (range 1–6 days).

Modality	Number Of Valid Cases	Significance
CTHA + ceCT vs ceCT	332	0.000*
CTHA + ceMRI vs ceMRI	277	0.000*
CTHA + 18F-FDG PET-CT vs 18F-FDG PET-CT	240	0.000*

Table 2. McNemar analysis.

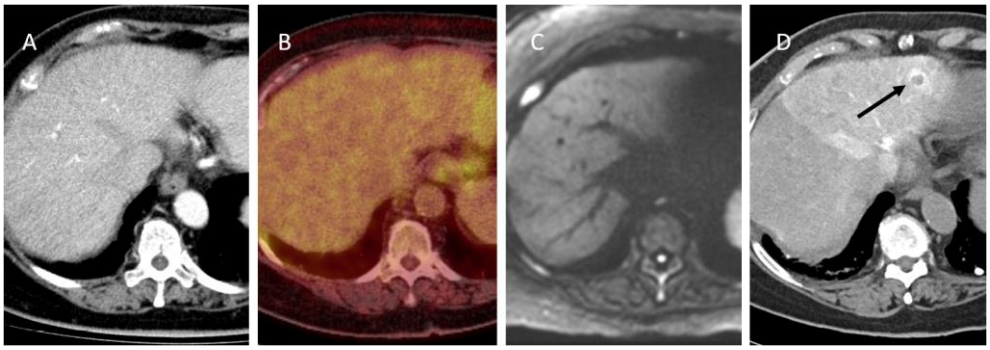

Figure 2. Case with concomitant CRLM: **A** and **B**; pre-procedural contrast-enhanced CT and 18F-FDG PET-CT. **C**: pre-procedural MRI (DWI). **D**: transcatheter CTHA in arterial phase. An additional ringenhancing lesion in segment II (arrow) was found intra-procedurally. This lesion was considered highly suspect for CRLM and consequently ablated in the same procedure. This lesion was not detected with the conventional pre-procedural diagnostic modalities.

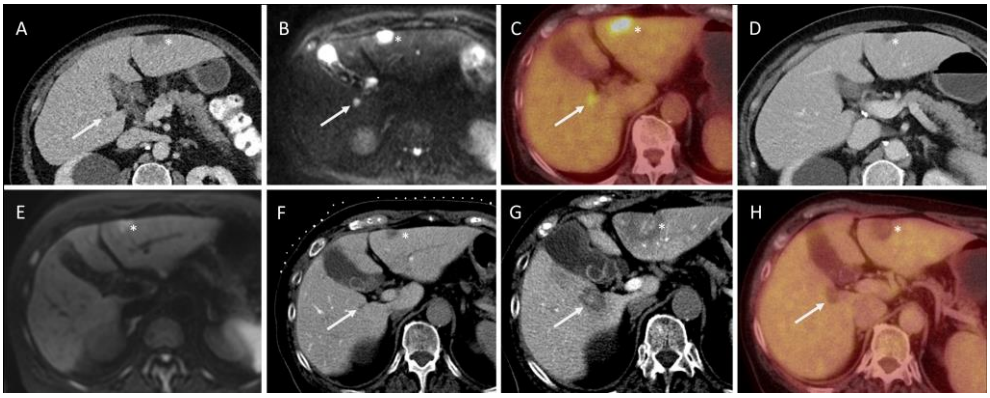

Figure 3. Contrast-enhanced (ce) CT and ceMRI images (**A**, **B**) and an 18F-FDG PET-CT image (**C**) from a 60-year-old men with two colorectal liver metastases in segment III (*) and segment V (white arrow) from a primary rectal carcinoma. After treatment with chemoradiotherapy for the primary rectal carcinoma, the metastasis in segment V disappeared on both ceCT (**D**) and ceMRI (**E**). On the intraprocedural CT hepatic arteriography (CTHA), both the metastases in segment III as well as the 'disappeared' metastasis in segment V were detected (**F**) and treated with percutaneous MWA (**G**) in the setting of the randomized controlled COLLISION trial. Six months after the ablation, there were no signs for local or distant tumour progression on the follow-up 18F-FDG PET-CT (**H**).

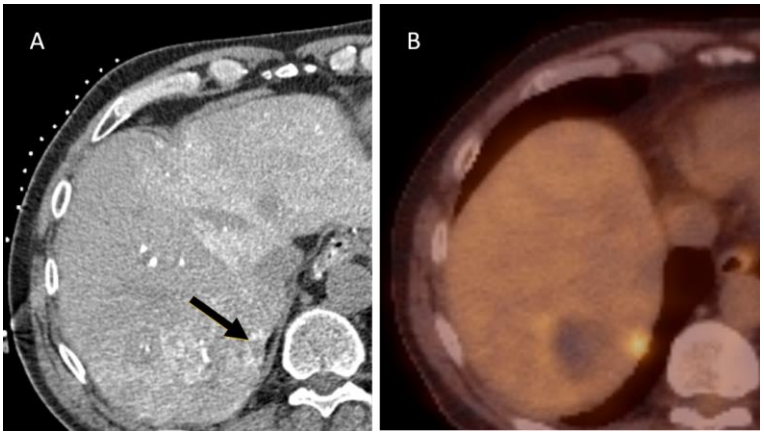

Figure 4. A: intraprocedural transcatheter CTHA. **B**: follow-up 18F-FDG PET-CT 2,5 months after CTHA-guided ablation. Retrospectively, an enhancing ring lesion was identified in segment VII on the CTHA (arrowheads), which had not been noticed during the microwave ablation.

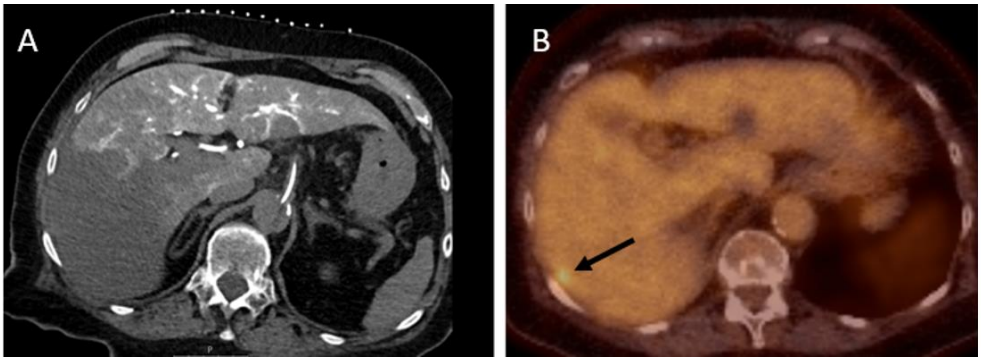

Figure 5. Case with aberrant anatomy: aberrant right hepatic artery from the superior mesenteric artery. This case presents a patient with an aberrant right hepatic artery originating from the superior mesenteric artery, resulting in a CTHA (catheter in the common hepatic artery originating from the celiac trunk) of which a large part of the right hepatic lobe could not be assessed. The follow-up 18F-FDG PET-CT reveals a subcapsular CRLM in segment VII that was subsequently invisible on CTHA, due to the segmented vascular supply.

Retrospective assessment of CTHA after new CRLM in follow-up

A total of 49 patients who were treated with 62 transcatheter CTHA-guided percutaneous ablations developed 121 new CRLM in follow-up (Table 3). After a blinded assessment of all 62 CTHA scans, additional lesions suspect for CRLM were scored in 24 scans (n_{crlm} = 24/62; 39%). In retrospect, a total of 60 additional tumours were detected on CTHA: 56 true positives (93.3%) and 4 (6.7%) false positives (positive predictive value 93%). In retrospect,

46.3% (n_{crlm} = 56/121) CRLM were already visible on CTHA (Fig. 4). Another 13 CRLM (n_{crlm} = 69/121; 57.0%) were discovered after revealing the follow-up scans and hence unblinding the location where the CRLM would later appear. Ring enhancement was the most frequently reported imaging characteristic of retrospectively identified CRLM (75.0%). Interobserver agreement per CTHA scan was considered substantial (k = 0.75). Seven patients had an aberrant anatomy leading to a part of the liver not enhancing with CTHA (Fig. 5).

Retrospectively detected tumours	
Blinded	
No. of CTHA scans with additional tumours (%)	24 (39%)
No. of concomitant true positive CRLM, N (%)	56 (93.3%)
No. of False positive lesions scored on CTHA, N (%)	4 (6.7%)
Unblinded	
No. of concomitant true positive CRLM, N	69
Tumour Characteristics (N = 56)	
Enhancing ring, N (%)	42 (75.0%)
Hypodense tumour, N (%)	2 (3.5%)
Hyperdense tumour, N (%)	8 (14.0%)
Mixed attenuation, N (%)	2 (3.5%)
Aspecific nodule, N (%)	2 (3.5%)

Table 3. Retrospective assessment and tumour characteristics.

DISCUSSION

Compared to the conventional cross-sectional imaging modalities (ceCT, ceMRI and 18F-FDG PET-CT), adding CTHA was superior for the detection of CRLM. Furthermore, retrospective CTHA image assessment showed a remarkable number of true-positive CRLM (46.3%), unappreciated during the initial treatment, but detected on follow-up imaging. Taking into account the low number of false positives (6.7%), the favourable safety profile of percutaneous thermal ablation and the substantial interobserver agreement (kappa = 0.75), the immediate ablation of typical ring-enhancing supplementary lesions seems justified and sufficiently validated.[16] Although, in this series, only three patients with rapid disease progression, were not treated with thermal ablation because of the detection of additional CRLM, the depiction of multifocal and scattered disease will prevent some patients from receiving futile ablative procedures.

Compared to other diagnostic modalities, CTHA is considered an effective diagnostic technique with a higher detection rate of both primary and secondary hepatic tumours as is further confirmed by our results.[12,17-21] Due to its invasive nature and limited influence on the treatment strategy, CTHA is not widely used as a diagnostic tool. However, CTHA-guided percutaneous ablation has an important and increasing role in today's curative-intent treatment options for CRLM, as several studies have demonstrated that CTHA correlates with a reduced risk of local tumour progression (LTP) and increased odds of progression free survival (PFS).[6,9-12,22] This study also suggests that adding CTHA to conventional cross-sectional imaging may help visualize vanished tumours. Furthermore, van Tilborg et al. found transcatheter CTHA to increase operator's confidence by improving distinction between (vital) residual or recurrent tumour tissue and non-enhancing scar tissue ('incomplete ring sign').[11]

To our knowledge, no previous report has assessed the validity to immediately ablate additionally detected lesions suspect for metastases versus to opt for a more conservative wait-and-see approach and treat the lesions at a later stage whenever confirmed on conventional cross-sectional imaging. Arguments in favour of immediate ablation would be to reduce the number of repeat procedures and hence improve quality of life and potentially recurrence-free survival, whereas arguments for the conservative approach would be that these potential benefits may not outweigh the added risks of ablating concomitant potentially false-positive benign liver lesions. Given the very low risk of serious adverse events to ablate small-size CRLM and the high positive predictive value of ring-enhancing lesions found in this study, we suggest to immediately treat the concomitant CRLM as long as the location allows for a safe procedure.

This study has some limitations. First, our inclusion criteria consisted in large part of additionally detected CRLM that were immediately ablated within the same session without histopathological or follow-up confirmation that these actually represented CRLM. For this reason, we were unable to identify false-positive lesions, potentially leading to an overestimation of the accuracy of CTHA. Specificity and positive predictive values could not be analysed due to the missing of false-positive lesions. Therefore, we added a retrospective analysis, where follow-up confirmation was available. However, despite the blinded retrospective assessment, there may still have been confirmation bias due to the fact that our observers knew additional CRLM would appear somewhere in the assessed liver. Though it remains unclear how the intra-procedurally detected and ablated CRLM correlate to the retrospectively found CRLM, it seems likely that the more typical and highly suspect lesions were immediately ablated, which would further strengthen our recommendation to immediately ablate. Furthermore, it should be noted that patients did not all receive identical pre-operative imaging (ceCT, ceMRI and/or 18F-FDG PET-CT). Another limitation is the fact that CTHA is in fact an expansion of ceCT, and the operators were aware of the findings on the pre-procedural ceCT. As a result, the McNemar test has to be interpreted with prudence

as CTHA was not assessed as a standalone method. Nonetheless, the high number of additionally detected CRLM on CTHA does render the combination of ceCT and CTHA superior for the detection of CRLM compared to ceCT alone.

The CTHA technique also comes with limitations. Variations in hepatic arterial anatomy such as aberrant right or left hepatic arteries frequently occur.[23] In patients with aberrant anatomy, selective catheterization of the segmental vascular supply makes CTHA of other regions not assessable. Additionally, non-selective catheterization within the aorta or catheter luxation also contributes to a decrease in the quality of the CHTA. In this study, the catheter luxated during transport in 12 out of 273 procedures (4.4%), a weakness that can be overcome by the future implementation of combined angio-CT systems. Additionally, CTHA has well-known pitfalls such as non-tumorous perfusion abnormalities and subsequent formation of pseudo-lesions.[18,24,25] Our paper demonstrated no catheter-related complications. However, other studies showed that CTHA comes with a non-negligible risk of vascular complications related to catheter placement, occasionally leading to re-interventions, increased direct costs and radiation dose.[12,19] Though comparative data are not available, CTHA presumably is more time consuming as the estimated time to place the hepatic artery catheter, to transfer patients to the CT suite, to acquire and assess the CTHA scans and to place a femoral artery closure device (estimated additional time per procedure 20–25 min) questionably outweighs time saved by a superior tumour delineation and a theoretical reduction in required treatments. Several of these shortcomings will likely be solved by the advent and rapid spread of combined angio-CT systems.

In conclusion, this study supports that the hypothesis CTHA is able to detect CRLM not visualized on pre-procedural ceCT, ceMRI and 18F-FDG PET-CT, including CRLM that disappeared after systemic chemotherapy. Due to its invasive character, CTHA is unlikely to replace conventional diagnostic modalities soon. We recommend using transcatheter CTHA in percutaneous ablation procedures (a) to improve visualization and detection of (previously unknown) tumours, (b) to improve the outcome of the percutaneous ablation and (c) to allow for targeted follow-up of indeterminate tumours. The latter requires the interventional radiologist to thoroughly review all liver segments before starting the ablative procedure. Taking into account the low number of false positives and the favourable safety profile of percutaneous thermal ablation, we postulate that immediate ablation of typical ring-enhancing supplementary lesions is sufficiently validated and justified and likely to reduce the number of repeat procedures.

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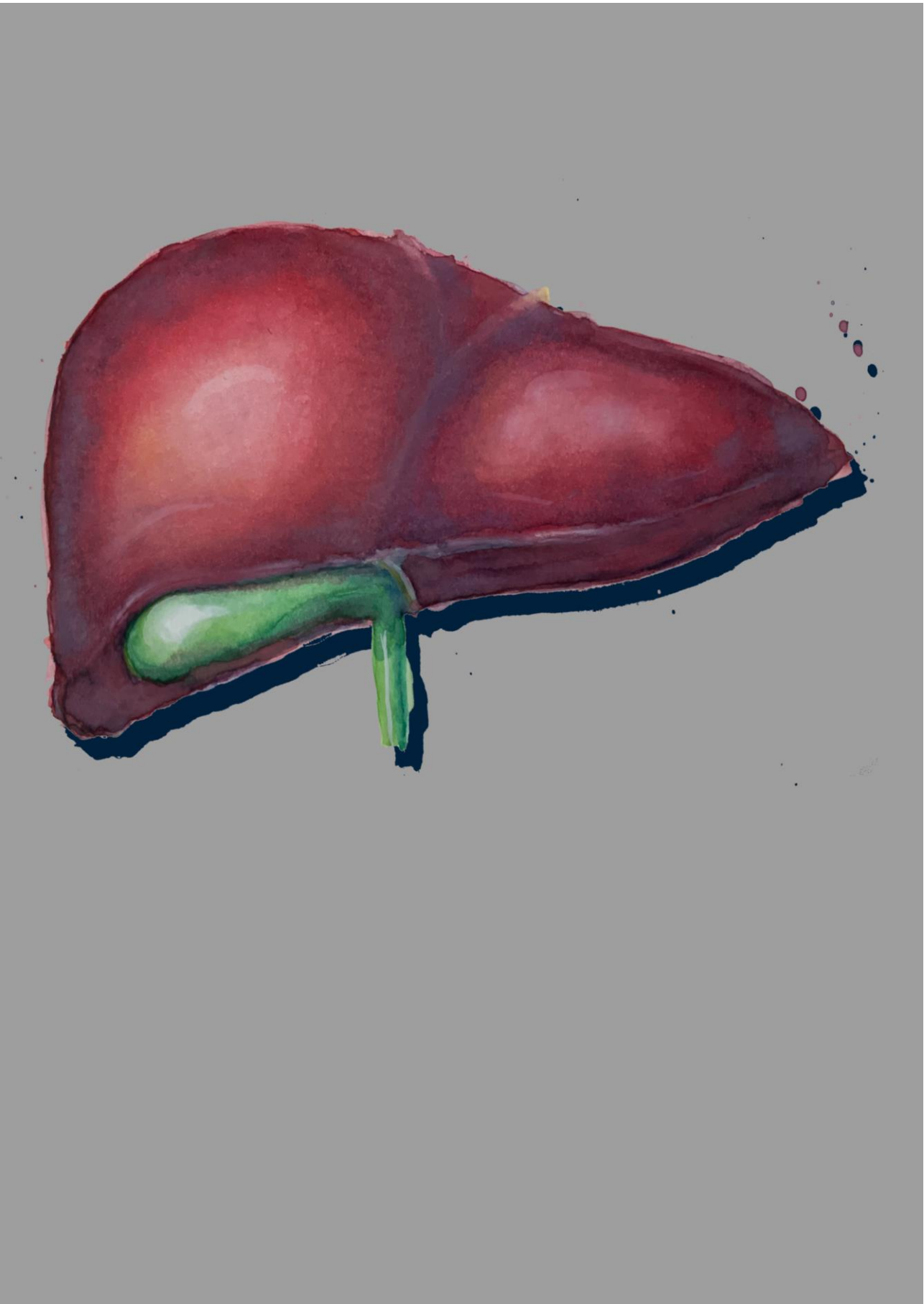

CHAPTER 8

Surgery versus ablation for colorectal liver metastases

8.1

Colorectal liver metastases: surgery versus thermal ablation (COLLISION) – a phase III single-blind prospective randomized controlled trial

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ABSTRACT

Background: Radiofrequency ablation (RFA) and microwave ablation (MWA) are widely accepted techniques to eliminate small unresectable colorectal liver metastases (CRLM). Although previous studies labelled thermal ablation inferior to surgical resection, the apparent selection bias when comparing patients with unresectable disease to surgical candidates, the superior safety profile, and the competitive overall survival results for the more recent reports mandate the setup of a randomized controlled trial. The objective of the COLLISION trial is to prove noninferiority of thermal ablation compared to hepatic resection in patients with at least one resectable and ablatable CRLM and no extrahepatic disease.

Methods: In this two-arm, single-blind multi-center phase-III clinical trial, six hundred and eighteen patients with at least one CRLM (≤3 cm) will be included to undergo either surgical resection or thermal ablation of appointed target lesion(s) (≤3 cm). Primary endpoint is OS (overall survival, intention-to-treat analysis). Main secondary endpoints are overall disease-free survival (DFS), time to progression (TTP), time to local progression (TTLP), primary and assisted technique efficacy (PTE, ATE), procedural morbidity and mortality, length of hospital stay, assessment of pain and quality of life (QoL), cost-effectiveness ratio (ICER) and quality-adjusted life years (QALY).

Discussion: If thermal ablation proves to be non-inferior in treating lesions ≤3 cm, a switch in treatment-method may lead to a reduction of the post-procedural morbidity and mortality, length of hospital stay and incremental costs without compromising oncological outcome for patients with CRLM.

Trial registration: NCT03088150, January 11th 2017.

BACKGROUND

Colorectal cancer is the third most common malignancy worldwide and the second most common cause of cancer related death in developed countries.[1,2] Approximately half of the patients will develop colorectal liver metastases (CRLM). Only 10–15% are considered eligible for partial hepatectomy (PH), due to (1) an impaired general health status, (2) a history of extensive abdominal surgery, (3) the presence of lesions with an unfavourable anatomical location or (4) an insufficient future liver remnant to resect all lesions [3–7]. These patients are usually treated with chemotherapy and/or thermal ablation, alone or in combination with PH.

Contradictory to most cancer types, long-term survival and even cure is possible in a subset of patients with CRLM.[8] Median overall survival (OS) of untreated CRLM (receiving only symptomatic therapy) is 4.5–12 months.[9] Chemotherapy has improved OS, but OS remains humble at 15–20 months.[10,11]

Surgical resection of the metastases has long been considered the only curative treatment option. In the past few years, radiofrequency ablation (RFA) and microwave ablation (MWA) techniques have rapidly worked their way into clinical guidelines for treatment of unresectable liver tumours.[12] For solitary small (<2 cm) hepatocellular carcinomas, international guidelines have shifted from surgery to minimally-invasive percutaneous thermal ablation because local control rates have reached 100%.[6,13-17]

Four recent series reported a comparable OS for thermal ablation versus surgical resection.[14,18-20] These results have led to the discussion whether or not thermal ablation – being less invasive – should be favoured over resection for smaller lesions. Despite this, 5-year OS (25–55%) of thermal ablation for patients with unresectable CRLM has been labelled inferior to surgical resection for patients with resectable CRLM according to previous meta-analyses and systematic reviews.[21-29]

These results should be interpreted with caution due to the apparent selection bias. At this point, there are no high-quality randomized controlled trials comparing thermal ablation to surgical resection for resectable CRLM, even though the need has previously been suggested by various authors.[8,30,31] To prove non-inferiority, we have designed a two-arm single-blind multi-center phase-III randomized controlled trial comparing surgical resection (standard of care) to thermal ablation (experimental arm) for resectable and ablatable CRLM ≤3 cm.

DESIGN AND METHODS

Design

COLLISION is a national, single-blind, multi-center, phase-III trial that is organized by the Amsterdam University Medical Centres (location VUmc) in Amsterdam, the Netherlands. The study is accommodated by the Dutch Colorectal Cancer Group (DCCG) and formally endorsed by the Dutch national covering patient federations, Dutch national societies for interventional radiology (NVIR), radiology (NVvR), surgery (NVvH), and the liver surgery working group (WLC). Patients will be recruited in, at least sixteen, high-volume centres for liver surgery throughout the Netherlands: Amsterdam UMC (location VUmc), Amsterdam; Amsterdam UMC (location AMC), Amsterdam; Leiden University Medical Center (LUMC), Leiden; Radboud University Medical Center, Nijmegen; Maastricht University Medical Center (MUMC), Maastricht; Antoni van Leeuwenhoek (AvL), Amsterdam; Medical Center Leeuwarden (MCL), Leeuwarden; Ziekenhuis Gelderse Vallei (ZGV), Ede; Isala Klinieken, Zwolle; Deventer Ziekenhuis, Deventer; Westfriesgasthuis, Hoorn; Erasmus Medical Center (EMC), Rotterdam; Jeroen Bosch Ziekenhuis (JBZ), Den Bosch; Medisch Spectrum Twente (MST), Enschede; Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam; University Medical Center (UMCU), Utrecht). The protocol has been approved by the Medical Ethical Review Board (METc) of the Amsterdam University Medical Centres (location VUmc) for Dutch national approval (no. 2016.561). The trial is investigator-sponsored by Medtronic PLC, independent of industry and registered at clinicaltrials.gov (*NCT03088150*, January 11th 2017). The trial will be conducted in accordance with the Declaration of Helsinki (64th version, October 2013) and the guidelines for Good Clinical Practice (GCP). The in- and exclusion criteria are summarized in Table 1.

The total duration of the study is around 13 years considering an inclusion time of 3 years and a minimum follow-up period of 10 years. All participants will provide written informed consent.The flow diagram of is shown in Fig. 1.

Start COLLISION trial

Inclusion, randomization and treatments started in two hospitals by the end of 2017. Due to formal approval procedures by local authorities, only AmsterdamUMC (location VUmc) and ZGV Ede were able to include patients from the beginning. From May 2018, RadboudUMC, LUMC, MCL, Isala Klinieken and Westfries Gasthuis were also able to participate. Numerous other Dutch high-volume liver centres, which are mentioned above, are waiting for local approval and will participate in the near future.

Eligibility

Potential candidates will be registered and undergo routine pre-procedural work-up: baseline full blood examination, carcinoembryonic antigen (CEA), bone marrow, liver, and renal function-, anaesthetic review, ceCT of the chest and abdomen and either an upper abdominal ceMRI or a total body 18F-FDG PET-CT using upper abdominal ceMRI as problem solver. Patients with ≥1 resectable and ablatable CRLM (≤3 cm), no extrahepatic disease and a good performance status (WHO 0–2) are considered eligible. Supplementary resections for resectable lesions > 3 cm and thermal ablations for unresectable CRLM ≤3 cm are allowed with a maximum number of CRLM of 10 (Table 1).

Inclusion criteria	**Exclusion criteria**
Histological documentation of primary colorectal tumour	No target lesions suitable for both resection and ablation
Age >18 years	Radical treatment unfeasible or unsafe (e.g. insufficient future liver remnant [FLR])
At least one CRLM size ≤ 3 cm eligible for both surgical resection and thermal ablation (target lesions)	Any surgical resection or focal ablative liver therapy for CRLM prior to inclusion
Additional unresectable CRLM should be ≤ 3 cm and ablatable	The presence of extrahepatic nodal or non-nodal metastases
Additional unablatable CRLM should be resectable	Immunotherapy ≤ 6 weeks prior to the procedure
Maximum number of CRLM 10	Chemotherapy ≤ 6 weeks prior to the procedure
Resection for resectable lesions considered possible obtaining negative resection margins (R0) and preserving adequate liver reserve	Pregnant or breast-feeding subjects. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment
Resectability and ablatability should be re-confirmed by intra-operative ultrasound (IOUS) and full surgical exploration	Compromised liver function (e.g. signs of portal hypertension, INR > 1,5 without use of anticoagulants, ascites)
Eastern Cooperative Oncology Group status (ECOG) 0-2	Uncontrolled infections (> grade 2 NCI-CTC version 3.0)
American Society of Anesthesiologists (ASA) grade 1-3	Severe allergy to contrast media not controlled with premedication
Life expectancy of at least 12 weeks	Any condition that is unstable or that could jeopardize the safety of the subject and their compliance in the study;
Adequate bone marrow, liver, and renal function as assessed by local usual laboratory tests. As usual, these results should be judged by the local investigator and should be conducted within 7 days prior to definite inclusion. Written informed consent	Substance abuse, medical, psychological or social conditions

Table 1. In- and exclusion criteria.

Eligible patients will be stratified into low-, intermediate- and high disease burden after assessment by an expert panel (Fig. 1). The panel, consisting of at least two diagnostic radiologists, two interventional radiologists and two hepatobiliary and/or oncological surgeons, will appoint lesions that are resectable and ablatable as target lesions, resectable and unablatable lesions as unablatable lesions and ablatable but unresectable lesions as unresectable lesions. All unablatable lesions should be resectable and all unresectable lesions should be ≤3 cm and ablatable. Because definitions of resectability and ablatability can vary dramatically from one center to the other and from one specialist to the other, the panel has to agree with the treating physicians' treatment plan. If the panel disagrees, the panel and the treating physicians must reach consensus before the patient can be enrolled.

Methods

Participating centres should have extensive experience in the field of both hepatic surgery and thermal liver tumour ablation, defined as performing ≥20 procedures annually. Treating surgeons and interventional radiologists should be board certified and have performed and/or supervised ≥100 procedures.

Inclusion

After having obtained written informed consent by the outpatient clinic doctor, patients will be formally included. The patient should be scheduled to undergo the procedure within a time-frame of maximum 6 weeks hereafter. Patients suitable for either laparoscopic resection or percutaneous ablation (Subgroup A, low disease burden; 1–3 target lesions) will be randomized prior to the procedure. All other patients will undergo open laparotomy with surgical inspection of the abdominal cavity and intra-operative ultrasound (IOUS).

Exclusion (drop-outs)

Despite improvements in preoperative imaging technology, the intraoperative use of ultrasonography remains of crucial importance.[32] The detection rate of preoperatively unknown lesions is still high (up to 50%) with considerable consequences on treatment strategy.[32] Following surgical inspection and IOUS the inclusion criteria need to be reconfirmed prior to randomization. If (1) a radical procedure is no longer considered safe or feasible, if (2) > 10 CRLM are present, if (3) extrahepatic disease is detected, or if (4) no lesion can be appointed as target lesion, the patient cannot be included in the study and will be treated as non-study object. Additional CRLM suitable for both resection and ablation ≤3 cm will be appointed as new target lesions. Additional unresectable lesions ≤3 cm that are suitable for thermal ablation should be ablated if possible and vice versa additionally detected

unablatable lesions should be resected. Lesions, preprocedurally appointed as target lesions, that prove unsuitable for one treatment modality based on IOUS lose their status and should be treated with the alternate modality (lesion shifts from target lesion to unablatable or unresectable lesion).

Laparotomy

The surgical explorative procedure of participants in this study is identical to standard procedures for non-study objects. A right subcostal incision is performed. The abdominal cavity will be explored in order to exclude extrahepatic tumour manifestations. An IOUS to exclude additional CRLM and for final confirmation of resectability will always be performed.

Randomization

Patients with limited disease burden (max. 3 lesions ≤3 cm) that are suitable for percutaneous ablation or laparoscopic resection will be randomized, prior to the procedure, into one of two arms, arm A and arm B. All other patients will undergo laparotomy with IOUS and surgical inspection and will, if still considered eligible, be randomized during general anaesthesia. Patients included in study arm A will undergo resection of hepatic metastases, allowing thermal ablation for additional unresectable lesions. Patients included in study arm B will undergo ultrasound guided thermal ablation of hepatic metastases, allowing resection for additional unablatable lesions (Fig. 1).

Randomization is centralized and performed through a web-based module (Castor EDC®)[33], which is accessible 7 days a week, 24 h per day. For open procedures randomization will be performed shortly after surgical inspection and IOUS with the patient under general anaesthesia. Both the experimenter(s) and the participant will be unaware of the eventual treatment arm prior to the procedure; after the procedure the patient will remain unaware (single-blind).Because follow-up imaging will reveal the nature of the focal therapy and because knowledge about the actual procedure and pathological confirmation of tumour free margins is required to reliably assess 18F-FDG PET-CT follow-up scans, the panel's diagnostic abdominal radiologists and nuclear physicians need to be informed about the specific treatment history.

Changes in insights detected after randomization do not allow patient's exclusion. These patients will remain in their originally appointed group according to the intention-to-treat analysis. For example, if, after being randomized into the resection arm, a target lesion proves unresectable during surgical tissue preparation and dissection, the patient will remain in arm A (resection) even if the lesion was eventually ablated or left untreated.

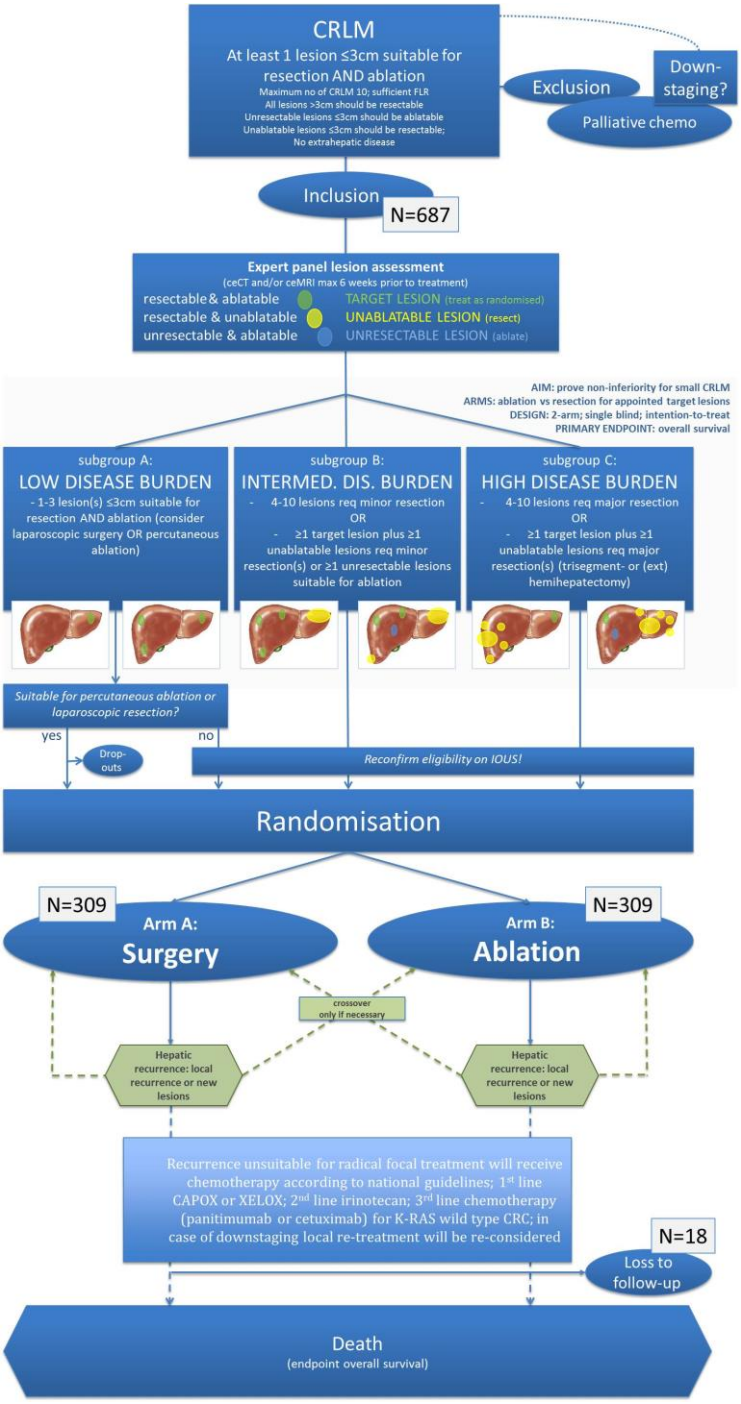

Figure 1. Flow diagram of study procedure

Surgical resection

In case of randomization to surgical resection, the surgeon will remove all target lesions as well as all additional unablatable lesions. The extent of the resection, the resection margins and the specific technique is at the discretion of the performing liver surgeon. Complications encountered during the procedure will be noted.

Postoperative care will be on the recovery and subsequently on either the surgery ward or medium care whenever deemed necessary. General 'resectability' criteria are shown in Table 2.

Thermal ablation

The safety, feasibility and preferred type of thermal ablation(s) is at the discretion of the interventional radiologist. Ablations are performed according to the CIRSE quality improvement guidelines with an intentional tumour free ablation margin of at least 1 cm.[34]

Patients with limited disease burden (max. 3 lesions ≤3 cm) and no contra-indications for a percutaneous approach will be randomized prior to the procedure. Contra-indications for a percutaneous approach are proximity of critical structures. To avoid collateral damage to intestines a minimum distance to the stomach, small bowel and colon of 15 mm should be respected. Laparoscopic approach is allowed. Pneumo- and hydrodissections are allowed. Pringle-manoeuvres are not allowed.

Following percutaneous ablations, a ceCT or ceMRI should always be performed for ablated lesions > 2 cm and for lesions 0–2 cm with radiologically unclear margins after the ablation. Unequivocal local site residues or insufficient tumour-free margins should be re-ablated (completion ablation) within 4 weeks after the initial ablation. If re-ablated within 4 weeks, the residue/insufficient margins count as technically unsuccessful ablations, but not as a tumour recurring event when assessing the primary technique efficacy, local progression-free and disease-free survival. Patients with limited disease burden plus a contra-indication for both percutaneous ablation and for laparoscopic surgery and patients with intermediate or high disease burden will be randomized during open laparotomy.

The probes are connected to compatible and commercially available generators. Ablations will be performed according to the protocols provided by the manufacturers. If necessary, the needle electrodes will be repositioned for one or more overlapping ablations. The proximity of a large portal or systemic vein or hepatic artery is no contraindication for performing the thermal ablation.

The definition of a technically successful ablation is based upon the specific protocols established by the device manufacturers in combination with an immediate post-procedurally performed US (fully hyperechoic ablation zone with an intentional margin of at least 1 cm).[7]

Necessity for re-ablations and/or needle repositioning will be judged by the performing interventional radiologist. Postoperative care will be on the recovery room and subsequently on either the surgery ward or medium care whenever deemed necessary. A quality-control ceCT can be performed within 1–6 weeks after the initial treatment to assess for a completion-procedure.[7] General 'ablatability' criteria are shown in Table 2.

General 'resectability criteria'	General 'ablatability criteria'
No size limit	Maximum CRLM size ≤ 3 cm
Aiming at negative (R0) margins	Aiming at a tumour free margin of >10 mm
Leave sufficient FLR (>20% normal functioning liver parenchyma; >30% post-chemotherapy)	Leave sufficient FLR (>20% normal functioning liver parenchyma; >30% post-chemotherapy)
Portal vein embolization of the (most) affected liver lobe may be considered for patients with insufficient FLR	To preserve the major bile ducts (common, right and left hepatic duct) a minimum distance (lesion to major bile duct) of 15 mm is required
At least one of three hepatic veins should be preserved and both the portal venous and hepatic arterial blood flow in the future liver remnant should be remain unharmed	Radical ablation(s) with or without surgical resections for additional unablatable lesions
Approachable surgical field, without extensive scar formation, major surgical adhesions and/or intestinal herniations (risk of major morbidity estimated >20%; risk of mortality estimated >5%)	To avoid collateral damage to the intestines a minimum distance to the stomach, small bowel and colon of 15 mm should be pursued in open procedures and respected in percutaneous procedures; the use of pneumo- or hydrodissections to shift bowels are allowed
Maximum total number of CRLM ≤ 10	Maximum total number of CRLM ≤ 10

Table 2. General 'resectability' and 'ablatability' criteria.

Follow-up

Conferring to national guidelines follow-up will include imaging, laboratory tests including tumour markers (CEA) and clinical examination every 3 months for the first year and every 6 months hereafter. Follow-up cross-sectional imaging should include at least an abdominal ceCT or upper abdominal ceMRI at the given time-points. Participating centres are free to add 18F-FDG PET-CTs at specific time-points or to use alternating specific modalities, as long as the follow-up protocol is pre-approved by the trial coordinators and as long as follow-up imaging is identical for both treatment arms. Quality of life questionnaires will be assessed at baseline, every 3 months for the first year and every 6 months hereafter accordingly. Data will be collected in Castor EDC®[33], only available for related research investigators.

Primary and secondary objectives

The main objective is to prove non-inferiority of thermal ablation compared to hepatic resection in patients with at least one resectable and ablatable CRLM (≤3 cm) and no extrahepatic disease. Primary endpoint is OS. Main secondary endpoints are overall disease-free survival (DFS), time-to-progression (TTP), time-to-local-progression (TTLP), primary and assisted technique efficacy (PTE, ATE), procedural morbidity and mortality, length of hospital stay, assessment of pain and quality of life (QoL), cost-effectiveness ratio (ICER) and quality-adjusted life years (QALY).

Pain analysis will be performed using visual analogue scale questionnaires (VAS) assessed prior to, directly after and every 3 months after local treatment; administered pain medication will be registered. Quality of life analysis will be performed using European Organisation for Research and Treatment of Cancer Quality of Life questionnaires (EORTC-QLQ-CR29, EORCT QLQ-C30, EQ-5D) prior to, and every 3 months after local treatment. Patients who complete the quality-of life questionnaires at baseline and at least once during treatment and follow-up will be included in the analysis. The largest decrease in quality of life with respect to baseline will be calculated. The Wilcoxon rank sum test will be used to detect statistical differences between the two treatment arms.

Sample size calculation and statistical considerations

We hypothesize (null-hypothesis) that thermal ablation is non-inferior to surgical resection for the selected patient groups in terms of the primary objective (OS). The Cox proportional hazards model (1-sided; non-inferiority or superiority) is used for sample size calculations (Table 3). Given the superior safety profile we consider a hazard ratio (HR) of 1.3 to represent the upper limit of non-inferiority (non-inferiority margin). An HR of 1.3 corresponds to a 56.5% chance of the ablated patients to die first ((P = HR/(1 +HR) = 1.3/(1 + 1.3) = 0.565 (56.5%)). We will have reached 60% of events (death) approximately 6.5 years after having included the last patient (overall probability of event, pE = 0.6). The calculated sample size therefore is 599 (NS). To account for a 10% drop-out ratio (NDO= 69) prior to randomization and a 3% loss to follow-up (NLTFU = 18) after randomization we need to recruit 687 patients (NI). A total number of 618 patients (687–69 (NDO)) will be randomized (NR) into one of two arms: arm A will undergo surgical resection (n = 309) and arm B thermal ablation (n = 309) for appointed target lesions.

Significance level (α)	0.05
Power (1-β)	0.80
Hazard Ratio (HR), θ (non-inferiority margin)	1.3
Null-Hypothesis Hazard Ratio, θ_0	1.0
Recruitment time / study accrual (months)	36
Follow-up time (months)	60
Ratio control vs. experimental: m_2/m_1	1.0
Total sample size (N_S) / total number to be randomized (N_R)	599
Accounting for 3% loss to follow-up after randomization (N_{LTFU})	18
Accounting for 10% drop-out ratio pre-randomization (N_{DO})	69
Initial pre-randomization sample size – number of included patients (N_I)	687

Table 3. Sample size calculation

Statistical methods

All clinicopathological and procedural variables will be described and analysed. Continuous variables will be summarized with standard statistics including, means, standard deviations, medians and ranges. Categorical variables will be summarized with frequencies. When appropriate, box plots and cross tables will be used for descriptive statistics of continuous and categorical variables, respectively. P-values below 0.05 will be considered significant. All calculations will be generated by statistical package for social sciences software (SPSS®). Calculation of the number of patients that will be needed to address our primary endpoint with a power of 80% and a 5% type I error rate is described in the sample size calculation section.

Univariate survival analysis will be performed using the Kaplan-Meier method. Differences in survival lengths will be analysed using the log rank test. To determine hazard ratios (HR) for multivariate analysis, Cox regression will be used. Significance of differences for continuous and categorical data will be analysed using the Mann-Whitney U test and Chi-square test respectively. When appropriate, box plots and cross tables will be used for descriptive statistics of continuous and categorical variables, respectively. OS will be estimated by the Kaplan-Meier method with corresponding two sided 95% Cl's for survival proportions.

Primary and assisted technique efficacy rates (PTE, ATE) defined as the percentage of target lesions that have recurred after the initial local treatment and after additional local treatments

regardless of the technique(s) used to treat the recurrence with a minimum follow-up period of 12 months after the last focal therapy;- Direct and indirect total cost of care for both treatment arms will be registered in the cost-effectiveness data collection matrix. Based on this matrix a cost–utility analysis, measured in terms of years of full health lived, using quality-adjusted life years will be prospectively calculated. Cost-effectiveness will be expressed as an ICER, the ratio of change in costs to the change in effects.

Data monitoring

The investigators believe that an independent data safety and monitoring committee (DSMB) is unnecessary given the much less invasive nature and superior safety profile of the experimental treatment arm (thermal ablation). An independent monitor committee (Clinical Research Bureau; CRB) is appointed to safeguard the quality of all investigator-initiated studies. A quality officer from the CRB will monitor all study data according to Good Clinical Practice (GCP). The informed consent of selected individual participants will be checked. Source Data verification will be performed during onsite monitoring (to verify if all data on the Case Report Form are in accordance with the source data). The intensity of this verification is in relation to the risk associated with the intervention investigated, which is considered acceptable. For all subjects, the informed consent forms, the in- and exclusion criteria and the primary outcome (overall survival from the date of randomization to the date of death due to any cause) will be verified. The monitor will also verify if all (S)AE's are reported adequately and within the time that is determined by legal rules and regulations.

Shortly after beginning of the study the research group and epidemiologists will compose a detailed plan regarding futility and criteria to end the study prematurely. The interim analysis will be performed on the primary endpoint using a non-inferiority analysis. If at interim analysis, after having randomized 30% of the patients, the number of deaths due to treatment is significantly higher in patients included in the experimental arm B compared to patients included in the control arm A, the study will be ended prematurely. If the interim analysis shows a trend towards a type 1 or type 2 error, we will add a Data Safety and Monitoring Board (DSMB) to our study. A new interim analysis will be conducted after having randomized 50% of the patients.

(Serious) adverse events (AE's and SAE's) and serious adverse device effects (SADE)

All serious adverse events that occur in the first 90-days after the procedure that are life threatening or result in death, both related and unrelated to the research, and serious adverse events that happen during complete study follow up, that are life threatening or result in death

and are related (unlikely, possible, probable or definite) to the research according to one of the principal investigator, will be reported within 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report. Relationship of the event to the research will be established by the primary investigator as: 1 = Unrelated (clearly not related to the research), 2 = Unlikely (doubtfully related to the research), 3 = Possible (may be related to the research), 4 = Probable (likely related to the research), 5 = Definite (clearly related to the research). All participating clinicians will be made aware of the necessity to report (serious) adverse events to the principal investigators. The sponsor will report the SA(D)E's through the web portal ToetsingOnline.nl to the accredited EC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events.

The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of July 1st, 2015). This insurance provides cover for damage to research subjects through injury or death related to study participation.

Cost-effectiveness analysis

General considerations

For this clinical trial, a cost effectiveness (utility) analysis will be performed from a societal perspective, using a 3-year time horizon. The direct and indirect costs will be included. Direct costs taken into account will include treatment costs, cost of hospitalization, medication, imaging, laboratory testing and pathology.

Within the trial, resource use will be monitored and this will be linked to integral cost prices or Dutch tariffs.

Patient outcome analysis

To assess indirect cost, patients will be asked to fill out the Productivity and Disease Questionnaire (PRODISC) every 6 months. To calculate total indirect costs, the friction cost approach will be used.

Cost analysis

The primary health outcome measure in this economic evaluation will be the total quality adjusted life years (QALY) per trial arm. QALYS will be calculated by using the utility scores linked to the various health states of the EQ-5D; in essence the length of time a patient spends in a particular health condition is weighed by the corresponding utility. Missing data on costs and utilities will be imputed using multiple imputation. The difference in total costs and total QALYs in both arms will be used to calculate the incremental cost-effectiveness ratio (ICER): the cost per QALY gained (or cost-savings per QALY gained or lost), using the formula: ICER = (Cintervention - Ccontrol)/(QALYintervention - QALYcontrol). Cost and health effect will be discounted using the Dutch discount rates of 1.5% for health effects and 4% for costs. In addition, to allow comparison with international studies, discount rates of 3% for both health effects and costs will be used as well. To assess the impact of uncertainty, a probabilistic sensitivity analysis will be performed using the non-parametric bootstrap with 5000 replications. The results will be presented on cost-effectiveness planes. In addition, ICER acceptability curves will be presented and univariate sensitivity analyses will be performed focusing on uncertainty around most important costs-items.

Dissemination policy

To ensure optimal implementation we used the framework of Fleuren et al.[35]; consisting of patient, innovation, organization and socio-political determinants. Although clinical equipoise between surgery and ablation is reached for small CRLM, the results from recent meta-analyses, such as the most recent one by Meijerink et al.[36], do not support thermal ablation for resectable CRLM outside clinical trials. Hence, patients suitable for COLLISION will have to choose between surgery (+/− ablation for unresectable CRLM) and trial participation.

With 15.549 new cases of colorectal cancer in the Netherlands (2015) approximately 4% of them will have ≥1 resectable and ablatable CRLM [1]. At this moment, these lesions are treated by resection, whilst ablation may be associated with less complications and an equal or even superior oncological outcome. In other words, in the Netherlands alone an estimated target population of 625 patients per year should be eligible for COLLISION trial participation. To further facilitate implementation the trial is formally supported by the following concerning patient federations who joined the trial advisory board: The Dutch Federation for patients with cancer (NFK), the Dutch society for patients with gastro-intestinal and hepato-, pancreatico-, biliary cancers (SPKS) and the Dutch society for image-guided treatment of cancer (SBBvK).

The study is embedded within the multidisciplinary Dutch Colorectal Cancer Group (DCCG). DCCG is a collaboration between medical disciplines that are relevant for the

diagnosis and treatment of colorectal cancer (surgical oncology, radiotherapy, medical oncology, pathology, radiology, gastroenterology, genetics). Patients will be recruited throughout the country and treated in one of the qualifying and selected high-volume centres. We will ensure that the scientific community, patients and professional organizations will be constantly kept up to date on the obtained results.

In order to qualify for reimbursement the Dutch health care institute (ZiNL) demands the best available evidence. Currently, thermal ablation is only approved for truly unresectable and small CRLM. Outside the setting of the trial ablations of resectable CRLM are off-guideline and hence not reimbursed. The direct and indirect costs of thermal ablation are considerably lower than that of surgery. We expect even lower indirect costs for patients treated within the study, primarily because thermal ablation of resectable CRLM in patients who by definition qualify as suitable for surgery may be associated with an even lower complication-rate.

DISCUSSION

The recently published primary efficacy rates (complete ablation after the first procedure) of RFA and MWA for small CRLM have approached the reported resection plane recurrence rates for similar sized lesions.[6,14-17,21] Hence the issue of ablation site recurrences, that has previously prevented its widespread adoption, may be outdated. The relative ease to percutaneously re-ablate potential site recurrences, nowadays in the setting of a one-day admission under conscious sedation, has further downgraded its relevance.

Partial hepatectomy

Until relatively recent, patients with CRLM could only be cured by surgical resection of the lesions. Although no formal upper limit regarding number and size of CRLM has been established, surgical resection is nowadays considered safe and effective for patients with an adequate performance status if radical resection will leave sufficient future functioning liver parenchyma. In addition, one of the three main hepatic veins must be uncompromised and the liver remnant has to comprise a portal vein, hepatic artery and a bile duct. Clear definitions of what is regarded as resectable are lacking and vary dramatically from center to center on the basis of aggressiveness of the surgical team and the perception of the medical oncologist on when to refer patients.[37] To achieve consensus several societies for surgical oncology and hepatobiliary surgery have previously attempted to postulate resectability criteria (Table 2).[38,39] The objective of surgical resection for CRLM should be to remove all macroscopically visible tumour tissue with the intent to achieve cure. Histological tumour

free margins and hence the confirmation of having radically resected the metastases remains essential.

Surgical resection has a 5-year OS reaching 31–58%.[3,40] Although the number of serious adverse events of hepatic resection has decreased considerably in the past two decades, the 90-day mortality (4%) and the complication-rate (40%; major plus minor) are still high.[41-43] In 2007 data from 1059 non-cirrhotic patients who underwent major hepatectomy were analysed.[43] The total percentage of complications was 453 (43%), divided as follows: minor complications 26% (grade I 7%; grade II 19%) and major complications 17% (grade IIIa 10%, grade IIIb 2%, grade IVa 4%, grade IVb 1%). Most frequently encountered complications include per-operative major bleeding, bile duct/gallbladder injury, perforation of adjacent structures, intra-abdominal infection, wound infection, liver abscess, haematoma at incision site, pneumothorax, liver failure and death (4%).[41,42]

Radiofrequency ablation

Since its introduction in the late 90's, RFA is the most studied and widely adopted ablative technique. It has emerged as a promising approach in the treatment of patients with unresectable CRLM. RFA has acquired its role in the treatment of patients with unresectable CRLM as a safe, well tolerated, easily repeatable and less invasive procedure.[44,45]

One major drawback of RFA is the heat-sink effect in highly perfused organs, such as the liver where a large tumour located near large vessels (> 3 mm diameter) is not properly treated because heat is lost to the flowing blood. Another risk of RFA is heat injury to vital structures in or surrounding the ablated area. For this reason, treatment of lesions in the proximity of other organs, large vessels and major bile ducts has to be performed with caution, and is sometimes contra-indicated.[46]

The 90-day mortality of thermal ablation alone is very low (< 1%) and the complication rate is also low (6–9%).[6] Applied to unresectable CRLM, 5-year survival rates are approaching the results reported after surgical resection, especially for patients presenting with a limited number of small-size lesions. The reported 5-year OS is 25–55%.[21-29] The recently presented long-term results from the only available randomized controlled trial shows a survival plateau of 36% after 8-years in patients with unresectable CRLM.[6] It is important to realize that these percentages are derived from studies where thermal ablation was used to treat unresectable lesions. Ruers et al. found a PFS of 16.9 months (95%CI 11.7–22.1) in a group of patients who received chemotherapy plus RFA (HR 0.63 [95%CI 0.42–0.95]). Of those 56 patients treated with RFA, 9 developed a local site recurrence (LSR) (16,1%).[6]

Complications can be divided into three different groups: related to probe placement (bleeding 0,7%, infection, tumour seeding 0–0,3%), related to energy delivery (damage to bowel, gallbladder, bile ducts 4,2%, grounding pad burns, post-ablation syndrome, hepatic

vascular damage, liver failure 2,1%) and related to the general procedure (deep venous thrombosis, pulmonary embolism, referred pain, fever, nausea, vomiting, kidney failure).[47]

Microwave ablation

MWA is known as ablative technique for tissues with a high percentage of water and has several theoretical advantages that may result in improved performance near blood vessels. Due to a much broader field of power density, MWA results in a larger zone of active heating. This increased zone allows for a more homogeneous zone of tumour cell death, both within the targeted zone and next to blood vessels. This feature is thought to make MWA less affected by heat sink. Recent developments in the field of MWA, employing higher frequency bands (2.45 GHz) or spatial energy control (thermal, field, and wavelength), claim to create more predictable, larger and more spherical ablation zones regardless of target location, tissue type or changes in tissue properties during the ablation.[48]

Several studies reported a 3-,4- and 5-year OS for MWA between 35 and 79%, 35–58% and 17–18%.[15,16,49-54]. Mortality is ranging between 0 and 2%.[15,49,50] The median DFS ranges between 8 and 12 months.[15,50,54] Overall recurrence ranges between 39 and 72%.[15,17,50,51,55,56] In several observational studies complications ranged between 0 and 54%.[15,16,50,55-57] No studies reported the effect on quality of life after MWA.

Partial hepatectomy versus thermal ablation

Numerous studies reported OS rates for surgery and thermal ablation techniques. Comparing RFA alone to surgery alone numerous observational studies reported corrected hazard ratios for OS between RFA and surgery alone; treatment with RFA was associated with an inferior OS (HR = 1.92; 95%CI 1.44–2.56).[22,23,25,27,58-61] Comparing RFA plus surgery to surgery alone other studies reported corrected hazard ratios and allowed for pooling between surgery and surgery plus RFA; no significant difference in OS was found (HR = 1.29; 95% CI 0.71–2.327).[14,18,61,62]

For MWA, a 3-year OS of 23% after surgery and 14% after MWA has been reported.[54] Another study showed a 4-year OS of 70% after surgery and 41% after MWA, although no formal statistical comparison with surgery alone was reported.[53] A more recently published study found 5-year OS rates for surgery versus percutaneous ablation as first intervention of 51.9 and 53%, with a median OS of 65.0 (95%CI 47.3 to 82.6) and 62.1 (95%CI 52.2 to 72.1) months, respectively.[19]

Another study reported no significant difference in OS for MWA plus surgery versus surgery alone (3-year OS: 50.9% vs 48.8%).[63] Median OS was 39 months after surgery and 28 months after MWA plus surgery. In multivariate analysis MWA was no prognostic factor for OS.

Several studies revealed that complications were significantly more common after surgery compared to RFA (relative risk [RR] = 0.47; 95%CI 0.28–0.78).[22-29,59,64-66] Two studies reported serious adverse events in 21–28% after surgery vs 13–37% in the surgery + ablation group.[18,24]

Some studies compared RFA to surgery alone regarding local progression-free survival (LPFS) and DFS; RFA was inferior to surgical resection (+/− RFA).[25,28,58] Comparing RFA plus surgery to surgery alone, RFA plus surgery was associated with a poor LPFS.[14,18,24,58,61] Assessing DFS, no significant difference between RFA + surgery vs surgery alone was found.

In conclusion, a recently published systematic review and meta-analysis reported that further randomized assessments of thermal ablation with curative intent to current-day palliative chemotherapy alone should be considered unethical.[36] Therefore, the highest achievable evidence level for unresectable CRLM seems to be reached. According to above mentioned superior safety profile, lower complication-rate and competitive long term survival after thermal ablation for CRLM challenges liver surgery and fiats the setup of this randomized controlled trial. If thermal ablation for resectable CRLM proves to be non-inferior to surgery, a reduction of the post-procedural morbidity and mortality, length of hospital stay and incremental costs can be expected, with better quality of life and without compromising oncological outcome.

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8.2

Surgery versus thermal ablation for colorectal liver metastases (COLLISION): interim results of a phase III, prospective randomized controlled trial

Under embargo. *Chapter based on lectures and presentations given at multiple international scientific conferences and intersociety meetings*

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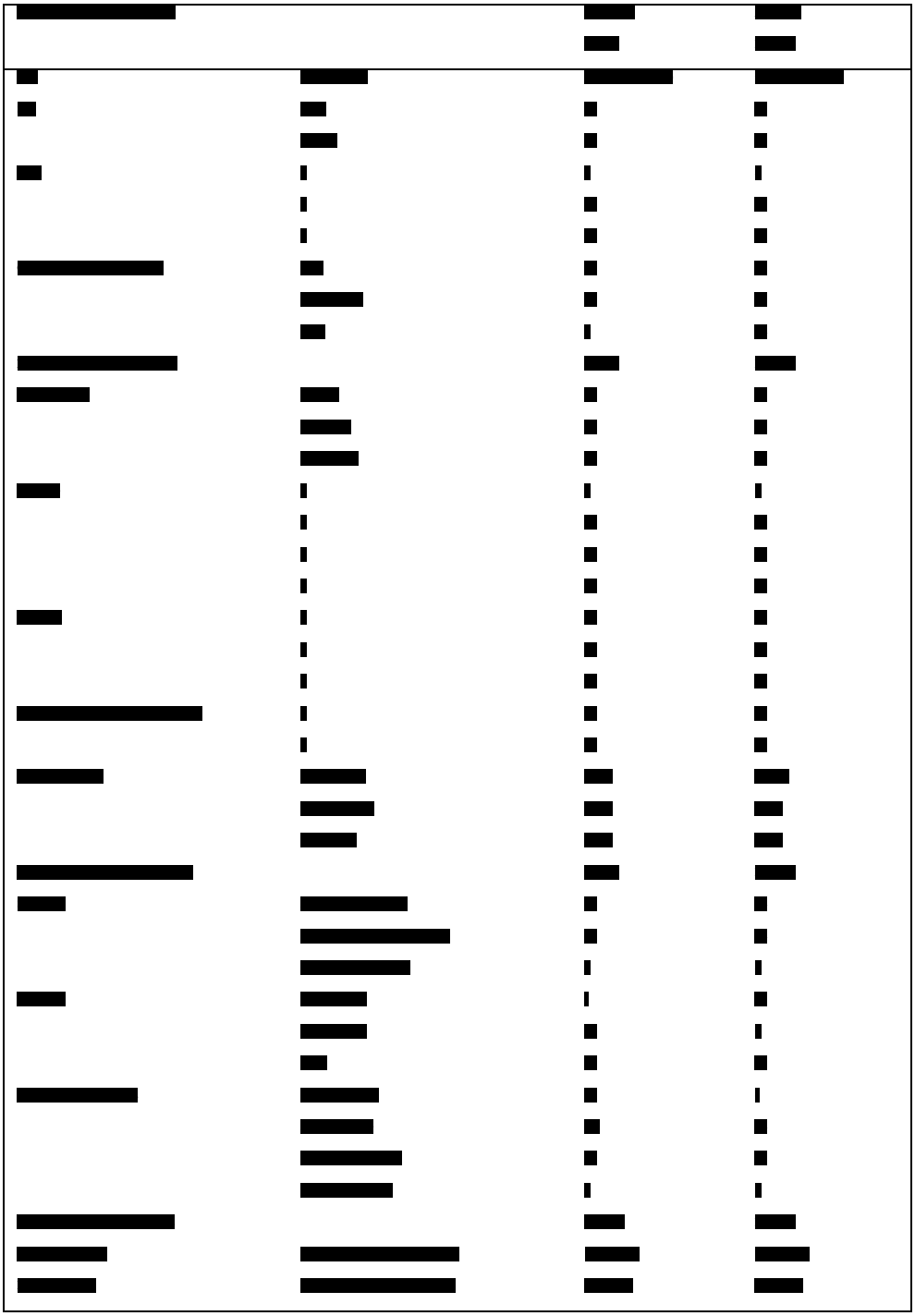

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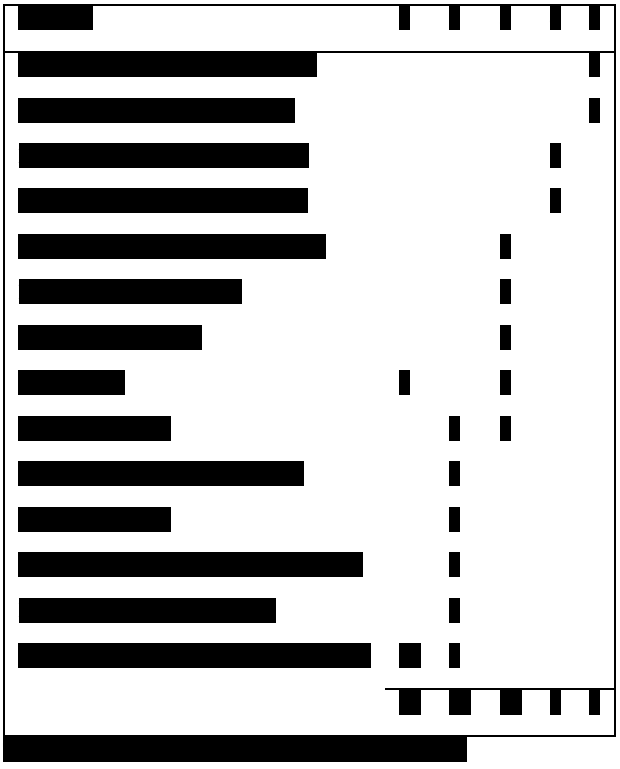

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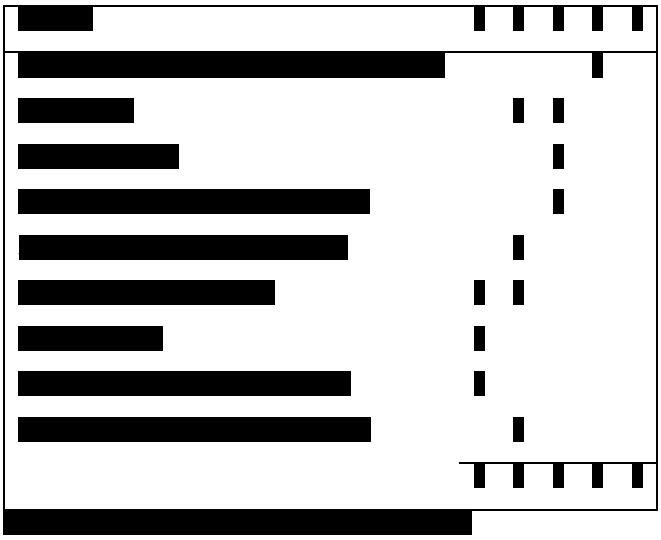

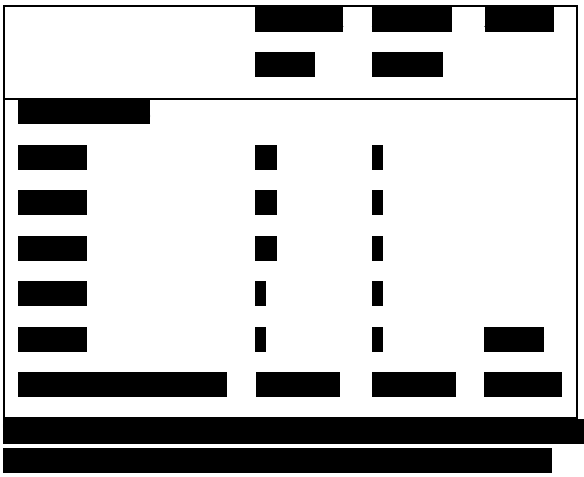

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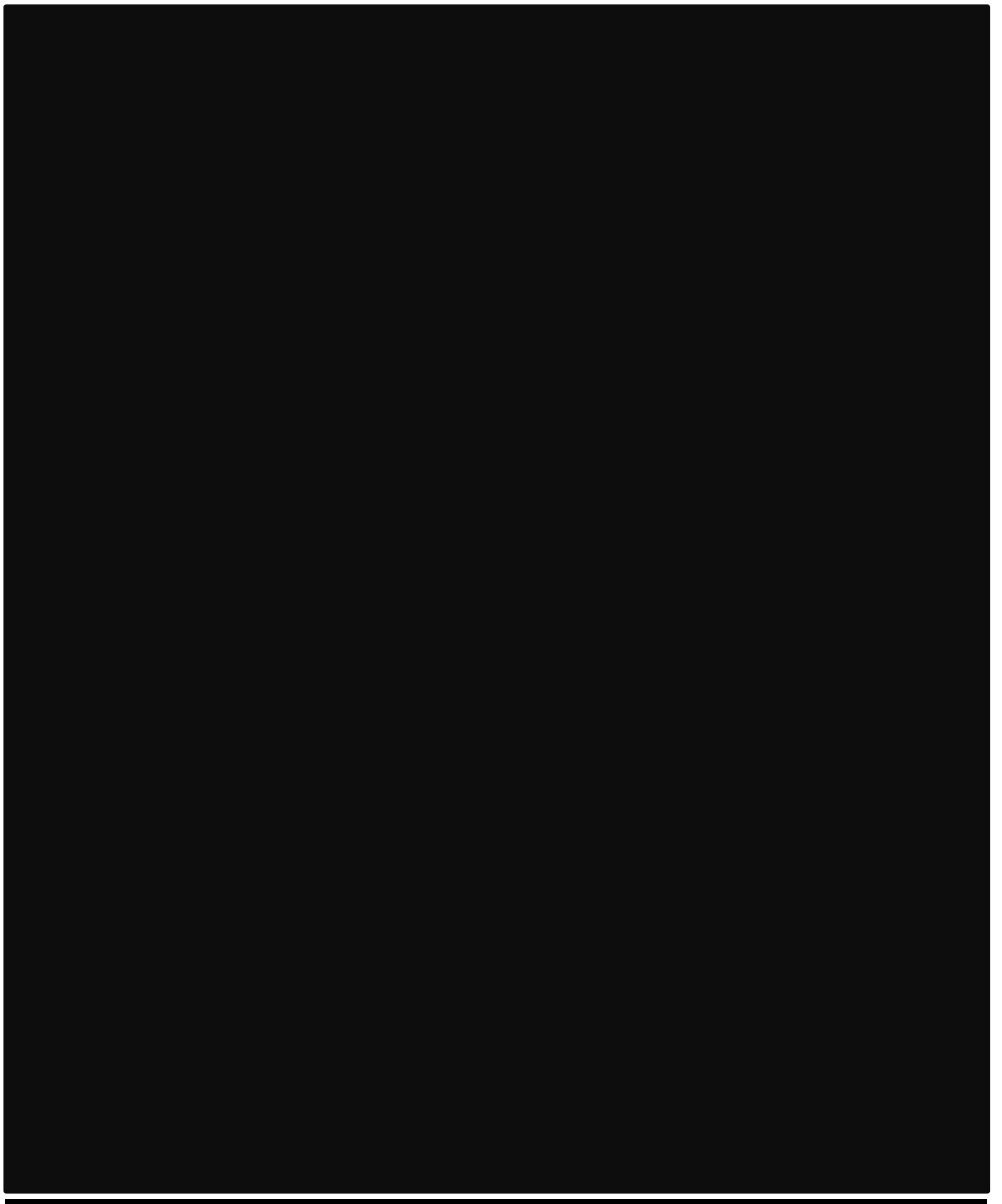

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8.3

COLLISION Trial Seeks to Answer Time-Honored Question: ‘‘Thermal Ablation or Surgery for Colorectal Liver Metastases?’’

M.R. Meijerink, R.S. Puijk, M.P. van den Tol

Cardiovascular and Interventional Imaging 2019

We are honored to highlight the recently started COLLISION trial that will compare thermal ablation to surgical resection for small resectable colorectal liver metastases (CRLM 0–3 cm).[1] Since colorectal cancer is the third most common malignancy worldwide and the second most common cause of cancer-related deaths in developed countries, this trial encompasses a major medical concern.[2] Although approximately half of all patients develop liver metastases in course of their disease, only 15–20% is considered eligible for curative intent surgical resection. For patients with an impaired general health status, history of extensive abdominal surgery, the presence of lesions with an unfavorable anatomical location or an insufficient future liver remnant to perform partial hepatectomy, thermal ablation nowadays is accepted worldwide to eliminate small unresectable CRLM. The minimal invasive and parenchyma-sparing nature, good and still improving efficacy with the potential to repeat procedures in case of local tumor progression, low costs and short hospital stay of thermal ablation have made it impossible to postulate generally accepted resectability criteria, especially for small and deep-seeded CRLM that require major hepatectomy.[3]

With a remarkable difference in eight-year overall survival, 8.9% for the chemotherapy alone group vs. 35.9% for the radiofrequency plus chemotherapy group, the recently published long-term results of the EORTC-CLOCC trial demonstrate that aggressive local treatment can considerably prolong survival or in a subset of patients even provide cure.[4]

Although previous series and meta-analyses routinely labeled thermal ablation inferior to surgical resection, these results have to be interpreted with caution as there is an apparent selection bias when comparing patients with unresectable disease (who receive ablation) to those who were surgical candidates. Recent series, using multivariate analysis or case matching, reported a comparable survival for ablation alone versus resection alone.[5-9] These results have revitalized the discussion whether thermal ablation, given its superior safety profile, should be favored over partial hepatectomy for smaller CRLM.

We have designed a two-arm, multicenter, phase III, single-blind prospective randomized controlled trial for patients with liver-only resectable CRLM up to 3 cm to prove or disprove non-inferiority of thermal ablation compared to the current gold-standard: partial hepatectomy.

The COLLISION trial (registered at clinicaltrials.gov: *NCT03088150*) is initiated by the Amsterdam University Medical Center, in Amsterdam and part-funded by a research grant from Medtronic–Covidien. The trial is embedded within the Dutch Colorectal Cancer Group (DCCG), a multidisciplinary collaboration that aims to improve preclinical and clinical colorectal cancer research. At present, ten high-volume centers for liver surgery throughout the Netherlands and Italy are enrolling patients and several (inter)national institutions are awaiting local review board approval.

Patients with at least 1 resectable and ablatable CRLM (≤ 3 cm), up to ten lesions, a good performance status, no extrahepatic disease and no prior liver treatment are considered

eligible (Fig. 1). Supplementary resection(s) for resectable tumors >3 cm and ablation(s) for unresectable tumors ≤ 3 cm are allowed. The primary endpoint is overall survival. Secondary endpoints are disease-free survival, time-to-(local)-progression, primary and assisted technique efficacy, mortality, length of hospital stay, assessment of quality of life and cost-effectiveness. If thermal ablation proves to be non-inferior (i.e., equal or superior), a switch in treatment method will lead to a reduction in morbidity and mortality, length of hospital stay and incremental costs without compromising oncological outcome for patients with small resectable CRLM. The first study results are expected at the end of 2025.

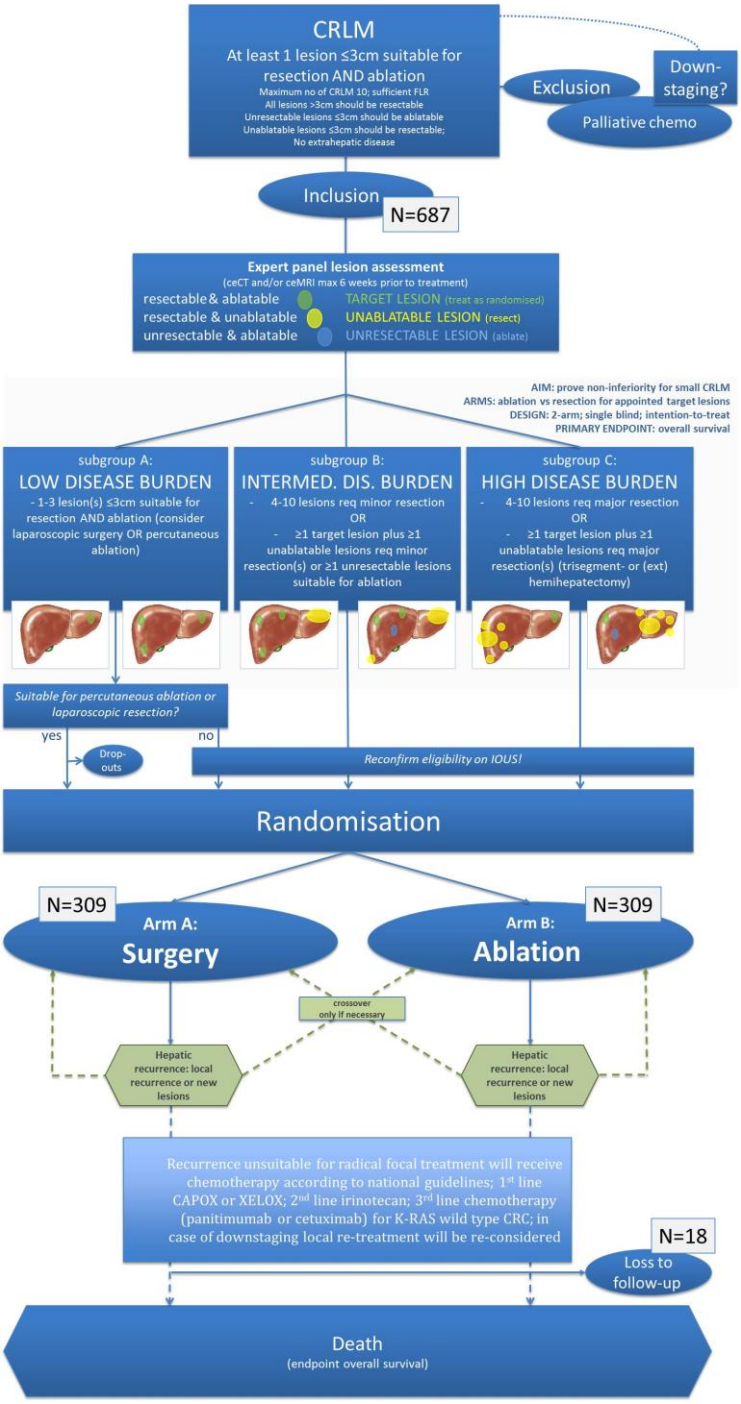

Figure 1. Flowchart

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8.4

The rapidly expanding role of thermal ablation in the treatment of colorectal liver metastases

M.R. Meijerink, M.P. van den Tol, R.S. Puijk

HepatoBiliary Surgery and Nutrition 2019

According to last year's status report on the global burden of cancer, colorectal carcinoma is a rising major medical concern with an estimated rate of over 1.8 million new patients and 881,000 cessations annually, making it the second main cause of cancer-related mortality worldwide.[1] Of all colorectal cancer patients, 40–76% will develop colorectal liver metastases (CRLM) in the course of their disease.[2-4]

In this month's edition of *HepatoBiliary Surgery and Nutrition* Takahashi and Berber present a review that clearly describes the current and expanding role of radiofrequency ablation (RFA) in the management of CRLM patients. The four main indications for thermal ablation are highlighted: (I) for unresectable lesions, (II) in combination therapy with hepatic resection, (III) for an impaired general health status, and (IV) for a small solitary lesion which would otherwise necessitate a major hepatectomy. Partial hepatectomy is considered the first-line therapeutic option for curative intent treatment of CRLM, though unfortunately the majority of patients (80–85%) are not eligible for surgical resection.[2,4,5] Global guidelines have already accepted thermal ablation as the gold standard technique to eliminate unresectable CRLM and the expanding toolbox of ablative therapies is rapidly working its way up in the management of patients with small and difficulty resectable tumors.

Thermal ablation compared to partial hepatectomy and to chemotherapy

Two recently issued systematic reviews and one meta-analysis enumerated all available series regarding thermal ablation, systemic chemotherapy and surgical resection in the treatment of CRLM.[5,6]

For unresectable disease, the maximum achievable level of evidence seems to have been reached with the recently issued long-term results of the EORTC-CLOCC trial.[7] RFA (± surgical resection) plus chemotherapy versus chemotherapy alone showed a remarkable difference in 8-year overall survival of 35.9% *vs.* 8.9%, respectively. These results irrefutably reveal that aggressive local therapy can considerably prolong overall survival or in a subcategory of patients even provide cure. As a consequence, further randomized comparisons of local ablative therapy to curative intent chemotherapy alone should be considered unethical.[5]

Comparing surgical resection alone for resectable di sease with RFA for unresectable disease, RFA demonstrated inferior survival rates but significantly fewer complications.[5] In these series there is an evident selection bias when comparing patients with unresectable disease who receive ther of RFA and partial hepatectomy resulted in comparable overall survival compared to partial hepatectomy alone for resectable lesions. To clarify, in patients with at least one unresectable CRLM, partial hepatectomy plus RFA offers patients an overall and disease-free survival comparable to that of surgery alone candidates. The more recent retrospective cohorts, published after 2012, after case matching or multivariate analysis,

reported comparable survival rates for thermal ablation alone *vs.* surgery alone.[8-12] All observational studies were confounded by indication, because thermal ablation was solely performed for unresectable disease. Although microwave ablation (MWA), presumably being superior to RFA, is being used more frequently as an alternative to RFA over the last years, the available evidence in terms of comparative series was limited.[5]

These outcomes and the apparent selection bias from previous studies have revitalized the debate whether ablation, given its less invasive character, should be favored over surgical resection for smaller (≤3 cm) resectable CRLM.

COLLISION trial

For resectable and ablatable disease, we have designed the COLLISION trial (clinicaltrials.gov *NCT03088150*).[13] This is an international phase-III prospective randomized trial, initiated by the Amsterdam University Medical Center (location VUmc) in the Netherlands. The trial is embedded within the Dutch Colorectal Cancer Group (DCCG), a multidisciplinary collaboration that tents to improve the quality of diagnosis and treatment of colorectal cancer patients through the initiation of preclinical and clinical scientific research. The trial is partly funded by an investigator sponsored research grant by Medtronic PLC.

Inclusion started by the end of 2017. Patients are currently being recruited in 11 specialized institutions for hepatic surgery and thermal liver tumor ablation: Amsterdam UMC (location VUmc: trial initiator), Gelderse Vallei Ede, Maastricht UMC, RadboudUMC Nijmegen, Leiden UMC, MC Leeuwarden, Isala Zwolle, Maxima MC Veldhoven, UMC Groningen, Deventer Ziekenhuis and Ospedale San Raffaele (Milan, Italy). Several other (inter)national centers are awaiting local review board authorization.

The COLLISION trial's main purpose is to test the hypothesis of non-inferiority of ablation compared to surgical resection in patients with small (≤3 cm) CRLM. Participants should have at least one ablatable and resectable lesion (target lesion) without having extrahepatic disease or having received prior focal liver treatment. Additional resection(s) for resectable lesions (>3 cm) and ablation(s) for unresectable lesions (≤3 cm) are permitted. The main study endpoint is overall survival (OS). Subordinate endpoints are local (tumor) progression-free survival, disease-free survival, primary and assisted technique efficacy, mortality, morbidity, length of hospital stay, assessment of quality of life and cost-effectiveness.

A total of 618 patients will be randomized into study-arm A (surgical resection) or study-arm B (thermal ablation) for appointed target lesions (*Figure 1*). At present, over 110 patients have been treated according to their randomization arm. If thermal ablation for resectable CRLM proves to be non-inferior (i.e., equal or superior) to partial hepatectomy, a decrease in postoperative morbidity and mortality, length of hospitalization and accumulative costs

with superior quality of life can be expected. All without compromising oncological outcomes. The first study results are eagerly awaited and foreseen at the end of 2025.

COLLISION XL

In the footsteps of COLLISION, the Dutch study team has separately designed the COLLISION XL trial (clinicaltrials gov *NCT04081168*) which will compare stereotactic body radiotherapy (SBRT) and MWA in patients with unresectable larger-size CRLM (3–5 cm). The primary endpoint is 1-year local (tumor) progression-free survival.

This trial will soon start recruiting patients.

To conclude, the widespread adoption of minimally invasive thermal ablation in the treatment of unresectable hepatic metastases of colorectal cancer is an inevitable development in clinical oncology. Future results of the ongoing COLLISION trial will undoubtedly give us answers on the pressing question whether to perform thermal ablation or resection for small (≤3 cm) resectable CRLM.

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8.5

Thermal ablation compared to partial hepatectomy for recurrent colorectal liver metastases: an Amsterdam Colorectal Liver Met Registry (AmCORE) based study

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Cancers 2021

ABSTRACT

The aim of this study was to assess safety, efficacy and survival outcomes of repeat thermal ablation as compared to repeat partial hepatectomy in patients with recurrent colorectal liver metastases (CRLM). This Amsterdam Colorectal Liver Met Registry (AmCORE) based study of two cohorts, repeat thermal ablation versus repeat partial hepatectomy, analyzed 136 patients (100 thermal ablation, 36 partial hepatectomy) and 224 tumors (170 thermal ablation, 54 partial hepatectomy) with recurrent CRLM from May 2002 to December 2020. The primary and secondary endpoints were overall survival (OS), distant progression-free survival (DPFS) and local tumor progression-free survival (LTPFS), estimated using the Kaplan–Meier method, and complications, analyzed using the chi-square test. Multivariable analyses based on Cox proportional hazards model were used to account for potential confounders. In addition, subgroup analyses according to patient, initial and repeat local treatment characteristics were performed. In the crude overall comparison, OS of patients treated with repeat partial hepatectomy was not statistically different from repeat thermal ablation ($p = 0.927$). Further quantification of OS, after accounting for potential confounders, demonstrated concordant results for repeat local treatment (hazard ratio (HR), 0.986; 95% confidence interval (CI), 0.517–1.881; $p = 0.966$). The 1-, 3- and 5-year OS were 98.9%, 62.6% and 42.3% respectively for the thermal ablation group and 93.8%, 74.5% and 49.3% for the repeat resection group. No differences in DPFS ($p = 0.942$), LTPFS ($p = 0.397$) and complication rate ($p = 0.063$) were found. Mean length of hospital stay was 2.1 days in the repeat thermal ablation group and 4.8 days in the repeat partial hepatectomy group ($p = 0.009$). Subgroup analyses identified no heterogeneous treatment effects according to patient, initial and repeat local treatment characteristics. Repeat partial hepatectomy was not statistically different from repeat thermal ablation with regard to OS, DPFS, LTPFS and complications, whereas length of hospital stay favored repeat thermal ablation. Thermal ablation should be considered a valid and potentially less invasive alternative for small-size (0–3 cm) CRLM in the treatment of recurrent new CRLM. While, the eagerly awaited results of the phase III prospective randomized controlled COLLISION trial (*NCT03088150*) should provide definitive answers regarding surgery versus thermal ablation for CRLM.

INTRODUCTION

Colorectal cancer (CRC) is the third most common form of cancer worldwide.[1] Up to 50% of patients develop colorectal liver metastases (CRLM), a lethal condition in the vast majority of cases.[2,3] The only chance for cure entails a radical intent treatment of the CRLM, including partial hepatectomy and/or thermal ablation (i.e., radiofrequency ablation (RFA), microwave ablation (MWA)).[4] Although the 5-year overall survival (OS) nowadays reaches 50–60%[5,6], only 20% of patients with CRLM are eligible for curative intent treatment.

In the past few decades surgical resection has been considered the gold standard in upfront resectable CRLM, while thermal ablation emerged for small (≤ 3 cm) unresectable CRLM.[3,7-10] When compared to partial hepatectomy, thermal ablation is currently associated with a lower complication rate, reduced hospital stay and lower costs but also with an inferior survival according to two recent meta-analyses and propensity score analyses.[3,10-14] Given the high risk of selection bias when comparing partial hepatectomy for resectable tumors with thermal ablation for unresectable disease, survival outcomes of the two techniques are currently considered to be in equipoise and the results of the prospective COLLISION trial (*NCT03088150*) are eagerly awaited.[8] Although curative intent local treatment offers complete tumor eradication in most, 64–85% of patients develop new metastases, commonly detected within 12 months following the initial treatment[15-17], of which the liver is the sole site of recurrence in approximately 39–43%.[18]

Large international multi-institutional retrospective series and several other groups on repeat partial hepatectomy with curative intent of new CRLM demonstrated 5-year OS following the second treatment reaching 51%.[19-22] As a result the current standard of care for new CRLM is repeat local treatment, either upfront or after induction chemotherapy.[23-28] Although relatively safe and feasible, repeat partial hepatectomy can be challenging due to adhesions and due to the reduced liver volume after surgery.[29] Given its superior safety profile and the fact that thermal ablation is less affected by previous surgical injury, the question has arisen whether thermal ablation could be a safer and equally effective alternative to repeat partial hepatectomy for small-size recurrences.[30]

This Amsterdam Colorectal Liver Met Registry (AmCORE) based study aimed to analyze safety, efficacy and survival outcomes following repeat thermal ablation compared to repeat partial hepatectomy for recurrent CRLM.

MATERIALS AND METHODS

This single-center prospective cohort study was performed at the Amsterdam University Medical Centers—location VU Medical Center, the Netherlands, a tertiary referral center for hepatobiliary and gastrointestinal malignancies. Data were extracted from the AmCORE prospectively maintained CRLM database. The study was approved by the affiliated Institutional Review Board (METc VUmc: 2021.0121). The analyzed study data reported conform to the 'Strengthening the Reporting of Observational studies in Epidemiology' (STROBE) guideline.[31]

Patient selection

Data of all patients with recurrent new CRLM after initial curative intent local treatment, eligible for repeat local treatment were collected from the prospective database. Additional recollecting of data was performed by retrospectively searching the hospital's electronic patient database when required. Patients undergoing repeat thermal ablation or repeat partial hepatectomy were included. Patients with loss to follow-up or undergoing repeat stereotactic body radiation therapy (SBRT), irreversible electroporation (IRE) or a combination of resection and thermal ablation in the same procedure, were excluded.

Repeat local treatment procedures

Recurrent new CRLMs were detected during follow-up using cross-sectional imaging containing contrast enhanced computed tomography (ceCT) and 18F-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET)-CT scans, using contrast enhanced magnetic resonance imaging (ceMRI) with diffusion-weighted images prior to repeating local treatment. The choice of the repeat local treatment procedure was based on local expertise, determined by multidisciplinary tumor board evaluations attended by (interventional) radiologists, oncological or hepatobiliary surgeons, medical oncologists, radiation oncologists, nuclear medicine physicians, gastroenterologists and pathologists. Repeat local treatment was performed by an experienced interventional radiologist (mastery degree in image-guided tumor ablation, having performed and/or supervised >100 thermal ablation procedures) or by an experienced, certified oncological or hepatobiliary surgeon (with broad expertise, having performed and/or supervised >100 liver tumor resection procedures). Resections were performed at discretion of the performing oncological or hepatobiliary surgeon, comprising the extent and specific technique as well as resection margins (with the intention and preoperative estimation of a possible pathological R0 resection). Metastectomy was performed when eligible to preserve liver volume and

anatomical resection when necessary. Thermal ablation procedures were performed at the discretion of the interventional radiologist, according to the CIRSE quality improvement guidelines (with an intentional tumor free ablation margin >1 cm, confirmed with computational techniques and image fusion or estimated in the early years).[32] Percutaneous approach was preferred in patients with no contra-indications (proximity of critical structures). When insufficiently ablated margins were presumed and/or confirmed by ceCT or ceMRI following thermal ablation, residual unablated tumor tissue was retreated with overlapping ablations. Conformal to national guidelines, (neo)adjuvant chemotherapy was not routinely administered, with the exception of cases where downsizing would likely reduce procedural risk (induction chemotherapy) or for patients with biologically unfavorable early multiple intrahepatic recurrences (<6 months following the initial treatment).[27]

Follow-up

18F-FDG-PET-CT with diagnostic ceCTs of the chest and abdomen were performed in the first year 3/4-monthly, in the 2nd and 3rd year 6-monthly and in the 4th and 5th year 12 monthly after repeat local treatment, according to national guidelines.[27] CeMRI with diffusion-weighted images was used as problem solver. In the context of a presumably incomplete percutaneous ablation procedure, a ceCT-scan was performed within one to six weeks after the repeat local treatment. Local tumor progression (LTP) was defined as a solid and unequivocally enlarging mass or focal 18F-FDG PET avidity at the surface of the ablated tumor or resection margin, and histopathological confirmation in case of uncertainty.

Data collection and statistical analysis

Patient and treatment characteristics were obtained from the AmCORE database. Categorical variables are reported as number of patients with percentages and continuous variables are reported as mean with standard deviation (SD) when normally distributed and as median with interquartile range (IQR) when not-normally distributed. The patients were divided into two groups regardless of initial treatment: repeat thermal ablation and repeat partial hepatectomy. Characteristics between groups were compared using the Fisher's exact test for dichotomous variables, using the Pearson Chi square test for categorical variables and using independent samples t-test when normally distributed and Mann–Whitney U Test when not-normally distributed for continuous variables.

Primary endpoint OS and secondary endpoints local tumor progression-free survival (LTPFS) and distant progression-free survival (DPFS) were defined as time-to-event from repeat local treatment. Death without local or distant progression (competing risk) was

censored. Complications were described using Common Terminology Criteria for Adverse Events 5.0 (CTCAE).[33]

Primary endpoint OS was reviewed using the Kaplan–Meier method using the logrank test and comparison between the two groups was conducted using Cox proportional hazards regression models, accounting for potential confounders in multivariable analysis. Secondary endpoint complications, LTPFS and DPFS were analyzed using the chi-square test and the Kaplan–Meier method using the log-rank test and Cox proportional hazards regression models to account for potential confounders. Variables with $p < 0.100$ in univariable analysis were included in multivariable analysis using forward selection procedure. Significant variables, $p = 0.050$, were reported as potential confounders and further investigated. Variables were considered confounders when the association between the two treatment groups and OS, DPFS, LTPFS differed >10% in the corrected model. Corrected hazard ratio (HR) and 95 per cent confidence interval (95% CI) were calculated. Length of hospital stay was analyzed using the Mann–Whitney U test. Subgroup analyses were performed to assess heterogeneous treatment effects according to patient, initial and repeat local treatment characteristics.

Statistical analyses, supported by a biostatistician (BLW), were performed using SPSS® Version 24.0 (IBM®, Armonk, New York, NY, USA)[34] and R version 4.0.3. (R Foundation, Vienna, Austria).[35]

RESULTS

After identification of patients with recurrent CRLM in the AmCORE database, 136 patients were selected for the analysis of recurrent CRLM, of which 100 were treated with repeat thermal ablation and 36 with repeat partial hepatectomy (Figure 1). A total of 224 tumors were treated with repeat ablation (n = 170) or repeat partial hepatectomy (n = 54) between May 2002 and December 2020.

Patient characteristics

Table 1 presents patient characteristics of the 136 included patients. There were no significant differences between the two treatment groups. The age ranged between 27 and 86 years. Median time between initial treatment and diagnosis of recurrence was 6.9 (IQR 4.0–13.4) months, 6.4 (IQR 4.0–10.4) months in the repeat thermal ablation group and 12.2 (IQR 3.7–21.3) in the repeat partial hepatectomy group ($p = 0.056$). Most patients had 1 recurrent CRLM (62.5%) and size of largest metastasis was mostly small (1–30 mm; 84.7%). Median

follow-up time after repeat thermal ablation was 23.3 months and after repeat partial hepatectomy 34.9 months. Median tumor size was 21 (IQR 12.5–26.5) in the partial hepatectomy group and 16.5 (10.75–23.0) in the thermal ablation group.

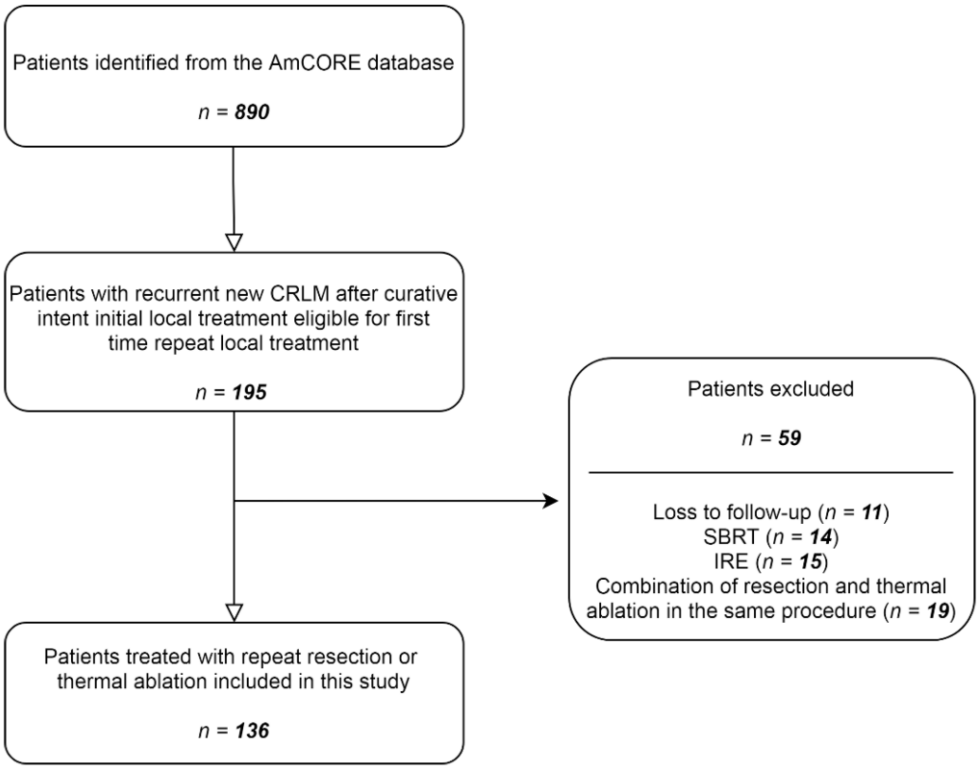

Figure 1. Flowchart of included and excluded patients.

		Total	Repeat Thermal Ablation Group	Repeat Resection Group	*p*-Value
Number of patients		136	100 (73.5)	36 (26.5)	
Number of tumors		224	170 (75.9)	54 (24.1)	
Patient Characteristics					
Gender	Male	104 (76.5)	79 (79.0)	25 (69.4)	
	Female	32 (23.5)	21 (21.0)	11 (30.6)	0.259 [a]
Age (years) *		66.0 (10.9)	66.9 (11.4)	63.3 (9.1)	0.092 [c]
ASA physical status	1	8 (5.9)	7 (7.0)	1 (2.8)	
	2	93 (68.4)	67 (67.0)	26 (72.2)	
	3	35 (25.7)	26 (26.0)	9 (25.0)	0.632 [b]
Comorbidities	None	67 (49.3)	47 (47.0)	20 (55.6)	
	Minimal	49 (36.0)	38 (38.0)	11 (30.6)	
	Major	20 (14.7)	15 (15.0)	5 (13.9)	0.663 [b]
BMI (kg/cm^2) *		26.1 (4.2)	26.4 (4.2)	25.0 (4.0)	
	Missing	3	0	3	0.094 [c]
Primary tumor location	Rectum	33 (24.3)	22 (22.0)	11 (30.6)	
	Colon left-sided	67 (49.3)	50 (50.0)	17 (47.2)	
	Colon right-sided	36 (26.5)	28 (28.0)	8 (22.2)	0.556 [b]
Characteristics Initial Local Treatment of CRLM					
Initial CRLM diagnosis	Synchronous	69 (51.9)	51 (52.6)	18 (50.0)	
	Metachronous	64 (48.1)	46 (47.4)	18 (50.0)	0.847 [a]
	Missing	3	3	0	
Number of tumors	1	38 (27.9)	26 (26.0)	12 (33.3)	
	2–5	65 (47.8)	45 (45.0)	20 (55.6)	
	>5	33 (24.3)	29 (29.0)	4 (11.1)	0.099 [b]
Size of largest metastasis (mm)	Small (1–30)	75 (62.5)	57 (61.3)	18 (66.7)	
	Intermediate (31–50)	36 (30.0)	28 (30.1)	8 (29.6)	
	Large (>50)	9 (7.5)	8 (8.6)	1 (3.7)	0.681 [b]
	Missing	16	7	9	
Extrahepatic disease	No	111 (92.5)	82 (93.2)	29 (90.6)	
	Yes	9 (7.5)	6 (6.8)	3 (9.4)	0.699 [a]
	Missing	16	12	4	
Type of procedure	Resection	44 (32.4)	27 (27.0)	17 (47.2)	
	Thermal ablation	43 (31.6)	35 (35.0)	8 (22.2)	
	Resection and thermal ablation	46 (33.8)	37 (37.0)	9 (25.0)	
	IRE	2 (1.5)	1 (1.0)	1 (2.8)	
	SBRT	1 (0.7)	0 (0.0)	1 (2.8)	0.057 [b]
Characteristics Repeat Local Treatment of CRLM					
Time between initial treatment and diagnosis recurrence (months) *		6.9 (4.0–13.4)	6.4 (4.0–10.4)	12.2 (3.7–21.3)	0.056 [d]
Number of tumors	1	85 (62.5)	59 (59.0)	26 (72.2)	
	2–5	50 (36.8)	40 (40.0)	10 (27.8)	
	>5	1 (0.7)	1 (1.0)	0 (0)	0.337 [b]
Size of largest metastasis (mm)	Small (1–30)	100 (84.7)	80 (85.1)	20 (83.3)	
	Intermediate (31–50)	16 (13.6)	13 (13.8)	3 (12.5)	
	Large (>50)	2 (1.7)	1 (1.1)	1 (4.2)	0.572 [b]
	Missing	18	6	12	
Chemotherapy	No	98 (72.1)	71 (71.0)	27 (75.0)	
	Yes	38 (27.0)	29 (29.0)	9 (25.0)	0.829 [a]

Table 1. Baseline characteristics at recurrent CRLM. Values are reported as number of patients (%), * = continuous variables reported as mean (standard deviation; SD) or median (interquartile range; IQR), a = Fisher's exact test, b = Pearson chi-square, c = independent t-test, d = Mann–Whitney U test, ASA = American Society of Anesthesiologists score, BMI = body mass index.

Treatment characteristics

Table 2 shows treatment characteristics of the procedures concerning type of system used for thermal ablation and partial hepatectomy (operation) technique. Comparison of local treatment method showed that the majority of the repeat thermal ablation group underwent a percutaneous approach and the majority of repeat partial hepatectomy group underwent an

open approach. A total of 40 patients received treatment with RFA (40.0%), all prior to 2017, and 60 patients (60.0%) received treatment with MWA. In the partial hepatectomy group, the majority of patients received minor repeat resection (97.1%). Median length of hospital stay of the entire cohort was 1.0 days (IQR 1.0–3.3), of the repeat thermal ablation group 1.0 days (IQR 1.0–1.0) and of the repeat partial hepatectomy group 5.0 days (IQR 4.0–6.0) (p = 0.009). Margin size was <5 mm in 14.8% of tumors in the resection group and in 5.1% of tumors in the thermal ablation group.

		Repeat Thermal Ablation Group ***n*** **= 100**	**Repeat Resection Group** ***n*** **= 36**
Type of repeat thermal ablation	**RFA**	40 (40.0)	-
	LeVeen™	35 (35.0)	-
	Cool-Tip™	4 (4.0)	-
	Others	1 (1.0)	-
	MWA	60 (60.0)	-
	Emprint™	46 (46.0)	-
	Covidien Evident™	5 (5.0)	-
	Others	9 (9.0)	-
Type of repeat resection	Minor (<3 segments)	-	34 (97.1%)
	Major (≥3 segments)	-	1 (2.9%)
	Missing	-	2
Approach	Open	17 (17.2%)	28 (84.8%)
	Laparoscopic	0 (0.0%)	5 (15.2%)
	Percutaneous	82 (82.2%)	-
	Missing	1	3

Table 2. Treatment characteristics of repeat local treatment. Values are reported as number of patients (%), RFA = radiofrequency ablation, MWA = microwave ablation.

Complications

No difference in complication rate was found between repeat thermal ablation and repeat partial hepatectomy (p = 0.063) (Table 3). Total complication rate was 21.8% (27/124 procedures), of which 19.2% (19/99 procedures) in the repeat thermal ablation group and 32.0% (8/25 procedures) in the repeat resection group. Two grade 4 complications were reported; one admission to the intensive care unit for respiratory insufficiency due to pneumonia (repeat resection group), and one patient suffered from intestinal wall injury resulting in colostomy (repeat thermal ablation group).

Grade	Total	Repeat Thermal Ablation Group *n* = 100	Repeat Resection Group *n* = 36	*p*-Value
None	97 (78.2)	80 (80.8)	17 (68.0)	0.063 [b]
Grade 1	8 (6.5)	8 (8.1)	NR	
Grade 2	8 (6.5)	4 (4.0)	4 (16.0)	
Grade 3	9 (7.3)	6 (6.1)	3 (12.0)	
Grade 4	2 (16)	1 (1.0)	1 (4.0)	
Grade 5	NR	NR	NR	
Missing	12	1	11	

Table 3. Complications of repeat local treatment (CTCAE).[33] Values are reported as number of patients (%), NR = not reported, b = Pearson chi-square

Local tumor progression-free survival

LTP was reported at follow-up in 25 out of 224 tumors (11.2%); 18/170 (10.6%) in the repeat thermal ablation group and 7/54 (13.0%) in the repeat resection group (Figure 2). Overall crude comparison between the two groups showed no significant difference in LTPFS (p = 0.959). Overall, 1-, 3- and 5-year LTPFS was 92.8%, 84.0% and 84.0%. The 1-, 3- and 5-year LTPFS was 91.6%, 85.8% and 85.8%, respectively, for the thermal ablation group and 96.1%, 81.4% and 81.4% for the repeat resection group. Univariable analysis identified three potential confounders: initial CRLM diagnosis (synchronous vs. metachronous; p = 0.002), time between initial treatment and diagnosis of recurrence (p = 0.003), and number of recurrent metastases (p = 0.016). These variables were included in multivariable analysis to analyze whether potential confounders associated with the two treatment groups influenced LTPFS (Table S1). Only the variable time between initial treatment and diagnosis of recurrence proved a significant confounder in multivariable analysis (p = 0.001). After adjusting for this confounder corrected HR for LTPFS after repeat thermal ablation was 1.486 (95% CI, 0.594–3.714; p = 0.397).

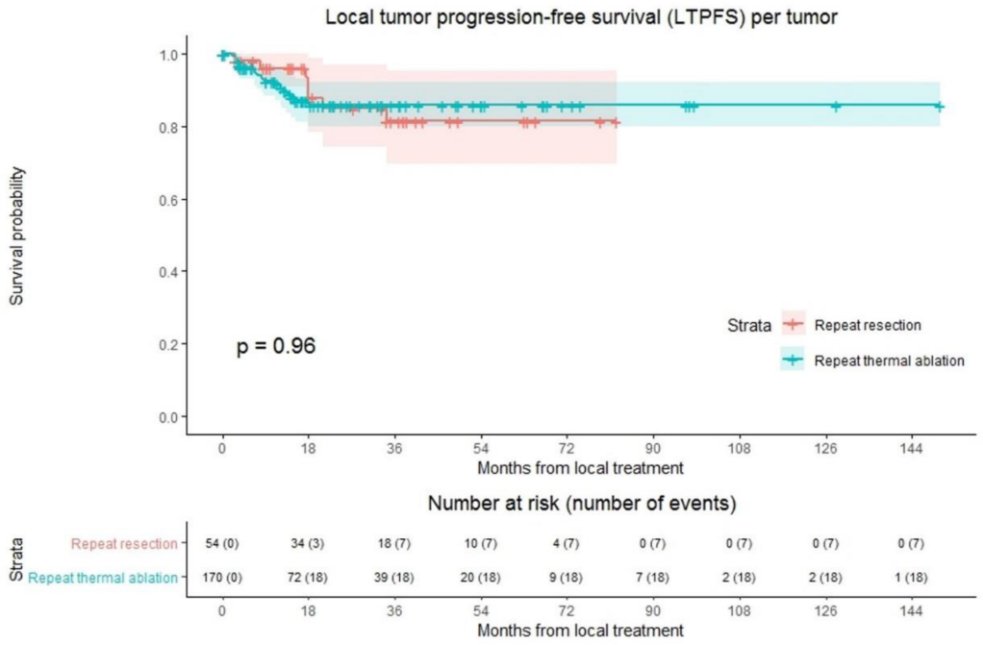

Figure 2. Kaplan–Meier curves of local tumor progression-free survival (LTPFS) per tumor after repeat resection (red) and repeat thermal ablation (green). Numbers at risk (number of events) are per tumor. Overall comparison log-rank (Mantel-Cox) test, p = 0.959. Death without local tumor progression (LTP; competing risk) is censored.

Distant progression-free survival

Ninety of 136 patients (66.2%) developed distant progression at follow-up with a median time to distant progression of 9.7 months (Figure 3). Following repeat thermal ablation and repeat resection, distant progression rate was 66.0% (66/100 patients) and 66.7% (24/36 patients), respectively. Overall, 1-year DPFS was 44.6%, 3-year DPFS was 24.7% and 5-year DPFS was 19.8%. The 1-, 3- and 5-year DPFS were, respectively, 44.4%, 24.0% and 19.8% for the thermal ablation group and 44.7%, 26.6% and 21.3% for the repeat resection group. No difference in DPFS was found in crude comparison (p = 0.803). Univariable analysis identified age (p = 0.092), initial CRLM diagnosis (synchronous vs. metachronous; p = 0.089), time between initial treatment and diagnosis recurrence (p = 0.032) and size of largest recurrent metastasis (p = 0.008) as potential confounders. Of these parameters, size of largest recurrent metastasis (p = 0.002) and time between initial treatment and diagnosis recurrence (p = 0.016) proved significant in multivariable analysis (Table S2). After adjusting for these confounders, corrected HR was 1.024 (95% CI, 0.545–1.922; p = 0.942).

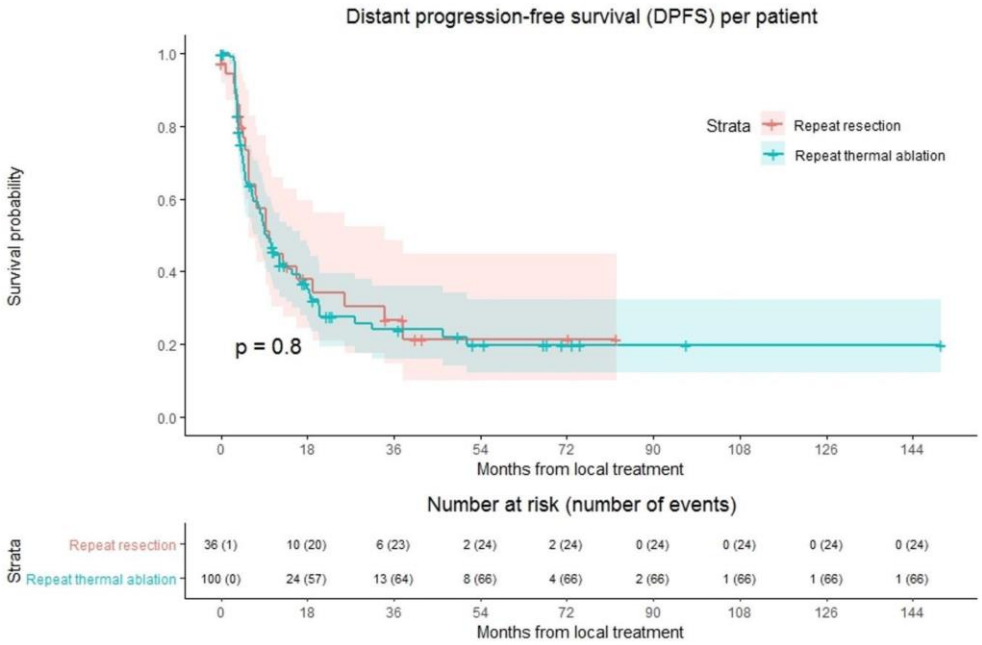

Figure 3. Kaplan–Meier curves of distant progression-free survival (DPFS) per patient after repeat resection (red) and repeat thermal ablation (green). Numbers at risk (number of events) are per patient. Overall comparison log-rank (Mantel-Cox) test, p = 0.803. Death without distant progression (competing risk) is censored.

Overall survival

Overall median OS as well as median OS of the repeat thermal ablation group was 54.4 months, whereas median OS of the repeat resection group was 49.2 months (Figure 4). During follow-up, a total of 46/136 patients (33.8%) died, 14/36 (38.9%) in the repeat resection group and 32/100 (32.0%) in the repeat thermal ablation group. The crude overall comparison of OS between the two groups revealed no significant difference (p = 0.927). Overall, 1-year OS was 97.5%, 3-year OS was 66.5% and 5-year OS was 44.1%. The 1-, 3- and 5-year OS were, respectively, 98.9%, 62.6% and 42.3% for the thermal ablation group and 93.8%, 74.5% and 49.3% for the repeat resection group. After identifying the association of comorbidities (p = 0.038) and primary tumor location (p = 0.083) with OS in univariable analyses, the variables were included in multivariable analysis to analyze their potential confounding influence on OS (Table 4). After adjusting for the confounder comorbidities (p = 0.038), corrected HR was 0.986 (95% CI, 0.517–1.881; p = 0.966). Subgroup analyses revealed no heterogeneous treatment effects according to patient, initial and repeat local treatment characteristics (Figure 5).

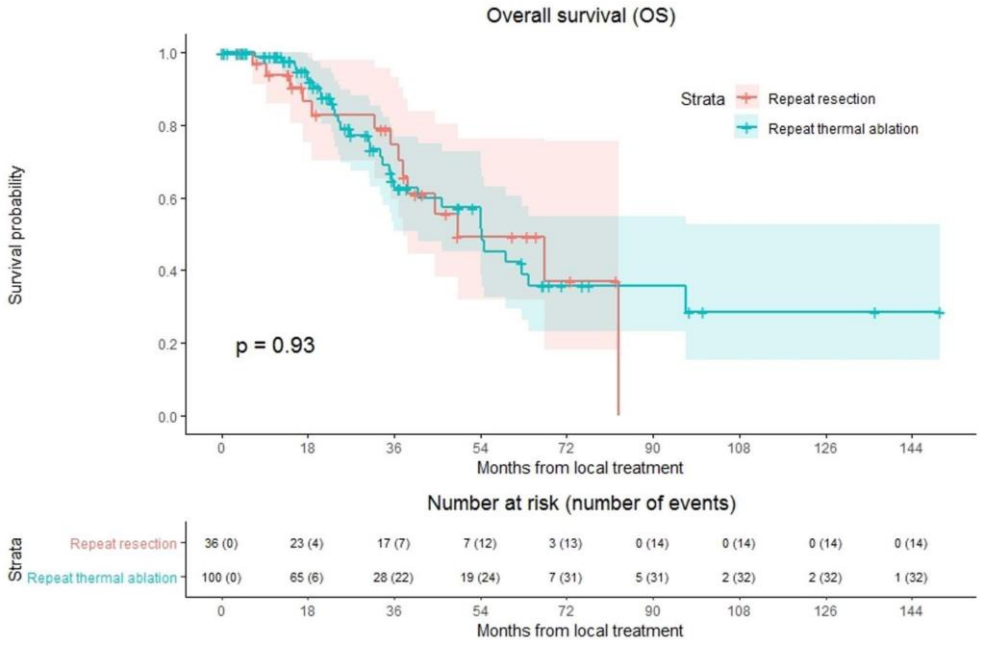

Figure 4. Kaplan–Meier curves of overall survival (OS) after repeat resection (red) and repeat thermal ablation (green). Numbers at risk (number of events) are per patient. Overall comparison log-rank (Mantel-Cox) test, p = 0.927.

		Univariable Analysis		Multivariable Analysis	
		HR (CI)	**P-value**	**HR (CI)**	**P-value**
Repeat local treatment	Repeat resection	Reference	.927	Reference	.966
	Repeat thermal ablation	0.971 (0.515-1.831)		0.986 (0.517-1.881)	
Patient-related factors					
Gender	Male	Reference	.593		
	Female	0.826 (0.409-1.668)			
Age (years)		1.027 (0.994-1.062)	.114		
ASA physical status	1	Reference	.177		
	2	3.790 (0.894-16.078)			
	3	2.979 (0.644-13.780)			
Comorbidities	None	Reference	**.038**	Reference	**.038**
	Minimal	1.615 (0.853-3.061)		1.618 (0.850-3.079)	
	Major	2.940 (1.264-6.838)		2.936 (1.258-6.848)	
BMI (kg/cm^2)		0.978 (0.906-1.056)	.570		
Primary tumor location	Rectum	Reference	**.084**	Reference	**.**060
	Colon left-sided	0.902 (0.434-1.877)		0.879 (0.421-1.835)	
	Colon right-sided	1.918 (0.862-4.268)		2.002 (0.890-4.503)	
Factors regarding initial local treatment of CRLM					
Initial CRLM diagnosis	Synchronous	Reference	.778		
	Metachronous	0.917 (0.503-1.672)			
Number of tumors	1	Reference	.618		
	2-5	0.906 (0.465-1.764)			
	>5	0.663 (0.287-1.535)			
Size of largest metastasis	Small (1-30)	Reference	.349		
(mm)	Intermediate (31-50)	0.864 (0.438-1.706)			
	Large (>50)	0.333 (0.075-1.478)			
Extrahepatic disease	No	Reference	.250		
	Yes	0.311 (0.042-2.277)			
Type of procedure	Resection	Reference	.798		
	Thermal ablation	1.360 (0.669-2.765)			
	Resection and thermal ablation	0.867 (0.413-1.822)			
	IRE	1.128 (0.147-8.645)			
	SBRT	*			
Factors regarding repeat local treatment of CRLM					
Time between initial treatment and recurrence (months)		1.001 (0.980-1.022)	.943		
Number of tumors	1	Reference	.620		
	2-5	1.350 (0.740-2.464)			
	>5	*			

Size of largest metastasis	Small (1-30)	Reference	.251
(mm)	Intermediate (31-50)	1.795 (0.812-3.971)	
	Large (>50)	2.092 (0.481-9.103)	
Chemotherapy	No	Reference	.825
	Yes	1.071 (0.582-1.970)	

Table 4. Univariable and multivariable cox regression analysis to detect potential confounders associated with overall survival (OS). After removal of primary tumor location and adjusting for the confounder comorbidities, corrected HR of repeat local treatment was 0.986 (95% CI, 0.517–1.881; p = 0.966). H R = hazard ratio, CI = 95% confidence interval, ASA = American Society of Anesthesiologists score, BMI = body mass index, * = insufficient subgroup size for each treatment group.

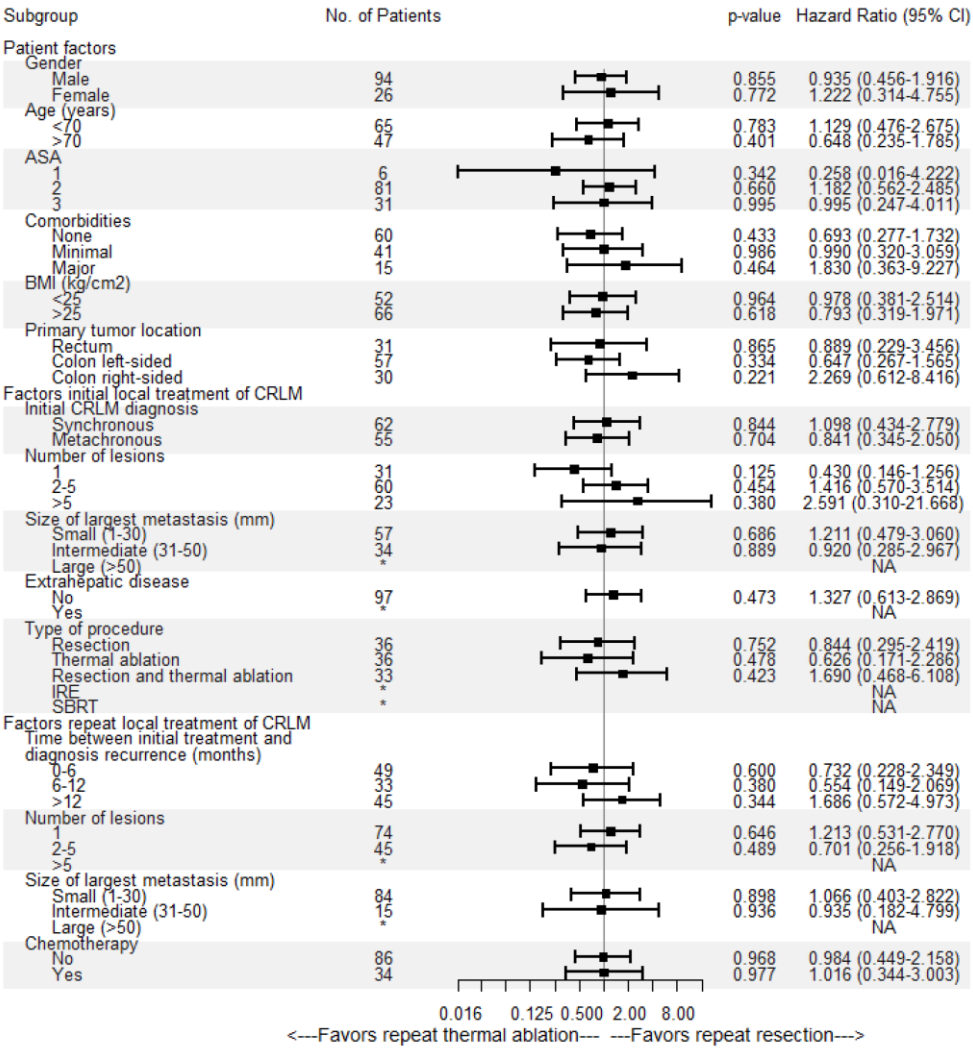

Figure 5. Univariable subgroup Cox regression analyses of repeat resection versus repeat thermal ablation associated with overall survival (OS). No = number, CI = confidence interval, ASA = American Society of Anesthesiologists score, BMI = body mass index, * = insufficient subgroup size for each treatment group, NA = not available.

DISCUSSION

Repeat partial hepatectomy of recurrent new CRLM was not statistically different from repeat thermal ablation with regard to crude overall comparison of OS (p = 0.927), complications (p = 0.063), LTPFS (p = 0.959) and DPFS (p = 0.803). Further quantification of OS, LTPFS and DPFS, after accounting for potential confounders, demonstrated concordant results for OS (HR, 0.986; 95% CI, 0.517–1.881; p = 0.966), LTPFS (HR, 1.486; 95% CI, 0.594–3.714; p = 0.397) and DPFS (HR, 1.024; 95% CI, 0.545–1.922; p = 0.942). Subgroup analyses identified no heterogeneous treatment effects according to patient, initial and repeat local treatment characteristics.

Notably, length of hospital stay was longer in the repeat resection group compared to the repeat thermal ablation group (p = 0.009). Therefore, in addition to outcomes reported of thermal ablation versus partial hepatectomy for the initial local treatment of CRLM[10], this study no longer validates repeat partial hepatectomy as the only curative intent local treatment option for recurrent CRLM. The results even suggest that thermal ablation might be favored for small-size recurrent lesions suitable for both resection and ablation[7], given the lower invasiveness[30], lower costs[36] and reduced hospital stay when compared to surgery.

As a result of strict follow-up protocol after initial local treatment, new recurrent CRLM are detected relatively fast and therefore we observed merely small-sized recurrent metastases. In accordance with the presented results, the multidisciplinary COLLISION trial expert panel recommended thermal ablation as standard of care to treat small-size recurrent CRLM[7], because percutaneous thermal ablation is unaffected by post-surgical adhesions and a reduced liver volume.[29,30]

Previous research on outcomes of repeat partial hepatectomy and repeat thermal ablation support our findings.[37-40] In the past, most studies analyzed survival outcomes of repeat resection compared to initial local treatment or to palliative chemotherapy. Yet, Dupré et al. analyzed well-matched patient groups with liver-limited recurrence after initial liver resection, treated with either repeat thermal ablation or resection.[37] No differences in median OS were found (both 33.3; 95% CI, 28–54.7 months) and the reduction in length of hospital stay (1 versus 5 days; p < 0.001) and lower rates of post-procedural complications (12.1% versus 38.7%; p = 0.021).

In contradiction to our results, Dupré et al. found inferior overall progression free survival for repeat partial hepatectomy compared to thermal ablation (10.2 versus 4.3 months; p = 0.002).[37] One explanation can be the suboptimal comparison between pathology reports following partial hepatectomy and follow-up imaging exams following ablation. Dupré et al. did not take imaging based on recurrences following plane resections, for presumed R0 resections into account, nor did they compare A0 ablations, based on crosssectional imaging

directly after the procedure, with R0 resections, based on pathology reports. Nonetheless, even if in some centers the LTP rates following ablation are slightly higher than following partial hepatectomy, this does not automatically favor repeat surgery, given the relative ease to repeat thermal ablation and given the fact that it does not result in a worse oncological outcome.[40]

Over the years, multiple improvements in ablative techniques, such as computed tomography hepatic arteriography (CTHA) guidance of percutaneous ablation, and developments in image fusion and navigation systems have resulted in increased tumor visualization with accurate needle tracking and positioning, and reduced complication rates.[41,42] By using image fusion and prediction of peri-ablational safety margins, technical success (A0 ablations) can be established and important prognosticators of LTP—safety margins of at least 5mm, and preferably >10mm—can be achieved.[43-47] All recent and future improvements are ultimately contributing to enhanced local tumor control and LTPFS. The prospect of rapidly improving techniques even further advocates repeat thermal ablation in patients with recurrent CRLM. However, the results of the recent OSLOCOMET randomized controlled trial (RCT) showing advantages of laparoscopic over open resection in complications ($p = 0.021$) and length of hospital stay ($p < 0.001$) should be taken into account.[48]

Strengths of this study were the relatively high number of patients and tumors, which allowed sufficiently powered statistical analyses. Limitations are mainly inherent to the nonrandomized study design, considering that cohort studies are prone to selection bias and confounding. As analysis of OS, DPFS and LTPFS was conducted using Cox proportional hazards regression models, accounting for potential confounders in multivariable analysis, and subgroup analyses were performed to assess heterogeneous treatment effects according to patient, initial and repeat local treatment characteristics, risk of residual confounding is limited. An important limitation is that the MSI, RAS- and BRAF-mutation status were not routinely determined, therefore, these potential confounders could lead to residual bias. The long duration of the study may have caused underreporting of complications in the repeat partial hepatectomy group (11 patients missing), which may explain that no significant difference in complication rate was reported in this study compared to previous series.[37] Furthermore, choice of treatment and patient selection was based on local expertise, determined by multidisciplinary tumor board evaluations, preserving selection bias. In addition, the long study duration with gradual changes in indications for repeat local treatment, could have led to population bias. Nonetheless, no difference in patient characteristics between the two groups was identified. Furthermore, the thermal ablation techniques used in this study do not represent all contemporary, global thermal ablation techniques.

Conclusions

To conclude, in this AmCORE based study repeat partial hepatectomy was not statistically different from repeat thermal ablation with regard to OS, DPFS, LTPFS and complications. Length of hospital stay favored repeat thermal ablation over repeat partial hepatectomy. Thermal ablation should be considered a valid and less invasive alternative to partial hepatectomy for small-size (0–3 cm) recurrent new CRLM, while the eagerly awaited results of the phase III prospective randomized controlled COLLISION trial (*NCT03088150*) should provide definitive answers regarding surgery versus thermal ablation for CRLM.

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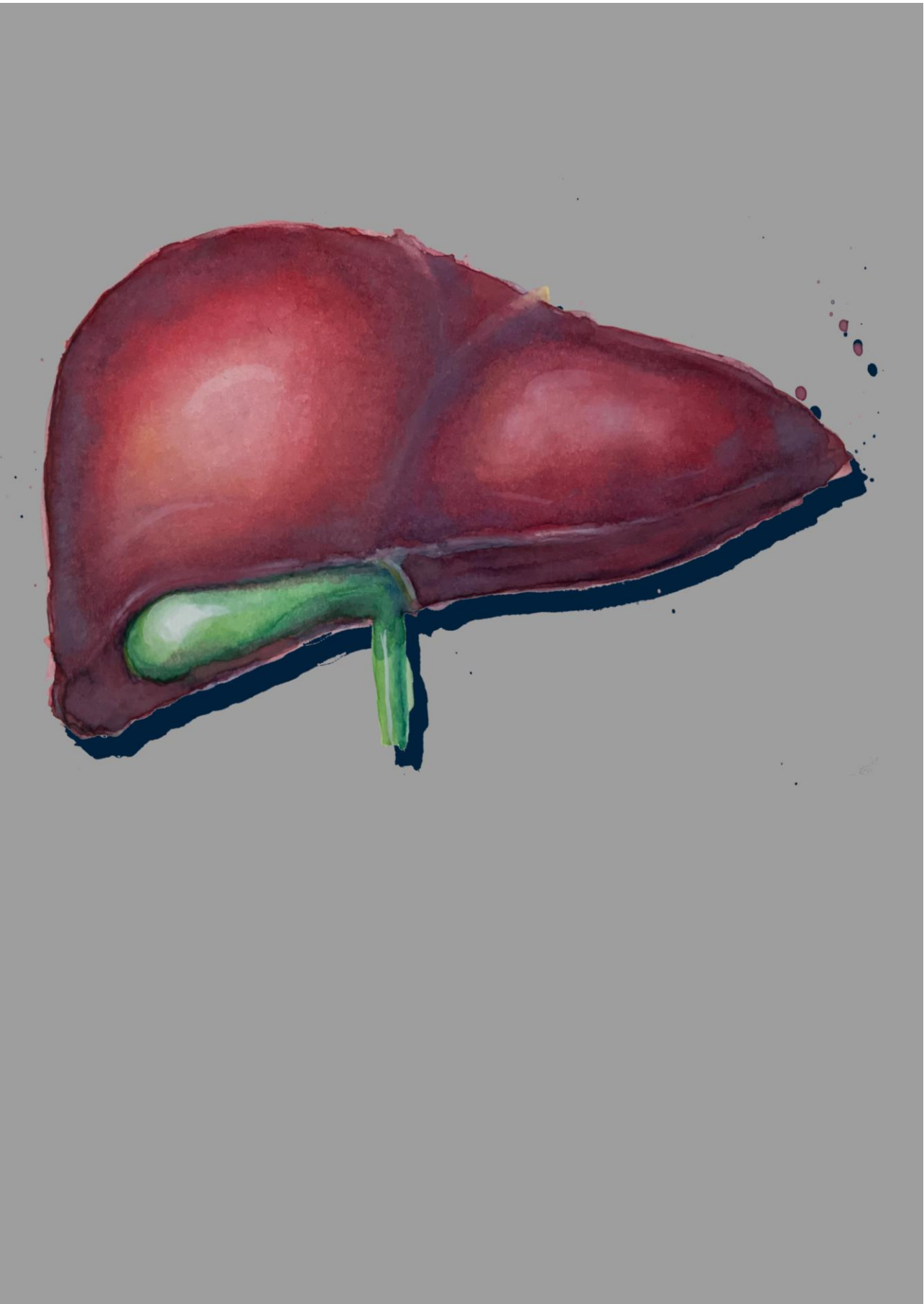

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Minimally invasive interventional techniques to eradicate unresectable, (smaller-size) liver-only metastatic disease from colorectal carcinoma are gaining ground clinically and for some indications, international guidelines have already entirely shifted or are about to shift their recommendations from resection to (percutaneous) radiofrequency (RFA) and microwave (MWA) ablation.[1-6] For patients with colorectal liver metastases (CRLM) who are not amenable for surgical resection, due to (1) an impaired performance status and/or high comorbidity score, (2) a history of extensive abdominal surgery, (3) (loco)regional tumor progression after prior liver surgery, and/or (4) deep-seated anatomically unresectable tumors or deep-seated anatomically resectable limited disease otherwise requiring major resection (parenchyma-sparing), (percutaneous) thermal ablation can offer a safe and effective alternative treatment option (Figure 1).[7,8] Since these limiting factors apply to a substantial percentage of patients with CRLM, thermal ablation has been increasingly studied and used in clinical practice.[9] However, evidence regarding the optimal percutaneous treatment strategy and long-term efficacy of thermal ablation (i.e. RFA and MWA) is still lacking and merely based on non-comparative series including relatively small patient numbers.

In this thesis, the results of a systematic review and meta-analysis comparing the golden standard surgical resection to thermal ablation (**Chapter 3.1**) and the long-term analysis of open and percutaneous ablation procedures (**Chapter 4**) are presented – which have contributed to the set-up of the international phase III 'COLLISION' trial where resection is being challenged by thermal ablation in patients with CRLM (ClinicalTrials.gov number NCT03088150) (**Chapter 8**). Furthermore, two comparative analyses regarding pre- and intraprocedural management are being presented (**Chapter 6** and **7**). Based on the results, we can conclude that long-term oncological outcomes of thermal ablation are promising and that proper anesthetic management and the use of real-time image-guiding features, such as CT hepatic arteriography (CTHA), are safe and effective tools in order to pursue for a potentially curative ablation treatment. Based on the interim analysis of the 'COLLISION' trial, preliminary results indicate that thermal ablation is associated with a superior safety profile, shorter length of hospital stay and higher local control rates – with similar local tumor progression-free (LTPFS) and overall survival (OS) outcomes to date. The next preplanned interim results have to be awaited to be able to formulate further statements.

As an overarching area, this thesis presents the outcomes of an internationally obtained consensus document which contains new guidelines regarding time-to-event endpoint definitions in image-guided tumor ablation (**Chapter 1**).

Several aspects of (percutaneous) thermal ablation procedures need to be addressed to improve oncological outcomes and to further define its role as (first line) treatment option for patients with CRLM.

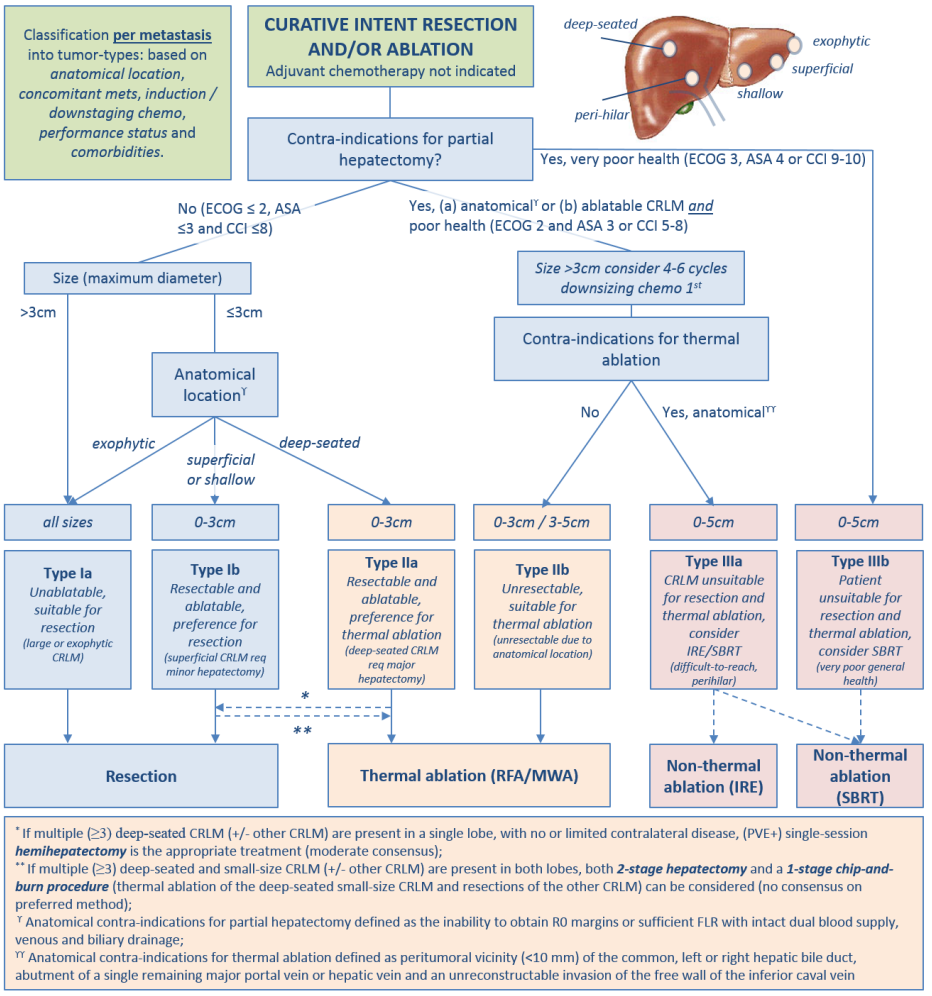

Figure 1. Per-tumor flowchart for the treatment of colorectal liver metastases (CRLM). *Reprinted with permission from Nieuwenhuizen et al.* [48]

One of the elementary difficulties encountered in clinical and scientific practice is the lack of properly defined time-to-event endpoint definitions and how to use and interpret them. Currently, throughout the interventional oncology (IO) literature, survival terms are loosely defined and are often incorrectly used interchangeably. Accurate comparisons between studies are hampered by the heterogeneous and unclear reporting of oncologic outcome parameters, which includes variability in the interpretation and use of time-to-event end point terms and definitions of starting and ending times. The standardization of terminology and reporting criteria by Ahmed and colleagues is seen as the fundament of IO research, although

it only describes a limited amount of endpoints and definitions and does not further explain how to use and read them.[10] The Delphi consensus document demonstrated in **Chapter 1**, shows an extensive framework of key opinion leader recommendations regarding patient-, procedure-, and tumor-related definitions, starting and ending time definitions, survival time definitions, time-to-event end points, and patient-reported outcome measures. Documentation of these clear definitions will provide the necessary foundation for scientific reproducibility between studies as they will ensure an objective and reliable interpretation of results, allow for accurate comparison of outcomes, and avoid misinterpretations. By the adoption of these recommendations we tend to facilitate worldwide communication of scientific advances in the field of IO. Although this document will undoubtedly help researchers and physicians, caution should be taken when studying locoregional interventional treatment options, such as transarterial chemo- or radioembolization (TACE or TARE, respectively), as the recommendations cannot be extrapolated for these kind of therapies.

Elaborating on the previous topic, the most important goals in the management of cancer and subsequently the hardest endpoints in oncology remain OS and quality of life (QoL). [11] However, when it comes to assessing the efficacy of local ablative techniques with or without real-time image-guiding techniques with the (curative) intent to eradicate malignancies, it makes more sense to use LTPFS because technical improvements will first of all reduce the number of repeat procedures which is not necessarily correlated to an improvement in OS, but rather to an improvement in QoL because it reduces the number of patients who require secondary ablative procedures. Nonetheless, when it comes to assess treatment efficacy, one of the obstacles in clinical practice is the absence of feasible intraprocedural endpoints that determine effective and complete ablation. An overview over different intraprocedural endpoints is given in **Chapter 5**. Looking at for example RFA, a precipitous rise in impedance occurs ("roll-off") when tissue necrosis is achieved, as tissue loses its ability to conduct current when is desiccates. This roll-off has been shown to be a significant predictor of local tumor control.[12] MWA is not limited by the conductive property of tissues, so higher frequencies of 915 MHz to 2.45 GHz and therefore higher target temperatures (>150°C) can be achieved and power is automatically adjusted to maintain this temperature for a fixed time. As a result larger ablation zones can be created in shorter times with less susceptibility to heat sink and tissue impedance. Although the manufacturers of RFA and MWA devices recommend preferred system settings, e.g. the temperature development and amount of energy delivery per timeframe (exposure time) as mentioned above, this cannot be the only used endpoints for successful liver tumor ablation. The lack of evidence regarding additional periprocedural factors which might have impact on the treatment outcomes brings us to the issue which subsequent periprocedural factors may contribute to improvement in local treatment efficacy. RFA and MWA systems appeared roughly equally effective for hepatocellular carcinoma and small-size CRLM, as described in previous reports.[13-18] For

CT-guided procedures, anesthetic management is a highly debated topic worldwide as it tends to differ among centers around the globe. Results of our paper in **Chapter 6** undescribed the relevance of anesthesia technique as it showed that, compared to midazolam sedation, propofol reduced the periprocedural perception of anxiety and pain, decreased patient movements and resulted in better control of breathing - probably causing more precise needle placements and tracking with higher ablation accuracy, which is reflected by the superior LTPFS.

Real-time, intraprocedural image-guiding and CT-based imaging directly after the ablation are promising additional factors which may be positively correlated with local efficacy, and are known to reliably visualize the target tumor in relation to surrounding structures, guide needle placement and adjustments, and oversee the created ablation zone. For example, CT hepatic arteriography (CTHA) and CT arterial portography (CTAP) have been previously investigated in diagnostic and therapeutic settings where they were found to have higher detection rates of (additional) lesions and local tumor progressions (LTP).[19] These results were in line with our findings, as presented in **Chapter 7** where we concluded that CTHA might reduce the number of repeat ablations required without adding risk or detrimental effect on survival. Other investigated advantages of intraprocedural, intra-arterial contrast are described in **Chapter 7.2** and **7.3**.

With the results of our systematic review and meta-analysis (**Chapter 3.1**) and comparable work by Van Amerongen and colleagues[20], there are two papers that support the widespread adoption of thermal ablation to treat small unresectable CRLM. The (1) long-term survival results from the EORTC-CLOCC trial (ClinicalTrials.gov no. *NCT00043004*), the (2) comparable survival results after ablation vs. resection for the most recently available comparative series, the (3) comparable survival results after ablation plus resection vs. resection alone, the (4) potential to induce long-term disease control and the (5) low complication rates all argue in favor of thermal ablation over stand-alone chemotherapy.[8,21-25] Now that we have proven the increasing role of thermal ablation, and the fact that further randomized comparisons of curative-intent ablation to chemotherapy alone should be considered unethical, the main shortcoming is the lack of a randomized controlled trial comparing ablation over current standard of care. Currently, surgical resection for resectable CRLM is being challenged by thermal ablation in a large multicenter, international, phase III, randomized controlled 'COLLISION' trial which assesses overall- and disease-free survival, local tumor progression (LTP), primary and secondary technique efficacy (local control), adverse events, QoL and incremental costs (**Chapter 8.1** and **8.2**). In light of the COLLISION's secondary endpoints, the MAVERRIC group from Sweden recently published promising outcomes from their quasi-randomised, multicenter study where MWA was found to be associated with decreased morbidity, hospitalization duration, and healthcare related costs compared to a propensity scored matched surgical cohort.

Besides the COLLISION trial, three other research groups are currently working on similar projects: (1) the ongoing HELARC trial (ClinicalTrials.gov number NCT02886104) from China comparing simultaneous resection of the primary tumor and CRLM with staged resection of the primary tumor and percutaneous thermal ablation of the CRLM, (2) the recently initiated NEW-COMET trial (ClinicalTrials.gov number NCT05129787) from Norway comparing 12-month LTP rates of patients randomly assigned to resection or ablation, and (3) the recently published prospective, observational MAVERRIC cohort (ClinicalTrials.gov number NCT02642185) from the Karolinska Institute in Stockholm, Sweden, comparing patients with 1-5 metastases (<30mm in size) both eligible for stereotactic MWA (study group, n=98 patients) and resection (propensity scored matched controls from the Swedish liver surgery registry - Sweliv, n=158 patients). Results showed similar 3-year survival percentages (78% vs. 76%, respectively) with significantly lower overall and major complication rates after stereotactic MWA ($p < 0.01$) at the cost of more frequent local re-treatments after MWA ($p < 0.01$).

The next pre-planned (50% randomization + 12 months follow-up) interim results of the COLLISION trial and the results of the HELARC and NEW-COMET projects are eagerly awaited.

Future perspectives

Future research, including the ongoing COLLISION trial, should focus on improving local efficacy and investigating the expanding role of thermal ablation in the armory as first line treatment option in patients with smaller-size CRLM, consequently replacing surgical resection as standard of care. For patients with unresectable intermediate-size CRLM (3-5 cm), the multicenter phase II COLLISION-XL trial (ClinicalTrials.gov number *NCT04081168*), comparing thermal ablation to stereotactic body radiation therapy (SBRT), is currently recruiting patients (Figure 2). In light of the high incidence of recurrent liver metastases and to assess the added value of neo-adjuvant chemotherapy in recurrent disease, the COLLISION RELAPSE trial, a phase III randomized controlled trial directly comparing upfront repeat local treatment with neo-adjuvant systemic therapy followed by repeat local treatment, is currently being constructed. Besides clinical trials, there's also need for large and prospective real-life data on effectiveness of thermal ablation. Periprocedural data on MWA is currently being collected in the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Emprint Microwave Ablation Registry (CIEMAR; ClinicalTrials.gov *NCT03775980*).[26] Although preliminary results were being presented at CIRSE2022, future study outcomes must be awaited in order to obtain a complete overview of the safety, duration of hospitalization, treatment success, long-term effectiveness (12-months local tumor control), and overall survival and quality of life data. In January 2023 the last patient will be included in the study. The close out phase is planned for January 2026.

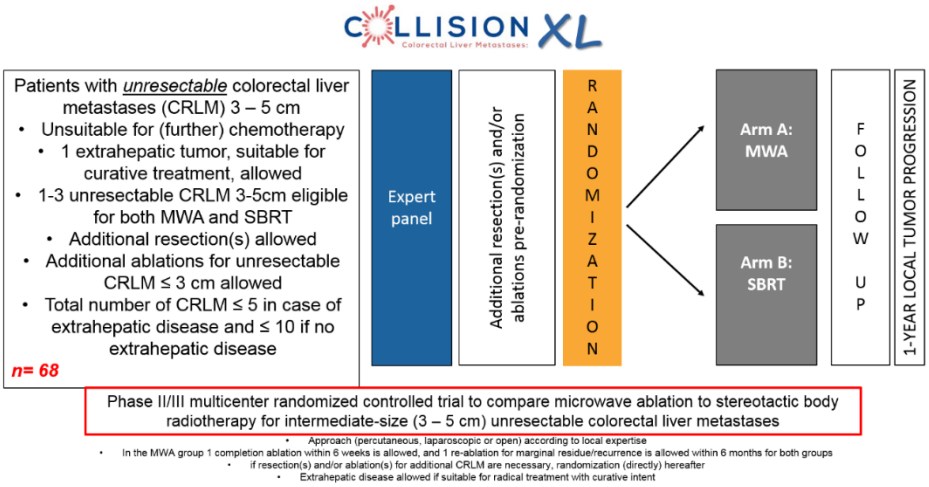

Figure 2. COLLISION XL flowchart. Van der Lei S, et al. CVIR 2023.

Planning, needle placement, real-time image guiding techniques, and ablation zone margin assessment by image fusion

With respect to the ablation procedure itself, high rates of LTP remain a major limitation for widespread acceptance of liver ablation. Insufficient minimal ablation margin (MAM) has been previously linked to treatment failure and LTP. [27] Assessment of ablation margins is crucial to guarantee complete tumour ablation, and margin quantification has gained increasing popularity. Nowadays, more physicians than ever are advocating to use precise 3-dimensional (3D) treatment planning with needle advancement/placement, navigation tools, and real-time image fusion software techniques.[28] With regards to the latter in particular, there are voices to introduce image fusion as the new standard to check your ablation margins.

At first, and in line with our findings, the added value of intrahepatic, intra-arterial contrast agent (CTHA) should get more attention in clinical day practice as neither the SIR Reporting Standards nor the CIRSE Quality Improvement Guidelines mention the use of CTHA as a real-time image guidance technique.[10,29,30] Although this technique comes at the cost of an additional procedure, with higher procedural costs and minimal higher radiation dose, one should realize that better tumour conspicuity leads to more accurate needle placement with superior coagulation necrosis visualization allowing more precise ablation zones, ultimately reducing the number of repeat procedures. The actual method of practice, i.e. hepatic arteriography via CT fluoroscopy or bone beam CT (CB-CT), needs to be investigated in more detail.

Odisio and colleagues are evaluating whether the intra-procedural use of a novel software for ablation confirmation increases the MAM on a 3D CT-generated quantitative (3D-MAM) analysis.[27] In the COVER-ALL trial, 100 patients with CRLM or HCC (≤ 3 tumours, 1 - 5 cm diameter) undergoing MWA or RFA will be randomized between intraprocedural AC assessment using 3D-MAM software (experimental arm) or using visual inspection (control arm). Re-ablation is allowed in both arms. During CIRSE 2022 results of the interim analysis (n=50 patients) demonstrated a mean MAM of 5.87 (experimental arm) and 2.21 mm (control arm), with $p < 0.001$.[31] An MAM of 0 mm was found in 2 vs 12 patients, and an MAM of > 5 mm was found in 18 vs 4 patients, both in favor of the experimental arm. Based on these results, the stopping rule was met and the data safety monitoring board (DSMB) ordered to stop the enrolment of patients in the control arm; currently only patients in the experimental arm are enrolled. Last inclusion is expected in March 2023. The investigators concluded that software for ablation confirmation is imperative and are advocating this should adopted in the standardized treatment strategy.

Intraprocedural assessment of thermal ablation margins using CT co-registration of pre- and post-ablation images is also investigated in patients with BCLC 0-A HCC in the IAMCOMPLETE study from Leiden UMC, the Netherlands.[32] The investigators developed software generated 3D models of the liver, tumour and ablation zone area using segmentation. The software was used to quantify the 3D ablation margins, resulting in a MAM. This study concluded that a feasible and robust workflow was found to perform MAM quantification. This workflow is now further investigated in a multicentre, prospective trial entitled the PROMETHEUS-study, and would be of important value in order to optimize the technical effectiveness and reduce LTP rates.[33]

Not only MWA is being investigated as Bale and colleagues are encouraging the use of RF ablation with stereotactic navigation plus 3D planning, including verification of precise coaxial needle placement by real-time image fusion.[28,34,35] This is thought to enable the interventional radiologist to treat more patients more consistently, with curative intent, minimally invasively, while sparing tissue at the same time. Also 3D volumetric margin assessment might be a predictor of LTP after thermal ablation. These novel tools, including the development of robot-assisted ablation systems, will be investigated and used more frequently in the future and will probably be included in the treatment toolbox for colorectal cancer metastatic disease.

Alternative treatment options for CRLM

As still many patients with CRLM are not amenable to curative-intent surgery or thermal ablation, there is a need for alternative (loco)regional therapies, potentially expanding the curative intent of local therapies for these patients with (oligo) metastatic liver disease. Irreversible electroporation (IRE) has already shown to have an acceptable safety profile and

effective method to eliminate unresectable and thermally unablatable, difficult-to-reach small (≤3 cm) and medium-sized (3-5 cm) liver metastases in the single-arm, phase II clinical COLDFIRE II trial.[36,37] Other alternative techniques have also found their way in the (future) treatment of CRLM. Transarterial chemoembolization (TACE) using Irinotecan-eluting beads is currently being investigated in an observational multicenter study across Europe, called the CIrse REgistry for LifePearl™ microspheres (CIREL).[38] Previously, a good safety profile of irinotecan-TACE was already presented at ESMO and ECIO. To improve the knowledge about early response and long-term effectiveness, results from the investigator-reported and independent central image review and survival data were analyzed and presented at CIRSE 2022.[39] The median OS (13.0 months), median hPFS (6.2 months) and median PFS (4.7 months), as well as the high rate of early disease control are promising.

Sequential lobar Yttrium-90 (Y90) radioembolization (TARE) has shown favorable results in the salvage setting for patients with liver only or liver-dominant metastatic disease, but the role of Y90 in earlier-stage disease has not demonstrated to be as promising up to now.[40] Recently, the final results of the phase-3 randomized 'EPOCH' trial were published showing that the addition of Y-90 glass TARE to systemic therapy led to longer PFS and hPFS in patients with second-line CRLM - who progressed on oxaliplatin- or irinotecan-based first-line therapy.[41] OS did not improve. The authors also concluded that further subset analyses are needed to better define the ideal patient population that would benefit from TARE. In addition, the future perspective of TARE should also focus on radiation segmentectomy, which involves a calculated super selective delivery of high (ablative) Y-90 microspheres to treat oligo metastatic disease involving 1 or 2 liver segments – sparing surrounding normal liver parenchyma.[40] Once radiation-dose thresholds for complete pathologic response are known, the combination with systemic therapy or thermal ablation might be promising for tumors that are too large at first or are in a location considered unsafe for local treatment.

With regards to time-to-event endpoint definitions for locoregional interventional treatment options, such as TACE or TARE, future additional guidelines should provide researchers and physicians with appropriate recommendations.

Immunotherapy and genetic alterations with molecular biomarker analyses

Besides promising novel locoregional treatment options, cancer immunotherapy has achieved great success in a variety of cancer types by reactivating the weakened immune cells of cancer patients.[42] However, despite promising clinical outcomes of several immune checkpoint inhibitors, favorable responses are only observed in a fraction of patients. In metastatic colorectal cancer, evidence regarding the combination of immunotherapy monotherapy / dual therapy and thermal ablation is still limited. As it is with IRE, where a massive amount of immunogenic apoptotic tumor cell remnants (immunogenic cell death) is

being released, the degree of immune response after thermal ablation still needs to be investigated in more detail.[43]

Another direction of future studies is the correlation of treatment effectiveness or survival with genetic alterations. In (metastatic) colorectal cancer there are two commonly known mutated genes: rat sarcoma viral oncogene homolog (RAS) and v-raf murine sarcoma viral oncogene homolog B (BRAF). A third genetic factor that is often being mentioned is microsatellite instability (MSI), which refers to a clonal change in the number of repeated DNA nucleotide units in microsatellites. This tends to arise in CRLM with deficient mismatch repair due to the inactivation of a certain mismatch repair gene. For patients with initially unresectable CRLM and a right-sided or RAS or BRAF(V600E) mutated tumour, or both, results of the recently published CAIRO5 trial opt for doublet systemic induction therapy (FOLFOXIRI + bevacizumab) as optimal treatment strategy, followed by local treatment. Upfront knowledge regarding molecular biomarkers has proven to be useful regarding choice of systemic (induction) therapy, but may also contribute to improved oncological outcomes after percutaneous thermal ablation, as previous studies have shown that RAS and BRAF mutations and MSI are markers of worse oncologic outcomes in these subset of patients.[44-46] These series call for the use of wider ablation margins (≥ 6 mm) to allow for superior local tumor control. Future studies in the field of focal liver therapies should therefore take into account molecular biomarker analyses.

Training program for liver tumor ablation

Viewed from a different angle, another approach to guarantee the quality of thermal ablation in the future is the in 2018 launched International Accreditation System for Interventional Oncology Services (IASIOS), which is based on the Standards of Quality Assurance in Interventional Oncology, a comprehensive quality assurance document developed by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE).[47] The IASIOS initiative looks at the whole process of patient care and treatment and what is required to deliver IO services at a highly effective level. This membership-based accreditation system provides a unique opportunity for medical facilities to gain formal recognition for the IO services offered, either as part of an existing institution or as an independent entity. The formal launch of IASIOS took place in April 2021, and it is now open for enrolment to all qualifying facilities. In line with this, the CIRSE and other related international societies are currently working on a global IO-training program for residents and fellows with the intend to establish the highest standards for patient care and to encourage good practice in IO.

Conclusion

As stand-alone treatment with chemotherapy for unresectable CRLM is proven to be inferior to thermal ablation, the latter has gradually become the standard treatment option to eliminate small unresectable CRLM (≤ 3 cm) and a fair alternative for deep-seated resectable CRLM that would otherwise require major liver surgery. The potential to reduce induce long-term disease control and the low complication rate have had a positive effect on the increased use of thermal liver ablation. Long-term oncological outcomes of open and percutaneous ablation procedures have become significantly better over time, not only due to technological improvements, but also the optimization of periprocedural factors, such as the use of proper anesthetic management with propofol sedation or general anesthesia and the use of real-time image guidance with intra-arterial, intrahepatic contrast agent (CTHA).

In this thesis, more knowledge on the clinical relevance and technical improvements of thermal ablation has been gained. However, as with any promising evolution in the field of clinical oncology, better insights have also led to even more questions to unravel. Patients-specific parameters, for example mutational status, and tumor-specific parameters, for example location, should eventually lead to a personalized treatment where thermal ablation will play a significant role for long-term disease control and overall survival. Periprocedural technical improvements, such as the consequent use of real-time CTHA guidance, should result in improved efficacy of thermal liver ablation. Possibly the greatest potential of thermal ablation is by combining it with new technical advancements, such as real-time stereotactic navigation and robot-assistance and real-time 3D image fusion with ablation confirmation software tools, in order to optimize treatment planning, energy delivery at the tumor site and adequately confirm the required ablation margins. Future advancements like these should undoubtedly result in improved technical success and thereby higher local tumor control.

Besides optimization of periprocedural factors, a sophisticated and internationally accredited training program for residents, fellows and interventional radiologists should eventually improve locoregional treatment outcomes and reduce the number of repeat procedures. In addition, when widespread adoption of the time-to-event endpoint recommendations given in this thesis could be realized, adherence to these consensus guidelines should improve worldwide communication of scientific advances in the entire field of interventional oncology research and clinical practice.

Ultimately, if the hypothesis and the interim results of the COLLISION trial are being confirmed by the final trial results, thermal ablation will play an even more dominant role in the treatment of colorectal liver metastases and international practical guidelines are forced to revise the current standard of care. At that moment, the question should not be “partial hepatectomy or thermal ablation for CRLM”, but rather in what formula both local treatment options can strengthen each other, and can contribute to a multidisciplinary toolbox of therapeutic options with which a personalized, patient-specific treatment plan can be

composed to pursue the most favorable oncological outcomes with the highest quality of life. Until then, thermal ablation should be reserved for patients with small-size, unresectable liver metastases or deep-seated resectable tumors.

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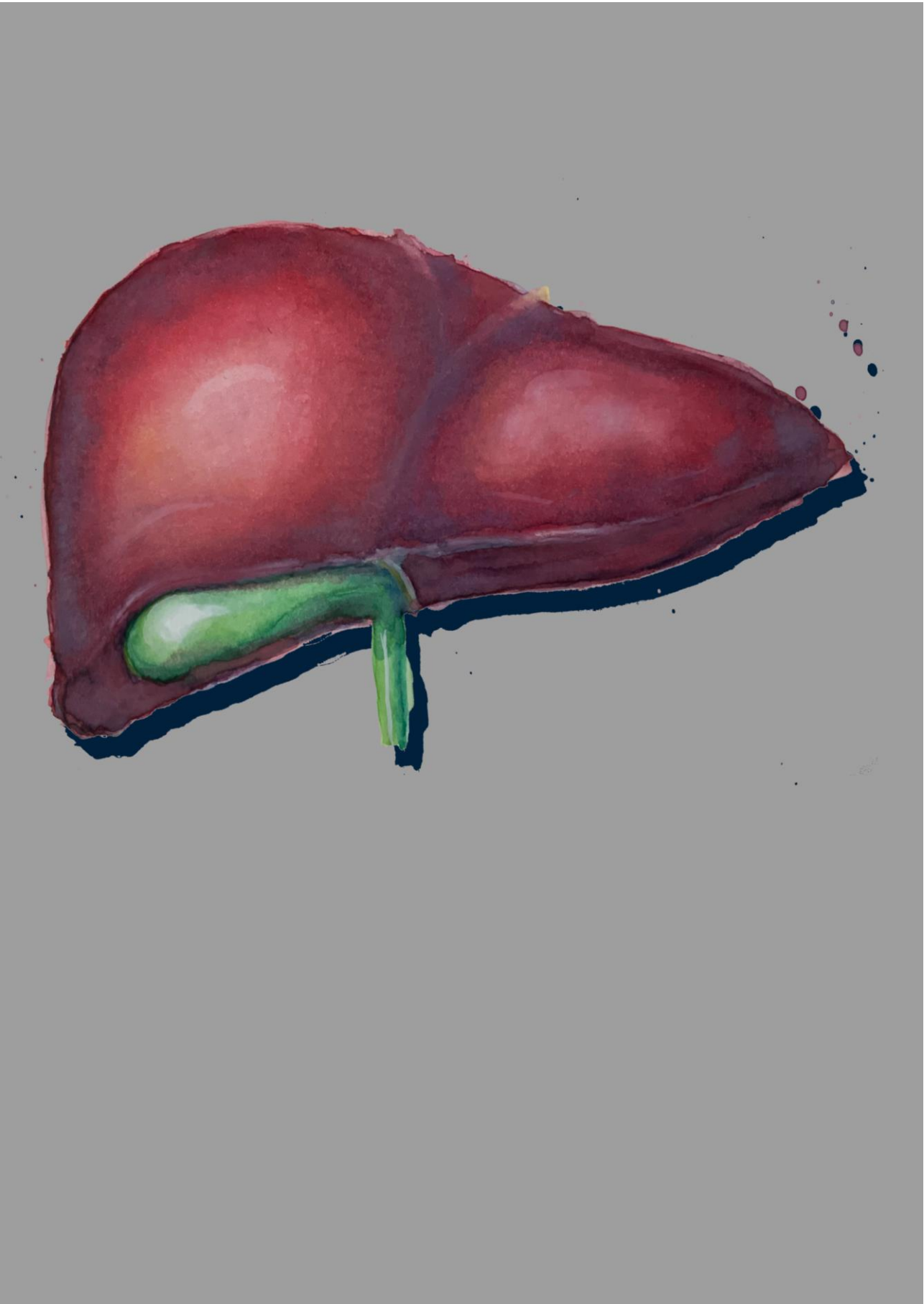


SUMMARY

Interventional oncology (IO) is the youngest offshoot of interventional radiology and the most rapidly growing subspecialty in clinical oncology and health care in general. It has successfully established itself as an essential and independent (fourth) pillar within the firmament of multidisciplinary oncologic care, alongside the three established pillars medical oncology, surgery and radiation oncology. Over the years, multiple locoregional treatment modalities have been added to the toolbox of IO physicians. Especially targeted minimally invasive image-guided tumor ablation, otherwise known as radiofrequency ablation (RFA) or microwave ablation (MWA), has proven to be highly effective against primary as well as metastatic disease throughout the body. Their success is chiefly based on the minimally invasive nature, superior safety and toxicity profile, repeatability and often comparable or superior mid- and long-term oncologic outcomes, compared with conventional systemic therapy and surgical resection. Nowadays, these heat-based ablation techniques are recommended curative-intent treatment options for a variety of cancer types, including colorectal liver metastases (CRLM) and hepatocellular carcinoma (HCC). To date, despite the gradual worldwide adoption of thermal ablation, safe and effective characteristics, and similar survival outcomes after partial hepatectomy, medical oncology related societies generally state that thermal ablation should only be reserved for patients who are not amenable for surgery, due to an impaired general health status and/or high comorbidity score, a history of extensive abdominal surgery, (loco)regional tumor progression after prior liver surgery, and/or deep-seated anatomically unresectable tumors or deep-seated anatomically resectable limited disease otherwise requiring major surgery (parenchyma-sparing). For thermal ablation to be considered a fair alternative treatment option for resectable disease, studies directly comparing surgery to thermal ablation need to be finished first.

The search towards further optimization of periprocedural management, mainly for the less invasive percutaneous approach, has led to the setup of several comparative cohort studies with the intent to improve long-term oncological outcomes. The results of the local effectiveness of thermal ablation trend over time, anesthetic management, and added value of real-time image guiding techniques are presented in this thesis. Furthermore, the setup of the COLLISION trial, comparing surgical resection to thermal ablation for curative-intent treatable small-size (≤3 cm) CRLM, is documented with the intent to explore the potential of ablation to replace resection as standard of care. As an overarching theme, the first part of this thesis presented new consensus guidelines with a range of oncological outcome related recommendations and time-to-event endpoint definitions in the field of image-guided tumor ablation.

Chapter 1. Standardized definitions of time-to-event end points in image-guided tumor ablation

Within oncological research standardization of preferred clinical outcome measures and clear definitions of oncologic end points and how to uniformly document, analyze, and report outcomes is crucial in order to allow for accurate comparisons of study results and avoid misinterpretations. Throughout the interventional oncology literature, survival-related terms are loosely defined and are often incorrectly used interchangeably. Accurate comparisons between studies are hampered by the heterogeneous and unclear reporting of oncologic outcome parameters, which includes variability in the interpretation and use of time-to-event end point terms and definitions of starting and ending times. To overcome this issue, **Chapter 1** of this thesis covers a consensus document proposing standardized definitions for a broad range of oncologic outcome measures in the clinical and scientific field of image-guided tumor ablation - based on key expert's opinions of the Society of Interventional Oncology (SIO) in collaboration with the Definition for the Assessment of Time-to-Event End Points in Cancer Trials (DATECAN). The document addresses recommendations on how to consistently document, analyze, and report study outcomes as well as when to assess outcomes per patient, per session, or per tumor. Furthermore, recommendations were given regarding definitions of starting and ending time, survival time, and time-to-event end points in retrospective and prospective studies and randomized clinical trials. The guidelines were developed to facilitate a clear interpretation of results and to standardize worldwide communication among researchers and clinicians.

An editorial by Robert P. Liddell, assistant professor at Johns Hopkins University School of Medicine (Baltimore, US), is added to the appendices.

Chapter 2. Colorectal liver metastases: resectability and ablatability criteria

The guidelines for metastatic colorectal cancer crudely state that the best local treatment option should be selected from a 'toolbox' of techniques according to patient- and treatment-related factors. In **Chapter 2** an interdisciplinary, consensus-based algorithm with specific per patient and per tumor resectability and ablatability criteria for the treatment of CRLM is being discussed. Consensus was based on key expert opinions from the multidisciplinary COLLISION and COLDFIRE trial expert panels. The panelists discussed statements regarding patient-, disease-, tumor- and treatment-related characteristics. They agreed that patients with ECOG≤2, ASA≤3 and Charlson's comorbidity index ≤8 should be considered fit for curative-intent local therapy. When easily resectable and/or ablatable (stage-IVa), (neo-)adjuvant systemic therapy is not indicated. When requiring major hepatectomy (stage-IVb), neo-adjuvant systemic therapy is appropriate for early metachronous disease and to reduce procedural risk. To downstage patients (stage-IVc), downsizing induction systemic

therapy and/or future liver remnant 3-dimensional augmentation is advised. Disease can only be deemed permanently unsuitable for local therapy if downstaging failed (stage-IVd). Liver resection remains the standard of care. Thermal ablation is reserved for unresectable CRLM, deep-seated resectable CRLM and can be considered when patients are in poor medical condition. Irreversible electroporation (IRE) and stereotactic body radiation therapy (SBRT) can be considered for unresectable perihilar and perivascular intermediate-size (0-5 cm) CRLM. These given criteria are intended to assist tumor board discussions, improve consistency when designing prospective trials and advance intersociety communications. Areas where consensus is lacking warrant future comparative studies.

Chapter 3. Colorectal liver metastases: current treatment status

With the rapidly evolving field of minimally invasive image-guided local therapies, the evidence regarding safety and effectiveness for RFA and MWA in the treatment of CRLM and the current clinical status of thermal ablation in international guidelines had to be sorted out first. In **Chapter 3.1** the current position of systemic chemotherapy, thermal ablation (RFA and MWA) and partial hepatectomy is being reported by means of a systematic review and meta-analysis. This study was commissioned by the Dutch National Health Care Institute (ZiNL), and the Dutch societies for interventional radiology (NVIR), surgery (NVvH) and medical oncology (NVMO), and executed in cooperation with the independent ME-TA (Medical Evaluation and Technology Assessment) bureau. Forty-eight studies and 13 guidelines were evaluated. In general, literature to assess the effectiveness of ablation was limited. RFA + systemic chemotherapy was superior to chemotherapy alone. Resection was superior to RFA alone but not to RFA + resection or to MWA alone. Compared to resection, RFA showed fewer complications, MWA did not. Outcomes were subject to residual confounding since ablation was only employed for unresectable disease. The combination of results from the EORTC-CLOCC trial, the comparable survival rates for ablation + resection versus resection alone, the potential to induce long-term local disease control and the low complication, all rate argue in favor of ablation over chemotherapy alone. Therefore, further randomized comparisons of ablation to chemotherapy alone should be considered unethical. Hence, the highest achievable level of evidence for unresectable disease seems reached. The apparent selection bias from the available studies and the superior safety profile of thermal ablation mandate the setup of randomized controlled trials comparing ablation to the golden standard treatment, surgical resection.

An editorial by Klaus A. Hausegger, professor at Klinikum-Klagenfurt am Wörthersee (AT), and CVIR Editor-in-Chief, is added to the appendices.

Chapter 3.2 covers a systematic literature overview for the preferred local treatment option for intermediate-size (3-5 cm) unresectable CRLM as treatment efficacy is known to decrease

exponentially with increasing tumor size. Literature to assess effectiveness of thermal ablation, irreversible electroporation (IRE) and stereotactic ablative body radiotherapy (SABR) was limited with no comparative studies or randomized trials available and there was substantial heterogeneity in outcomes and study populations. Per-patient local control ranged 22-90% for all techniques; 22-89% (8 series) for thermal ablation, 44% (1 series) for IRE, and 67-90% (1 series) for SABR depending on radiation dose. Focal ablative therapy is safe and can induce long-term disease control, even for intermediate-size CRLM. Although SABR and tumor-bracketing techniques such as IRE are suggested to be less susceptible to size, evidence to support any claims of superiority of one technique over the other is unsubstantiated by the available evidence. Future prospective comparative studies should address local tumor progression-free survival (LTPFS), local control (LC) rate, overall survival (OS), adverse events (AE), and quality-of-life (QoL).

Chapter 4. Colorectal liver metastases: long-term oncological outcomes of thermal ablation

As mentioned earlier, thermal ablation has proven to be highly effective in eradication of primary and secondary liver tumors. Nowadays, heat-based ablation techniques have been gradually accepted as first-choice or alternative treatment modality in international guidelines for liver malignancies. However, in general, oncological outcomes after thermal ablation of CRLM differ substantially among semi-recently published papers and evidence regarding the potential improvement of technical success over time, in terms of local control and time-to-local tumor progression, is lacking.

In **Chapter 4.1** the results of an Amsterdam Colorectal Liver Met Registry (AmCORE) based comparative study are given – aiming to analyze long-term oncological (survival) outcomes following open and percutaneous thermal liver ablation in patients treated for CRLM over the last 10 years. A total of 329 patients were included who underwent 541 procedures for 1350 tumors from January 2010 to February 2021. To evaluate the potential improvement of oncological outcomes over time, 3 cohorts were formed: initial procedures performed between 2010 - 2013, 2014 – 2017 and 2018 – 2021. Results revealed that LTPFS improved significantly over time for percutaneous ablations (2-year LTPFS 37.7% [2010-2013] vs. 69.0% [2014-2017] vs. 86.3% [2018-2021], $P < .0001$), while LTPFS for open ablations remained reasonably stable (2-year LTPFS 87.1% vs. 92.7% vs. 90.2%, respectively, $P = .12$). In the latter cohort (2018-2021), the open approach was no longer superior to the percutaneous approach regarding LTPFS ($P = .125$). No differences between the three cohorts were found regarding OS ($P = .088$), length of hospital stay (open approach, $P = .065$; percutaneous approach, $P = .054$), and rate and severity of complications ($P = .404$). The rate and severity of complications favored the percutaneous approach in all three cohorts ($P = .002$). As a result, the efficacy of percutaneous ablations has improved remarkably for the

treatment of CRLM over the last decade and oncological outcomes after percutaneous ablation seem to have reached results following open ablation. Given its minimal invasive character and shorter length of hospital stay, whenever feasible, percutaneous procedures may be favored over an open approach.

Chapter 5. Percutaneous liver tumor ablation: image guidance, endpoint assessment, and quality control

RFA and MWA are the most widely adopted local ablative methods for treat primary and secondary liver malignancies, although novel techniques, such as IRE and SBRT, are quickly working their way up to become routine treatment options. Especially the percutaneous approach is rapidly gaining popularity because of its minimally invasive character, low complication rate, acceptable efficacy rate, and repeatability. The major issue regarding the percutaneous approach is the relative high rate of local tumor progressions (LTP) when matched to open, laparoscopic or robot-assisted resection and open ablations. The exact reason remains unresolved and necessitates further improvement. **Chapter 5.1** provides an overview of several real-time image-guiding and needle navigation modalities for percutaneous liver tumor ablation that are available to improve tumor visibility, detect surrounding critical vascular and biliary structures, guide applicators, monitor treatment effect, and, if necessary, adapt or repeat energy delivery. Known predictors for technical success are tumor size, location, lesion conspicuity, tumor-free margin, and operator experience – which are described in detail in this chapter. In addition, and in line with the most desired aim of each ablation procedure, potential treatment endpoints are evaluated as the implementation of reliable technical endpoints to assess treatment efficacy allows for completion-procedures, either within the same session or within a couple of weeks after the procedure. And although the effect on OS may be trivial, LTPFS will indisputably improve with the implementation of reliable postprocedural endpoints. At the end of this article a clinical algorithm for intra- and postprocedural quality control is proposed to as a guide to interventional oncologists.

Chapter 6. Anesthetic management

As discussed in the previous chapter, periprocedural factors go hand in hand with local disease control. As such, periprocedural pain, unrest and respiratory concerns can be detrimental to achieve a safe and efficacious ablation and impair treatment outcome. In **Chapter 6** the association between anesthetic technique and local disease control is being investigated in patients undergoing percutaneous MWA of CRLM or HCC. Ninety patients, who underwent 114 procedures (22 procedures under general anesthesia; 32 conscious sedation by midazolam/fentanyl; and 60 under propofol sedation) for 171 liver tumors (n =

136 CRLM; n = 35 HCC) were included and analyzed. Date of the first ablation procedure was from January 2013 until September 2018. Results showed that propofol sedation and general anesthesia were superior to midazolam/fentanyl sedation regarding LTPFS (4/94 [4.3%] vs. 19/42 [45.2%] vs. 2/35 [5.7%]; P < 0.001, respectively). Overall LTP rate was 14.6% (25/171). Eighteen tumors (72.0%) were retreated by ablation. Of them, 14 (78%) were previously treated with midazolam. Propofol versus midazolam/fentanyl (P < 0.001), general anesthesia versus midazolam/fentanyl (P = 0.016), direct postprocedural visual analog pain score above 5 (P = 0.050) and more than one treated tumor per procedure (P = 0.045) were associated with LTPFS. Multivariate analysis revealed that propofol versus midazolam/fentanyl (HR 7.94 [95% CI 0.04-0.39; P < 0.001]) and general anesthesia versus midazolam/fentanyl (HR 6.33 [95% CI 0.04-0.69; P = 0.014]) were significantly associated with LTPFS. Pain during and directly after treatment was significantly worse in patients who received midazolam sedation (P < 0.001). In other words, midazolam/fentanyl sedation was associated with an increased periprocedural perception of pain and lower LTPFS compared to propofol sedation and general anesthesia. Therefore one should strive to use general anesthesia or propofol sedation over midazolam/fentanyl sedation in order to reduce the number of incomplete ablations and repeat procedures required to fully eradicate hepatic malignancies.

Chapter 7. Real-time image guidance

Reliable visualization of the target tumor in relation to surrounding vascular and biliary structures, the needle placement and adjustments, and the created ablation zone are crucial to reduce LTP rates and avoid repeated treatments. Real-time, intraprocedural image-guiding and CT-based imaging directly after the ablation are promising additional factors which may be positively correlated with local efficacy. In **Chapter 7.1** safety and local disease control outcomes of the AmCORE-based comparison of CT hepatic arteriography (CTHA) and conventional CT fluoroscopy guidance in percutaneous liver tumor ablation procedures are given. In case of CTHA-guided procedures repeated small amounts of contrast agent (40 cc of 1:1 mixed bolus of contrast and saline at 5 mL/s) is administered directly in the common hepatic artery, via an intra-arterial catheter which is introduced in the common femoral artery just prior to the procedure. CT imaging in the arterial phase or mixed late arterial to early portal venous phase tend to show typical ring-enhancing nodules representing the tumor. Data of 108 patients who underwent 156 percutaneous ablation procedures (n = 42 CT fluoroscopy guided [25 RFA vs. 17 MWA] and n = 114 CTHA-guided [18 RFA, 96 MWA]) for 260 CRLM between January 2009 and May 2019. There were no complications related to the transarterial catheter procedure. CTHA proved superior to CT fluoroscopy regarding 2-year LTPFS (18/202 [8.9%] vs 19/58 [32.8%]; P < .001, respectively). CTHA vs. CT fluoroscopy (hazard ratio = 0.28; 95% confidence interval, 0.15–0.54; P < .001) and MWA

vs. RFA (hazard ratio = 0.52; 95% confidence interval, 0.24–1.12; P = .094) were positive predictors for longer LTPFS. Multivariate analysis revealed that CTHA vs. CT fluoroscopy (hazard ratio = 0.41; 95% confidence interval, 0.19–0.90; P = .025) was associated with a significantly superior LTPFS. OS was similar (P = .3). These results underline the importance of clear tumor and ablation zone visualization as CTHA–guided procedures reduces the number of repeat ablations required without adding risk or detrimental effect on survival. This comes at the cost of adding procedure time and marginal patient burden.

The added value of CTHA guidance is further highlighted in **Chapter 7.2** by means of clinical illustrations. Several cases are summed-up showing the ability of CTHA to improve detectability of the liver tumor, detect additional tumors intraprocedurally, identify surrounding critical vascular structures, detect vanished tumors after induction chemotherapy, differentiate LTP from non-enhancing scar tissue, and to promptly detect and respond to iatrogenic liver hemorrhage.

Another historical AmCORE-based cohort study, presented in **Chapter 7.3**, showed that the subsequent use of CTHA has added value for the detection of previously unknown and vanished CRLM. Taking into account the low number of false positives (7%) and the favorable safety profile of percutaneous ablation, the authors believe that immediate ablation of typical ring-enhancing supplementary tumours is justified and sufficiently validated.

Chapter 8. Surgery versus ablation for colorectal liver metastases.

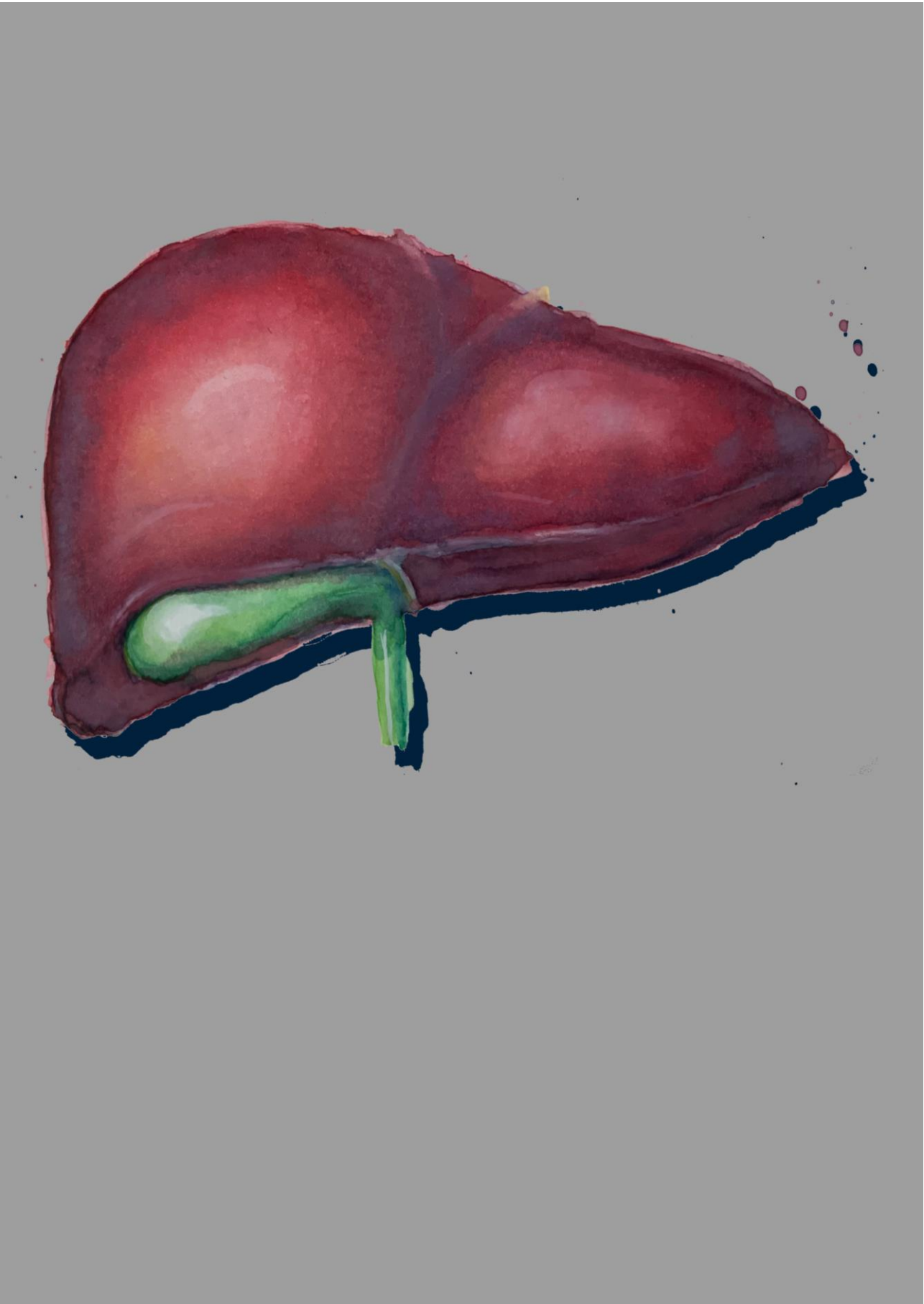
The current standard to treat resectable CRLM is surgical resection. Guidelines reserve thermal ablation for anatomically unresectable metastases and for patients whose comorbidities disqualify them as surgical candidates. Given a presumed superior safety profile, comparable local control and competitive survival outcome, thermal ablation and surgical resection have reached equipoise for small-size resectable CRLM. Therefore, further investigation is necessary with regards to the potential implementation of thermal liver ablation in clinical day practical guidelines. At the moment, resection is being challenged by thermal ablation for small-size (≤3 cm) resectable CRLM in the large international, phase-3, randomized 'COLLISION' trial (ClinicalTrials.gov, NCT03088150. The design and study protocol are presented in **Chapter 8.1**. The trial will explore potential non-inferiority of thermal ablation compared to resection. Patients with at least 1 resectable and ablatable CRLM (≤3cm, also known as target tumor), up to 10 metastases, a good performance status, no extrahepatic disease and no prior liver treatment are considered eligible. Patients are stratified into low-, intermediate- and high-disease burden subgroups and randomly assigned (1:1) to undergo resection (control arm) or thermal ablation. The primary endpoint is overall survival, according to an intention-to-treat analysis. Secondary endpoints are AE rates,

mortality, LTPFS, LC allowing repeat treatments, distant progression-free survival, length of hospital stay and assessment of quality of life and cost-effectiveness.

The results of the first pre-planned interim analysis of the COLLISION trial (30% randomization, n = 200 randomized patients) are presented in **Chapter 8.2**. [redacted]

Chapter 8.3 and **8.4** underline the clinical relevance and necessity of this time-honored question: *''thermal ablation or surgery for colorectal liver metastases?''*.

In line with the objective of Chapter 8, **Chapter 8.5** shows a comparison of repeat thermal ablation and repeat surgical resection in 136 patients with recurrent CRLM. Data was obtained from the AmCORE database with the intent to assess for safety, efficacy and survival outcomes of the two treatment options concerned. A total of 224 tumors (170 thermal ablation, 54 partial hepatectomy) were analyzed. In the crude overall comparison, OS of the two cohorts was found to be similar ($p = 0.927$). The 1-, 3- and 5-year OS were 98.9%, 62.6% and 42.3% respectively for the thermal ablation group and 93.8%, 74.5% and 49.3% for the repeat resection group. No differences in DPFS ($p = 0.942$), LTPFS ($p = 0.397$) and complication rate ($p = 0.063$) were found. Mean length of hospital stay was 2.1 days in the repeat thermal ablation group and 4.8 days in the repeat partial hepatectomy group ($p = 0.009$). Based on these results, repeat thermal ablation should be considered a valid and potentially less invasive alternative for small-size ($\leq$3 cm) CRLM in the treatment of recurrent new CRLM.



SAMENVATTING

Interventionele oncologie is de meest recente afsplitsing van de interventieradiologie en het snelst groeiende vakgebied binnen de medische oncologie en de gehele gezondheidszorg. Het heeft zichzelf in korte tijd ontwikkeld tot een essentiële en onafhankelijke (vierde) pilaar in de oncologische zorg, naast de drie gevestigde pilaren medische oncologie, chirurgie en radiotherapie. Gedurende laatste decennia zijn er meerdere locoregionale behandelopties toegevoegd aan de 'toolbox' van interventieradiologen. Vooral de zogeheten beeldgestuurde, minimaal invasieve lokale behandeltechnieken, beter bekend als radiofrequente ablatie (RFA) en microwave ablatie (MWA), zijn uiterst effectief gebleken in de strijd tegen allerlei soorten primaire en secundaire tumoren in het lichaam. Deze technieken zijn gebaseerd op het inbrengen van een naald direct in de tumor waarna het apparaat de tumor tot een dusdanige temperatuur verhit (vandaar de term 'thermale') dat de cellen doodgaan (Figuur 1). De opkomst en implementatie van minimaal invasieve beeldgestuurde tumor ablatie heeft ervoor gezorgd dat er veel meer keuze is om een bepaalde primaire tumor of metastase effectief te behandelen. Hierbij is de lever het meest onderzochte orgaan waarin thermale ablatie op dit moment wordt toegepast - daar zijn de artikelen in dit proefschrift dan ook op gebaseerd.

Het succes van deze thermale lever ablatie zit hem in het minimaal invasieve karakter, superieure veiligheid ten opzichte van andere behandelingen, mogelijkheid om relatief makkelijk nog een keer te behandelen en vergelijkbare oncologische uitkomsten op de mid- en lange termijn ten opzichte van de meest gebruikte vormen van behandeling – chemotherapie en chirurgie. Tegenwoordig worden deze op hitte gebaseerde technieken al aanbevolen in de richtlijnen als curatieve behandeloptie voor verschillende soorten leverkanker, dat wil zeggen niet weg te snijden levermetastasen van darmkanker (colorectale levermetastasen – CRLM) en kleine primaire levertumoren (hepatocellulair carcinoom – HCC). Op dit moment zijn, ondanks de wereldwijde adoptie, bewezen veiligheid en effectiviteit van thermale ablatie, de medische oncologie gerelateerde verenigingen nog steeds van mening dat thermale ablatie alleen gebruikt dient te worden bij patiënten die niet in aanmerking komen voor de eerste keus behandeling (chirurgische resectie). Reden om ablatie te verkiezen boven resectie kan zijn een slechte algehele conditie van de patiënt, eerdere uitgebreide buikoperaties, recidief tumorweefsel na eerdere leveroperatie, en/of voor tumoren die te diep in de lever liggen waardoor anders een grote leveroperatie nodig zal zijn. Om thermale ablatie voor CRLM toe te kunnen passen, zullen studies die de standaard chirurgische behandeling vergelijken met ablatie eerst een positief resultaat moeten laten zien in de toekomst.

Verdere optimalisatie van verschillende factoren rondom een thermale ablatie procedure is essentieel om zo de lange termijn uitkomsten van de behandeling te kunnen verbeteren. Dit is op een adequate manier te onderzoeken door verschillende factoren met elkaar te vergelijken in retrospectieve/prospectieve cohort studies. In dit proefschrift worden o.a. studieresultaten gepresenteerd van de lange termijn uitkomsten na thermale ablatie, voorkeur

voor anesthesie techniek, en de toegevoegde waarde van technische hulpmiddelen tijdens een (percutane) procedure. Daarnaast wordt de studie opzet van de COLLISION studie gedeeld – een internationale studie waar de standaard behandeling (resectie) wordt vergeleken met thermale ablatie voor kleine (≤3 cm) levermetastasen van dikke darmkanker. Resultaten van deze studie kunnen uiteindelijk een verschuiving in eerste keus therapie teweegbrengen met als doel de beste therapeutische optie te kunnen bieden voor de patiënt. Als overkoepelend thema wordt in het eerste gedeelte van dit proefschrift een nieuwe richtlijn gepresenteerd met daarin aanbevelingen op het gebied van onderzoek gerelateerde uitkomstmaten binnen het vakgebied beeldgestuurde tumor ablatie.

Hoofdstuk 1. Standaardisatie van uitkomstmaten in beeldgestuurde tumor ablatie

Standaardisatie van uitkomstmaten en het voorhanden hebben van duidelijke definities van eindpunten en hoe deze te documenten, analyseren en rapporten zijn cruciaal voor medisch oncologisch onderzoek - met name om studieresultaten met elkaar te kunnen vergelijken en misinterpretaties te voorkomen. Binnen de interventionele oncologische literatuur worden veel verschillende eindpunten en 'survival' definities door elkaar gebruikt omdat de betekenis en het gebruik niet goed omschreven zijn. Om dit probleem op te lossen wordt in **Hoofdstuk 1** een consensus document gepresenteerd dat gestandaardiseerde definities weergeeft voor een breed scala aan oncologische eindpunten – gebaseerd op de expertise van leden van de 'Society of Interventional Oncology (SIO)' in samenwerkingen met experts van 'the Definition for the Assessment of Time-to-Event End Points in Cancer Trials (DATECAN)' groep. Dit document bevat richtlijnen met aanbevelingen hoe men op een consistente manier studieresultaten zou moeten documenteren, analyseren en rapporteren en of dit dient te gebeuren door data per patiënt, per procedure, per tumor of een combinatie daarvan te onderzoeken. Al de aanbevelingen kunnen worden toegepast in retrospectieve, prospectieve en gerandomiseerde studies. Met het toepassen van deze richtlijnen zal de interpretatie van studieresultaten makkelijker worden, wat uiteindelijk zal moeten leiden tot een betere wereldwijde communicatie tussen onderzoekers en ander medisch personeel.

Er is een editorial van Robert P. Liddell, professor van Johns Hopkins Universiteit (Baltimore, VS), toegevoegd als bijlage aan het proefschrift.

Hoofdstuk 2. Colorectale lever metastasen: criteria voor resectabiliteit en ableerbaarheid

De huidige (inter)nationale richtlijnen voor uitgezaaide darmkanker stellen dat de beste lokale behandeloptie moet worden geselecteerd uit een 'toolbox' van technieken afhankelijk

van patiënt en behandeling gerelateerde factoren. In **Hoofdstuk 2** wordt een interdisciplinair, op consensus gebaseerd algoritme gepresenteerd met patiënt- en tumor-specifieke criteria voor resectabiliteit en ableerbaarheid van de behandeling van CRLM. Consensus kwam tot stand door meningen en stellingen samen te voegen van diverse experts binnen de multidisciplinaire COLLISION en COLDFIRE 'expert panels'. Er werd stelling genomen dat patiënten met een ECOG score ≤2, ASA ≤3 en Charlson's CI ≤8 moeten worden beschouwd als fit genoeg voor een curatieve lokale behandeling. Daarnaast zijn er voor elk ziektestadium diverse aanbevelingen toegevoegd. Zo adviseert men voor relatief eenvoudig lokaal te behandelen ziekte (stadium IVa) geen (neo-)adjuvante chemotherapie te geven. Wanneer uitgebreidere leverchirurgie vereist is (stadium IVb) is neo-adjuvante chemotherapie gerechtvaardigd bij vroeg metachrone ziekte en om peroperatieve risico's te beperken. 'Downstaging', het verkleinen van de tumorload middels chemotherapie, wordt geadviseerd bij patiënten met stadium IVc ziekte. Alleen wanneer dit 'downstagen' niet lukt kunnen patiënten worden beschouwd als permanent niet lokaal behandelbaar (stadium IVd). Leverchirurgie blijft vooralsnog de eerste keuze als het gaat om lokaal behandelbare CRLM. Thermale ablatie wordt geschikt bevonden voor niet-resectabele CRLM, diep gelokaliseerde resectabele tumoren, en voor patiënten met een slechte algehele conditie. Alternatieven zoals irreversibele elektroporatie (IRE) en stereotactische bestraling (SBRT) kunnen worden overwogen voor niet-resectabele CRLM (intermediate-size, 0-5 cm) die dicht tegen de galwegen of bloedvaten aanliggen. Al deze aanbevelingen zijn bedoeld als houvast in de besluitvorming tijdens een multidisciplinaire bespreking, consistentie bij het opzetten van een nieuwe studie en het bevorderen van intercollegiaal overleg.

Hoofdstuk 3. Colorectale levermetastasen: huidige behandelopties

De snelle ontwikkeling binnen de minimaal invasieve beeldgestuurde lokale behandelingen vraagt om periodieke bewijsvoering van veiligheid en effectiviteit van RFA en MWA en de huidige positie van deze technieken in de internationale richtlijnen. **Hoofdstuk 3.1** geeft een overzicht van verschillende behandelopties, chemotherapie, thermale ablatie en resectie, in het behandelarsenaal voor patiënten met CRLM. Deze meta-analyse is uitgevoerd in opdracht van het Zorginstituut Nederland (ZiNL), en de Nederlandse verenigingen voor interventieradiologie (NVIR), chirurgie (NVvH), en medische oncologie (NVMO) en in samenwerking met het onafhankelijke Belgische bureau ME-TA (Medical Evaluation and Technology Assessment). In totaal werden 48 studies en 13 internationale richtlijnen geëvalueerd waarbij gezegd moet worden dat over het algemeen de literatuur naar effectiviteit van thermale ablatie schaars was. RFA + systemische chemotherapie was superieur vergeleken met alleen chemotherapie. Resectie was superieur vergeleken met alleen RFA, maar niet vergeleken met RFA + resectie of met alleen MWA. Vergeleken met resectie liet RFA minder complicaties zien maar MWA niet. Uitkomsten werden beïnvloed

door ‘residual confouding’ omdat thermale ablatie alleen toegepast werd bij niet-resectabele ziekte. De uiteindelijke combinatie van de resultaten van de EORTC-CLOCC trial, de vergelijkbare overlevingscijfers voor ablatie + resectie versus alleen resectie, de potentie om langdurige lokale controle over de ziekte te verkrijgen en lage risico’s pleiten allemaal voor het gebruik van thermale ablatie in tegenstelling tot alleen systemische chemotherapie. Om die reden wordt een verdere vergelijking tussen ablatie en chemotherapie als niet ethisch verantwoord beschouwd. Dit maakt dat het hoogst haalbare niveau van wetenschappelijk bewijs voor de behandeling van niet-resectabele CRLM bereikt is. De ‘selectie bias’ van de tot nu toe beschikbare studies en het superieure veiligheidsprofiel van thermale ablatie rechtvaardigen het opzetten van gerandomiseerde studies die ablatie direct vergelijken met de gouden standaard, chirurgie.

Er is een editorial van Klaus A. Hausegger, professor aan het Klinikum-Klagenfurt am Wörthersee universitair medisch centrum in Oostenrijk, toegevoegd als bijlage aan het proefschrift.

In **Hoofdstuk 3.2** staan de resultaten van een systematisch literatuur overzicht met betrekking tot de beste lokale behandeloptie voor niet-resectabele CRLM in de categorie 3-5 cm – omdat bekend is dat de effectiviteit van lokale therapie exponentieel afneemt met toenemende tumor grootte. Er was weinig literatuur beschikbaar aangaande de effectiviteit van thermale ablatie, irreversibele elektroporatie (IRE) en stereotactische bestraling (SBRT/SABR). Er zijn geen vergelijkende of gerandomiseerde studies verricht waarbij de studies die wel beschikbaar zijn een substantiële heterogeniteit in uitkomsten en studiepopulatie hebben. Alle technieken tezamen laten een lokale controle zien tussen de 20-90% per patiënt; 22-89% na thermale ablatie (8 studies), 44% na IRE (1 studie) en 67-90% na SBRT (1 studie), afhankelijk van gebruikte stralingsdosis. Concluderend kunnen lokaal ablatieve behandelopties wel als veilig worden beschouwd waarbij ze langdurige controle over de ziekte kunnen verkrijgen, ook voor CRLM van 3-5 cm. Ondanks dat er wordt gesuggereerd dat SBRT en IRE minder hinder ondervinden van het behandelen van 3-5 cm tumoren, kan er op basis van de huidige literatuur niks geconcludeerd worden. Toekomstige vergelijkende studies moeten zich focussen op uitkomsten als lokale tumor progressievrije overleving (LTPFS), lokale controle (LC), algehele overleving (OS), complicaties (AE), en kwaliteit van leven (QoL).

Hoofdstuk 4. Colorectale levermetastasen: lange termijn uitkomsten van thermale ablatie

Zoals beschreven is thermale ablatie uiterst effectief gebleken in het elimineren van primaire en secundaire levertumoren. Deze op hitte gebaseerde technieken worden steeds populairder en mondjesmaat geïmplementeerd in de internationale richtlijnen. In de meest recent gepubliceerde studies verschillen de lokale effectiviteit uitkomsten van thermale ablatie

aanzienlijk waarbij er nauwelijks informatie beschikbaar is over de eventuele voortuitgang van de techniek in de tijd.

In **Hoofdstuk 4.1** worden de resultaten van een vergelijkende studie weergegeven met als doel de lange termijn uitkomsten van alle thermale lever ablatie procedures gedurende de laatste 10 jaar te analyseren. Deze data komt uit de 'Amsterdam Colorectal Liver Met Registry' (AmCORE) database. Er werden 329 patiënten geïncludeerd die 541 procedures hebben ondergaan voor 1350 CRLM – tussen januari 2010 en februari 2021. Om een potentiele vooruitgang te kunnen onderzoeken zijn de initiële procedures verdeeld in drie verschillende cohorten per tijdsframe: 2010-2013, 2014-2017 en 2018-2021. De resultaten lieten zien dat LTPFS significant verbeterde in de tijd voor percutane ablaties (2-jaars LTPFS 37,7% [2010-2013] vs. 69,0% [2014-2017] vs. 86,3% [2018-2021], $P < 0.0001$), terwijl de LTPFS na open ablaties min of meer stabiel bleef (2-jaars LTPFS 87,1% vs. 92,7% vs. 90,2%, respectievelijk, $P = 0.12$). In het laatste cohort (2018-2021), waren de LTPFS gerelateerde resultaten na open ablaties niet langer superieur aan percutane ablaties ($P = 0.125$). Er werden geen verschillen gevonden tussen de cohorten wat betreft algehele overleving ($P = 0.088$), opnameduur (open ablaties, $P = 0.065$; percutane ablaties, $P = 0.054$), en aantal en ernst van complicaties ($P = 0.404$). Het aantal en de ernst van complicaties waren in het voordeel van de percutane benadering in alle drie de cohorten ($P = 0.002$). Op basis van deze resultaten kan worden geconcludeerd dat de lokale effectiviteit van percutane ablaties enorm verbeterd is in de laatste 10 jaar waarbij deze zelfs in de buurt komen van de resultaten na een open ablatie. Derhalve kan men een percutane ablatie verkiezen boven een open ablatie, zeker gezien het feit dat een percutane behandeling minder invasief is en gepaard gaat met een kortere opnameduur.

Hoofdstuk 5. Percutane thermale lever ablatie: beeldsturing, eindpunten en kwaliteitscontrole

RFA en MWA zijn wereldwijd de meest gebruikte thermale ablatietechnieken, hoewel nieuwe technieken zoals IRE (niet-thermaal) en SBRT ook bezig zijn aan een snelle opmars in het behandelarsenaal. De percutane benadering wint daarbij het snelt terrein omdat deze techniek een nog minimaal invasievere impact heeft met lage complicatie aantallen, acceptabele effectiviteit en de eigenschap dat het relatief eenvoudig nog een keer toe te passen is. Het belangrijkste issue is dat percutane ablaties wereldwijd nog steeds gepaard gaan met een hoog aantal lokale tumor progressies (LTP) wanneer er wordt vergeleken met open, laparoscopische of robot-geassisteerde resecties en open ablaties. De exacte reden hiervoor blijft onbekend maar de percutane benadering verdient wel verdere technische verbetering. **Hoofdstuk 5.1** geeft een overzicht van verschillende beschikbare technische hulpmiddelen, zoals live beeldsturing en naald navigatie, die helpen de tumor en kritieke vaat- en galwegstructuren beter te kunnen detecteren, alsmede de naaldposities te kunnen

afbeelden en begeleiden, behandeleffect te visualiseren en indien nodig de energie afgifte aan te kunnen passen. Bekende voorspellende factoren voor het slagen van de lokale behandeling zijn tumorgrootte, locatie binnen de lever, de mate van zichtbaarheid van de tumor op het beeld, tumorvrije marge, en de ervaring van de interventieradioloog – welke allen in detail worden beschreven in dit hoofdstuk. Daarnaast beschrijft dit hoofdstuk ook potentiele (technische) eindpunten als handvat voor een uiteindelijke complete tumor behandeling. Deze eindpunten zullen misschien niet direct effect hebben op de algehele overleving, maar zullen wel de LTPFS helpen verbeteren. Aan het eind van dit hoofdstuk wordt nog een klinisch algoritme weergegeven als leidraad voor de interventieradioloog om te gebruiken als kwaliteitscontrole tijdens en na de procedure.

Hoofdstuk 6. Anesthesie technieken

Zoals beschreven in vorig hoofdstuk hebben periprocedurele factoren een directe invloed op lokale ziekte controle. Om die reden kan ook de keuze voor welke anesthesie techniek van invloed zijn op de uitkomsten van thermale ablatie aangezien pijnbeleving, onrust en controle van ademhaling essentieel zijn om een goede behandeling te kunnen uitvoeren. In **Hoofdstuk 6** wordt de associatie tussen anesthesie techniek en lokale ziekte controle onderzocht bij patiënten die een percutane MWA procedure hebben ondergaan voor primaire of secundaire levertumoren. Negentig patiënten hebben 114 procedures ondergaan (22 onder algehele anesthesie; 32 onder midazolam/fentanyl sedatie; en 60 onder propofol sedatie) voor 171 behandelde levertumoren (n = 136 CRLM; n = 35 HCC). Data tussen januari 2013 en september 2018 werd geanalyseerd. De resultaten lieten zien dat propofol sedatie en algehele anesthesie superieur bleek te zijn aan midazolam/fentanyl sedatie wat betreft LTPFS (respectievelijk 4/94 [4,3%] vs. 19/42 [45,2%] vs. 2/35 [5,7%]; P < 0.001). Het totaal aantal lokale tumor progressies was 14,6% (n = 25/171). Achttien tumoren (72,0%) konden opnieuw geableerd worden. Van deze 18 tumoren waren er 14 (78%) eerder behandeld onder midazolam/fentanyl sedatie. Propofol vs. midazolam/fentanyl sedatie (P < 0.001), algehele anesthesie vs. midazolam/fentanyl sedatie (P = 0.016), direct postprocedurele 'visual analog pain score' (VAS) >5 (P = 0.050) en meer dan een behandelde tumor per procedure (P = 0.045) waren geassocieerd met LTPFS. Multivariate analyse liet zien dat propofol vs. midazolam/fentanyl sedatie (HR 7.94 [95% CI 0.04-0.39; P < 0.001]) en algehele anesthesie vs. midazolam/fentanyl sedatie (HR 6.33 [95% CI 0.04-0.69; P = 0.014]) significant geassocieerd waren met LTPFS. Pijn tijdens en direct na de procedure was significant meer bij patiënten die midazolam/fentanyl sedatie kregen (P < 0.001). Met andere woorden, midazolam/fentanyl sedatie was geassocieerd met meer pijn rondom de procedure en slechtere LTPFS vergeleken met propofol sedatie en algehele anesthesie. Om die reden zou men moeten nastreven om, indien beschikbaar, algehele anesthesie of propofol sedatie te

gebruiken tijdens een percutane ablatie procedure om zo het aantal nieuwe procedures voor incomplete ablaties en lokale tumor progressie te beperken.

Hoofdstuk 7. Beeldsturing

Betrouwbare visualisatie van de tumor in relatie tot de omliggende levervasculatuur en galwegen, van de naald plaatsing en reposities, en van de gecreëerde ablatiezone zijn cruciaal om het aantal lokale tumor progressies (lees: randrecidieven) te reduceren en voorkomen van herhaaldelijke behandelingen. Directe beeldsturing tijdens de procedure en CT-beelden direct na de tumorablatie zijn veelbelovende ontwikkelingen die een positief effect kunnen hebben op de lokale effectiviteit van de behandeling. In Hoofdstuk 7.1 worden resultaat weergeven uit de AmCORE-database waarbij de CTHA-techniek (direct intra-arterieel contrast) uiteen wordt gezet tegen de conventionele CT fluoroscopie techniek (‘eyeballing’) m.b.t. veiligheid en lokale controle van de ziekte. Bij CTHA-geleide percutane ablaties worden kleine, herhaaldelijke contrastinjecties (40mL 1:1 gemixte bolus van contrastmiddel en natriumchloride oplossing, op 5 mL/sec.) gegeven via een arteriële katheter in de lies die direct contrast afgeeft in een grote lever arterie (a. hepatica communis). Der CT-scan in de arteriële fase of gemixt laat arteriële fase – vroege portoveneuze fase heeft dan de neiging om een typische ringvormige nodule te laten zien die overeenkomt met de tumor. Data van 108 patients die 156 procedures (januari 2009 – mei 2019) hebben ondergaan (n = 42 CT fluoroscopie [25 RFA vs. 17 MWA] en n = 114 CTHA [18 RFA vs. 96 MWA]) voor in totaal 260 CRLM is gedocumenteerd. Er werden geen complicaties gezien welke gerelateerd konden worden aan de arteriele katheter plaatsing. CTHA had betere uitkomsten dan CT fluoroscopie m.b.t. 2-jaar lokale LTPFS (respectievelijk 18/202 [8,9%] vs. 19/58 [32,8%]; P < .001). CTHA vs. CT fluoroscopie (hazard ratio = 0.28; 95% confidence interval, 0.15–0.54; P < .001) en MWA vs. RFA (hazard ratio = 0.52; 95% confidence interval, 0.24–1.12; P = .094) waren positieve voorspellers voor een langere LTPFS. Multivariate analyse liet zien dat CTHA vs. CT fluoroscopie (hazard ratio = 0.41; 95% confidence interval, 0.19–0.90; P = .025) was geassocieerd met een significant betere LTPFS. Algehele overleving was gelijk tussen de twee groepen (P = .3). Deze resultaten laten het belang zien van duidelijke tumor en ablatiezone visualisatie omdat CTHA-geleide ablaties het aantal uiteindelijke re-ablaties reduceren zonder extra risico’s te nemen of dat het de algehele overleving in nadelige zin zou beïnvloeden. Dit weliswaar ten koste van een extra procedure (katheterplaatsing zelf) en een iets grotere belasting voor de patiënt.

De toegevoegde waarde van CTHA-geleide ablaties wordt verder toegelicht in **Hoofdstuk 7.2** in de vorm van illustratieve voorbeeld cases. Deze tonen de mogelijkheid van CTHA om levertumoren beter te kunnen detecteren, additionele tumoren op te kunnen sporten tijdens de procedure, kritieke structuren zoals bloedvaten en galwegen goed in beeld te kunnen brengen, ‘verdwenen’ tumoren na chemotherapie alsnog in beeld te kunnen brengen, goed te

differentiëren tussen lokale tumor progressie en niet-aankleurend litteken weefsel na eerdere behandelingen, en om direct een adequate toegang te verschaffen in geval van een iatrogene leverbloeding die interventie behoeft.

In **Hoofdstuk 7.3** worden de resultaten weergegeven van een AmCORE cohort waarbij de toegevoegde waarde van CTHA wordt beschreven om eerder niet-zichtbare of door chemotherapie 'verdwenen' levertumoren alsnog te kunnen detecteren. In slechts 7% van de gevallen was tumordetectie met CTHA vals negatief, maar het is wel een veilige procedure gebleken. Om die reden zouden typische ringaankleurende tumoren, gevonden met CTHA, direct behandeld kunnen worden met thermale ablatie.

Hoofdstuk 8. Chirurgie versus thermale ablatie voor colorectale levermetastasen.

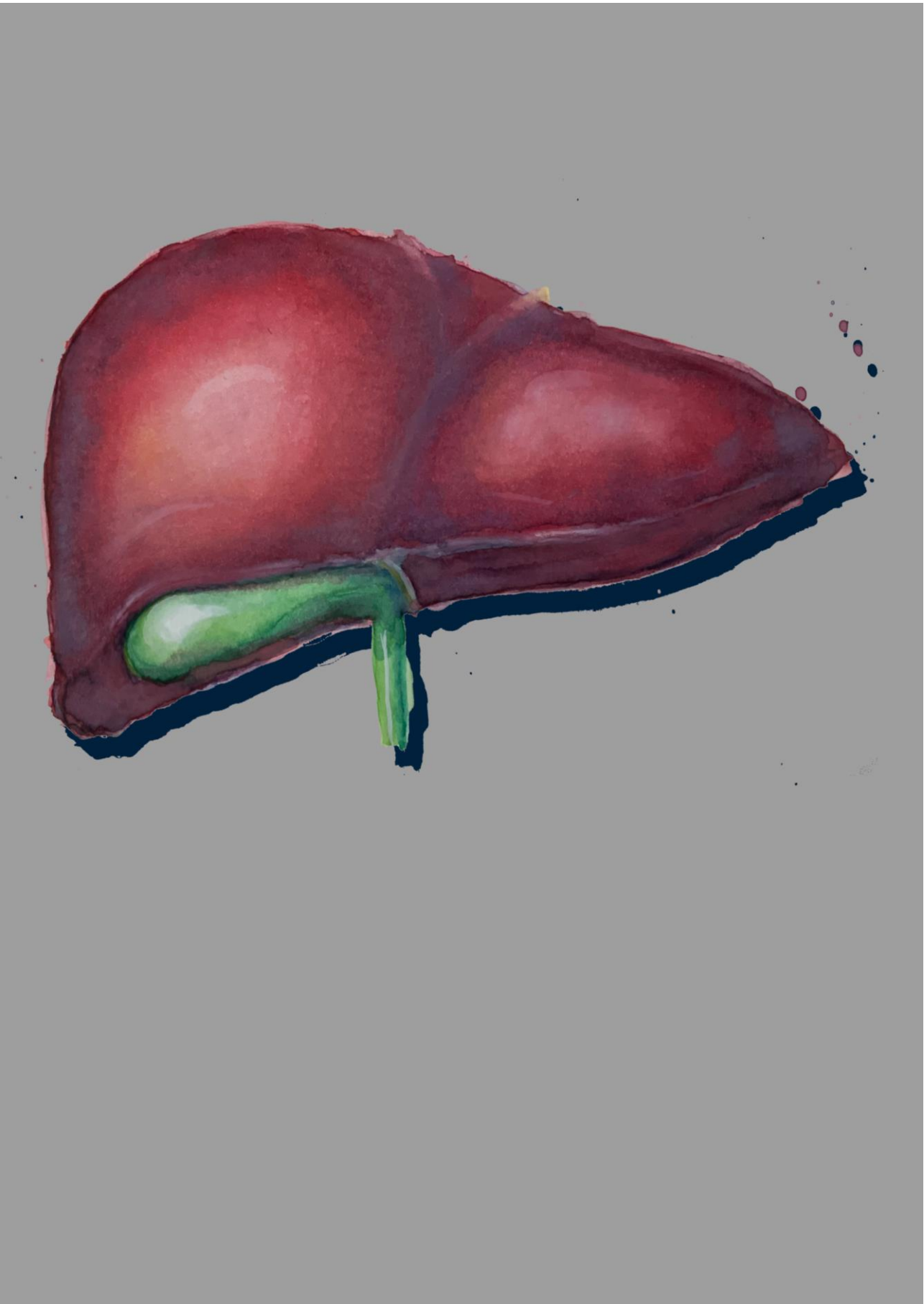
Nu thermale ablatie veelbelovende resultaten heeft laten zien is vervolgonderzoek nodig om deze behandeloptie in de toekomst te kunnen toevoegen aan de praktische richtlijnen. Op dit moment wordt chirurgische resectie vergeleken met thermale ablatie voor kleine (≤3 cm) resectabele CRLM in de internationale, fase-3, gerandomiseerde 'COLLISION' studie. Het studie design en protocol staan vermeld in **hoofdstuk 8.1**. De studie onderzoekt een potentiele non-inferioriteit van ablatie ten opzichte van chirurgie. Patiënten met tenminste 1 resectabele en ableerbare tumor (≤3 cm, ook wel target laesie genoemd), maximum van 10 metastasen, goede performance status, geen extrahepatische ziekte, en geen eerdere behandeling van de lever, worden geschikt geacht voor deelname. Het primaire eindpunt is algehele overleving, volgens een 'intention-to-treat' analyse. Secundaire eindpunten zijn complicatie(s), mortaliteit, lokale tumor progressie vrije overleving, lokale controle inclusief herhaaldelijke behandelingen, ziekte progressie buiten de lever, opnameduur, kwaliteit van leven en kosteneffectiviteit.

[redacted]

Hoofdstuk 8.3 en **8.4** onderstrepen de klinische relevantie en noodzaak voor de prangende vraag: *"chirurgie of thermale ablatie voor colorectale levermetastasen?"*.

In lijn met het onderwerp van hoofdstuk 8 laat **hoofdstuk 8.5** een AmCORE analyse zien van 136 patienten die opnieuw behandeld zijn met 're-ablatie' of 're-resectie' voor nieuw ontstane CRLM tijdens de follow-up. Data werd geanalyseerd op veiligheid, effectiviteit en overlevingsuitkomsten van de twee groepen. Een totaal aantal van 224 tumoren (170 opnieuw

behandeld met ablatie, 54 met resectie) zijn geanalyseerd. De OS tussen de twee groepen was nagenoeg gelijk (p = 0.927). De 1-, 3-, en 5-jaars overleving was 98,9%, 62,6% en 42,3% in de ablatie groep en 93,8%, 74,5% en 49,3% in de resectie groep. Er werden geen verschillen gevonden aangaande DPFS (p = 0.942), LTPFS (p = 0.397) en optreden van complicaties (p = 0.063). De gemiddelde opnameduur was 2,1 dagen in de ablatie groep vs. 4,8 dagen in de chirurgie groep (p = 0.009). Gebaseerd op deze resultaten zal thermale ablatie, gezien de veiligheid en het minimaal invasieve karakter, meegenomen moeten worden in de overweging om patienten met nieuw ontstane kleine (≤3 cm) CRLM te behandelen.



APPENDICES

APPENDIX 1.1

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Appendix E1. List of relevant definitions

The following definitions are suggested by the members of the Coordinating Committee and included in the surveys.

• **Local residual disease:** Macroscopic residual disease that remains after attempts to remove or ablate the tumor;

• **Local recurrence:** Reappearance of tumor tissue at the initial site after local therapy;

• **Local progression:** For locally treated tumors, growing of tumor tissue at the initial site;

• **Regional recurrence:** Relapse within the region, but beyond the area of the initially treated tumor, that does not imply systemic spread (for instance nodes close to the tumor);

• **Lost to follow-up:** Study subjects who cannot or do not complete participation in a study for unknown reasons.

Data

• **Collected data:** data which gets put into data system;

• **Analyzed information:** information which gets converted into data;

• **Reported data:** data which needs to appear in final report/manuscript.

Bias

• **Selection bias:** The bias introduced by the selection of individuals, groups or data for analysis in such a way that proper randomization is not achieved, thereby ensuring that the sample obtained is not representative of the population intended to be analyzed;

• **Referral bias:** Referral bias (admission rate bias) refers to a situation where the chance of exposed cases being admitted to the study is different to exposed controls. This happens frequently when cases are selected in a hospital whose activity is linked to the studied exposure;

• **Lead-time bias:** An apparent increase in survival due to detecting a health condition such as cancer at an early stage, when there is no actual effect on survival, just a longer period with the diagnosis;

• **Immortality-time bias:** Refers to a period of follow-up during which, by design, death or the study outcome cannot occur.

Survival analysis

• **Event:** The (date of the) manifestation;

• **Ignore event:** One should consider that a certain manifestation cannot exclude nor modify the probability of observing the event being evaluated, and continue to observe outcomes beyond this event. The patient remains at risk. For example, a consultation by phone reliably excludes death, but not the presence or absence of disease. When assessing disease-free survival, this consultation, even if it represents the last follow-up information available, should be ignored and one should continue to observe outcomes beyond this event;

• **Exclude event:** One should consider that the event did not happen, and continue to observe additional outcomes beyond this event. The patient remains at risk. Excluded events become censors at the time of final evaluation;

• **Censor event:** One should stop observing what is going on beyond this endpoint;

• **Competing-risk analysis:** One should consider that a certain manifestation can modify the probability of observing the event being evaluated. In other words, one should account for the manifestation in the statistical analysis by using a competing risks analysis.

Censoring

Lifetime data are often censored when you do not have the exact time an event occurred or when a certain event endpoint has not (yet) occurred. There are three types of data censoring; right-, left- and interval-censored data.

• **Right-censored:** the event may occur after the recorded time. For example, looking at overall survival when some patients in your cohort are still alive. In this example, death, for patients who are alive at the time of assessment, should be right-censored;

• **Left-censored and interval-censored data:** the event occurred before a particular time-point but one doesn't know exactly when. For example, looking into 1-year local tumor progression-free survival. A certain event (local tumor progression) occurred in the first year but it is unclear when. In this example there are two options: (A) the date of unequivocal presence of the event is considered the date of the event and all time points earlier are considered left-censored and (B) the virtual date halftime between the second latest and the latest cross-sectional imaging is considered the date of the event (interval-censored data). The latter method may be useful for studies where low or heterogeneous number of follow-up exams is available.

Table E1. Coordinating Committee

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Table E3. Addressing Outcomes per Patient, per Session or per Tumor

Parameter	Accepted acronyms	Per patient	Per session	Per tumor
Overall survival	OS	Yes		
Disease-specific overall survival		Yes		
Disease-free survival	DFS	Yes		
Recurrence-free survival	RFS	Yes		
Progression-free survival	PFS	Yes		
Distant progression-free survival	DPFS	Yes		
Procedure-related side effects			Yes	
Direct costs			Yes	
Short-term complications			Yes	
Anesthesia technique			Yes	
Hospital-stay characteristics			Yes	
Laboratory tests			Yes	
Technical success			Yes	Yes
Local tumor progression-free survival	LTPFS	Yes		Yes
Time-to-local (tumor) progression		Yes		Yes
Freedom from local or organ-specific recurrence		Yes		Yes
Primary technique efficacy		Yes		Yes
Secondary or assisted technique efficacy		Yes		Yes
Residual disease		Yes		Yes
Local progression		Yes		Yes
Recurrence rates		Yes		Yes
Local control		Yes		Yes

Online Supplemental Appendix 4. Items and level of agreement of the first questionnaire.

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APPENDIX 1.1

EDITORIAL

Consensus Guidelines in Image-guided Tumor Ablation: Toward Evidence-based Interventional Oncology

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Image-guided tumor ablation refers to a group of treatment modalities that have evolved over the past 2 decades as important minimally invasive tools in the treatment of a wide range of tumors throughout the body (1). Although most widely used in the treatment of hepatic and renal tumors, the role of image-guided tumor ablation has expanded to include lesions of the lung, bone, breast, prostate, and other organs and its clinical applications continue to increase. As more studies are published describing these techniques, an ever-increasing number of outcome measures have been used as surrogates for overall survival. These end points are generally composite "time-to-event" end points, such as progression-free survival or disease-free survival. Although these end points are commonly used in the interventional oncology literature, they are generally poorly defined and are often specific to the particular trial in which they are being used (2). The lack of standardized definitions within the interventional oncology literature limits the use of these end points as outcomes measures, directly impacting trial results by affecting the estimated treatment effects and trials' statistical power, and, importantly, limiting comparison between studies and techniques.

In response to the lack of standardization, the International Working Group on Image-Guided Tumor Ablation published a document that proposed terminology and reporting criteria related to image-guided tumor ablation (3). Their efforts were intended to facilitate effective communication for reporting the various aspects of image-guided tumor ablation, including classification of techniques, procedure terms, descriptors of imaging guidance, and terminology of imaging and pathologic findings. Also addressed were methods for standardizing reporting of technique, follow-up timing, complications, and clinical results. The guidelines proposed provided a framework with which to facilitate comparisons of studies and techniques in interventional oncology. However, clear definitions and recommendations on how to use and interpret outcome measures were not proposed.

In this issue of *Radiology*, Puijk and colleagues (4) attempt to advance the field of interventional oncology toward a more evidence-based clinical specialty by presenting the first consensus guidelines for collecting, analyzing, and reporting time-to-event outcomes related to image-guided tumor ablation. The method by which the authors achieved consensus on these definitions and recommendations is not new to health care consensus guideline development. It is, however, new to interventional oncology and therefore worthy of further discussion.

Consensus guidelines have increasingly become an integral part of evidence-based health care not only in individual and institutional clinical practices, but also with governments and payers (5). Consensus guidelines in health care are recommendations that are provided by a body of experts who conduct a systemic review of the data on how to treat or diagnose disease, with the aim of better patient outcomes. These guidelines provide evidence that is meant to *(a)* serve as a framework for informed clinical decisions intended to improve patient outcomes; *(b)* help incorporate best available evidence into clinical medicine—a tool to close the gap between the current standard of care and what evidence supports; *(c)* reduce variation, prevent errors, and increase clinicians' accountability in patient care; *(d)* reduce per capita health care costs and improve resource utilization; *(e)* focus on quality control; and *(f)* help researchers identify gaps in the evidence and what key research questions have yet to be answered.

It is important to be clear what consensus guideline development is and is not. It is a process for making guidelines, not a scientific method for creating new knowledge. At its best, consensus development makes the best use of available information, be that scientific data or the collective wisdom of the participants. It is only since the 1950s that formal consensus development methods have been used in the health care sector (6). The case for using formal methods is based on a number of assumptions about decision-making in groups, as follows: *(a)* Several people are less likely than a single individual to arrive at a wrong decision; *(b)* a selected group of individuals is more likely to lend some authority to the decision produced; *(c)* decisions are improved by a reasoned argument in which assumptions are challenged and members are forced to justify their views; *(d)* by providing a structured process, formal methods can eliminate negative aspects of group decision-making; and *(e)* formal consensus methods meet requirements of scientific methods.

Puijk et al used a modified Delphi method of consensus building to define outcomes measures for image-guided tumor ablation (4). The Delphi method was initially developed by the RAND Corporation in the 1950s to synthesize expert opinion, mainly in evaluating emerging technologies (6). Since then, the Delphi method has been used in health care as a reliable means of determining consensus for many clinical issues (7). This method is an iterative process that uses a systemic progression of repeated rounds of questionnaires and is an effective process for determining expert group consensus where there is little or no definitive

evidence and where expert opinion is important. Using this technique, Puijk et al effectively achieved consensus on 59 of 62 time-to-event definitions and recommendations (4). Included within these guidelines were when to assess outcomes per patient, per session, and per tumor; starting and ending times; survival time definitions; and time-to-event end points. The modified Delphi method consisted of two rounds of questionnaires and a final face-to-face meeting (8). The anonymous nature of the first two rounds of this method prevents participants from conforming to the opinions of others while providing a controlled feedback process. The final face-to-face round, on the other hand, is critical in consensus development, as it encourages participating experts to provide clarification and present arguments justifying their viewpoints. These characteristics are designed to offset the shortcomings of conventional means of pooling opinions obtained by group interaction (ie, influences of dominant individuals, noise, and group pressure for conformity).

Despite the many strengths of the Delphi method in consensus building, there are potential shortcomings. Choosing the appropriate experts to participate has been described as the most important step in the entire process because it directly relates to the quality of the results generated (8). Regarding any standards for selecting participants, there is, in fact, no exact criterion. It is generally accepted that participants should be experts within the specialized area of knowledge related to the target issue. It is also recommended that researchers use a minimally sufficient number of experts to provide a "representative pooling of judgements" regarding the target issue, with most Delphi studies using between 15 and 20 participants (8). If the number of participants is too large, the drawbacks inherent within the Delphi method, such as potentially low response rates and the obligation of large blocks of time by the experts, can be the result. In fact, Puijk et al (4) enlisted a relatively large number of opinion leaders in interventional oncology (n = 62), perhaps explaining the modest response rates of 58%, 56%, and 54% for rounds 1, 2, and 3, respectively. Given the large number of participants, it is also not surprising it took over 9 months to achieve consensus on 59 of the 62 recommendations and definitions. Consensus was unfortunately not reached for the preferred classification system to document, analyze, and report complications and adverse events and quality-of-life and health economics issues. One can hope that these will be addressed in the near future by a group of interventional oncology opinion leaders.

Ideally, clinical guidelines are based on evidence derived from rigorously conducted empirical studies. In practice, however, there are few areas of health care where sufficient research-based evidence exists or may ever exist. In such situations, the development of guidelines inevitably must be based largely on consensus opinions and experience of clinicians and others with knowledge of the subject at issue. The consensus guidelines presented by Puijk et al (4) in this issue of *Radiology* represent a significant step forward for evolving the field of interventional oncology toward its goal of becoming an established evidence-based clinical specialty.

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APPENDIX 1.1

EDITORIAL

Research Highlight: How to Use Technical and Oncologic Outcomes of Image-Guided Tumor Ablation According to Guidelines by Society of Interventional Oncology and DATECAN?

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Take-home points

• We highlight key points from recent consensus guidelines by Society of Interventional Oncology

(SIO) and Definition for the Assessment of Time-to- event Endpoints in CANcer trials (DETACAN) to

facilitate effective communication in the field of image-guided tumor ablation.

• The guidelines include recommendations for defining and analyzing various oncologic endpoints

at per-patient, per-procedure, or per-tumor levels and terminologies commonly used in image-guided tumor ablation.

• Precise definitions of various oncologic endpoints and terminologies will lead to an objective and

reliable interpretation of results and accurate comparison of oncologic outcomes of image-guided tumor ablation, ultimately providing scientific reproducibility among researchers.

To ensure a standardized interpretation and reporting of results and allow for accurate comparison of image-guided tumor ablation outcomes, the SIO and DATECAN group recently published consensus guidelines.[1] We want to highlight some key points, to facilitate their use in reporting and reviewing research studies.

Background of Guideline Development

In 2014, Ahmed et al.[2] published a paper regarding the updated standardized terminology and reporting criteria for image-guided tumor ablation, which has been cited by over 500 studies on tumor ablation over the past eight years. The document has contributed to interventional oncology by providing a common language to describe the treatments and their outcomes and has facilitated effective communication throughout the field. However, there is still variability in interpreting and using time-to-event endpoint terms, and definitions of starting and ending times, throughout the interventional oncology literature. Because of this unmet need, the SIO and the DATECAN group worked on a project with an international panel of 62 experts, and a consensus was reached on the use of the validated three step modified Delphi consensus method.

Table 1. Summary of the use of per-patient, per-procedure, or per-tumor analyses for different outcomes. Adapted from Puijk et al. Radiology 2021;301:533-540.[1]

Parameter	Accepted Acronyms	Per-Patient	Per-Procedure	Per-Tumor
Overall survival	OS	Yes		
Disease-specific overall survival		Yes		
Disease-free survival	DFS	Yes		
Recurrence-free survival	RFS	Yes		
Progression-free survival	PFS	Yes		
Distant progression-free survival	DPFS	Yes		
Procedure-related side effects			Yes	
Direct costs			Yes	
Short-term complications			Yes	
Anesthesia technique			Yes	
Hospital-stay characteristics			Yes	
Laboratory tests			Yes	
Technical success			Yes	Yes
Local tumor progression-free survival	LTPFS	Yes		Yes
Time-to-local (tumor) progression		Yes		Yes
Freedom from local or organ-specific recurrence		Yes		Yes
Primary technique efficacy		Yes		Yes
Secondary or assisted technique efficacy		Yes		Yes
Residual disease		Yes		Yes
Local (tumor) progression		Yes		Yes
Recurrence rates		Yes		Yes
Local control		Yes		Yes

How Can We Analyze Various Outcomes at Per-Patient, Per-Procedure, or Per-Tumor Levels and How Can We Define Them?

Outcome parameters should be analyzed appropriately at different levels, including per-patient, per-procedure, and per-tumor, when performing studies on image-guided tumor ablation, as summarized in Table 1. Of note, survival outcomes should be interpreted per-patient and not per tumor or per-procedure. However, as an exception, local tumor progression-free survival (LTPFS) can be assessed on a per-patient or per-tumor basis. The local (tumor) progression rate can also be used, instead of LTPFS, when analyzing on a per-tumor basis as the term has been widely used in previous studies.[3-5] Parameters closely related to the treatment session should be analyzed per-procedure, as a synonym for the session. Such items include procedure-related side effects, direct costs, short-term complications, anesthesia technique, hospital-stay characteristics, laboratory tests, and technical success. However, technical success can also be interpreted on a per-tumor basis. The parameters related to the local efficacy that are assessed on a per-patient and per-tumor basis are as follows: LTPFS, time-to-local (tumor) progression, freedom from local or organ-specific recurrence, primary and secondary or assisted technique efficacy, residual disease, local (tumor) progression, recurrence rates, and local control. In patients with multiple index tumors (e.g., multiple colorectal metastases), standard survival estimates (Kaplan- Meier or cumulative incidence functions) may not consider the dependency of partially correlated or clustered data. Therefore, this potential limitation must be considered.

The definitions of the various oncologic endpoints are summarized in Table 2. Overall survival, defined as death from all causes, is widely used to describe survival outcomes in oncologic studies.[6] However, if the occurrence of death from causes other than the disease being studied is substantial, both overall survival and disease-specific survival should be documented. Death from causes other than the disease being explored is considered a competing risk for disease-specific survival analysis. When tumor ablation is performed for early stage disease, recurrence-free survival should be used if the intervention is likely curative (i.e., ablation of small renal tumors). When the intervention is considered potentially curative for intermediate-stage disease (i.e., ablation of colorectal liver metastases), disease-free survival should be used.

Table 2. Definitions of various oncologic endpoints. Modified from Punt et al. J Natl Cancer Inst 2007;99:998-1003.[6] *Synonyms for cancer-specific survival. DFS = disease-free survival, DSS = disease-specific survival, OS = overall survival, RFS = recurrence-free survival, TTR = time to recurrence

Observation	DFS	RFS	TTR	DSS*	OS
Locoregional recurrence	Event	Event	Event	Ignored	Ignored
Distant metastases	Event	Event	Event	Ignored	Ignored
Second primary, the same cancer	Event	Ignored	Ignored	Ignored	Ignored
Second primary, other cancer	Event	Ignored	Ignored	Ignored	Ignored
Death from the same cancer	Event	Event	Event	Event	Event
Death from other cancer	Event	Event	Censoring	Censoring	Event
Non-cancer-related death	Event	Event	Censoring	Censoring	Event
Treatment-related death	Event	Event	Censoring	Censoring	Event
Loss to follow-up	Censoring	Censoring	Censoring	Censoring	Censoring

Unlike the diagnosis/prediction of static binary outcomes, the follow-up time should be considered for survival analysis and should be defined accurately.[7,8] The commonly used time-to-event endpoints are presented in Table 3.

The definition of the starting time should differ according to the study design. For randomized controlled trials, the starting time should be the randomization date, and it is recommended that the time taken from the interventional procedure be added to the data. For single-arm prospective studies and retrospective comparative and non-comparative studies, the starting time should be the date of the first intervention.

Table 3. Definitions of time-to-events endpoints commonly used in image-guided tumor ablation. * Definition of starting time differs according to the study design. LTPFS = local tumor progression-free survival.

Time-to-Event Endpoints	Starting Point*	Ending Point
Time to progression	Starting time	Any disease recurrence (local, regional, or distant)
Distant progression-free survival	Starting time	Distant tumor progression, but not local or regional progression
LTPFS	Starting time	Local tumor progression per tumor treated (per-tumor analysis) or per patient treated (per-patient analysis)
Time-to-local (tumor) progression, horizontally flipped LTPFS	Starting time	Local tumor progression per tumor treated
Disease-specific survival	Starting time	Death from the same cancer
Overall survival	Starting time	Death from all causes

Other Terminologies Commonly Used in Image-Guided Tumor Ablation

Ablation confirmation: This refers to postprocedural imaging or any alternative technique that is implemented to allow for additional overlapping (completion) procedures, either within the same session or in a complementary completion session, in the days or weeks hereafter.

Technical success: This addresses whether the tumor was treated according to a predefined protocol and covered completely by the ablation zone using ablation confirmation techniques. Technical success rates should be documented in a research paper.

Technique efficacy: This refers to the achievement of complete tumor ablation at a prospectively defined time point, as evidenced by imaging follow-up or any alternative technique (i.e., biopsy or serologic criteria). If a patient died due to any cause before that time point, then the event should be analyzed and reported as a competing risk.

Primary efficacy rate and secondary or assisted technique efficacy rate: The former refers to the percentage of target tumors that were successfully eradicated following initial ablation. In contrast, the latter addresses the percentage of target tumors that were eventually removed with repeat ablations using ablation therapy.

Local control: This is equivalent to assisted technique efficacy, except that repeat treatments using alternative methods (other ablation therapy, radiation therapy, or surgical excision) are allowed.

Residual unablated tumor and local tumor progression: The former refers to a residual viable tumor at the ablative margin at the initial follow-up imaging. In contrast, the latter refers to the appearance of a viable tumor, provided that a residual viable tumor was not found in at least one contrast-enhanced follow-up study at the ablative margin.

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APPENDIX 2.1

Appendix A: Statements

PATIENT CHARACTERISTICS

1. AGE: Curative-intent local therapy for CRLM is appropriate for all age groups at the prerequisite that the general health condition is adequate (ECOG ≤2, ASA ≤3 and CCI ≤8); Treatment cannot be withheld based on patients' age alone.[1-4].

Based on several comparative retrospective studies, that have used matching or multivariate analysis, overall survival was worse in elderly patients compared to younger patients. However, a substantial proportion of elderly patients did achieve long-term disease-free and overall survival and curative intent local therapies were superior to chemotherapy alone in this subset of patients. Hence, elderly patients should not be excluded from receiving curative intent local treatments.

EVIDENCE LEVEL LOW-MODERATE: SEVERAL RETROSPECTIVE COMPARATIVE CASE SERIES AND LARGER REGISTRY RESULTS

2. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) SCORE: Curative-intent local therapy for CRLM is appropriate for ECOG ≤2 patients, for ECOG ≥3 patients the risks of surgery, thermal ablation and IRE do not outweigh the benefits[5-8]; in select patients with limited disease (≤3 CRLM) SBRT can be considered for ECOG 3 patients with a life expectancy >1 year.[9-11]

Based on several studies, 3-month postoperative mortality of surgery +/- ablations was very high in patients with an ECOG score of 3 or 4 (29.6 and 57.6% respectively) compared to patients with an ECOG score of 0-1 or 2 (2.6 and 3.7% respectively). Consequently, for ECOG ≥3 the risks of surgery do not outweigh the benefits.

EVIDENCE LEVEL LOW-MODERATE: SEVERAL RETROSPECTIVE COMPARATIVE CASE SERIES AND LARGER REGISTRY RESULTS

Based on a limited number of studies, liver SBRT, which does not require anesthesia or conscious sedation, seems to be safe and locally effective in select patients with a poor performance status.

EVIDENCE LEVEL LOW: SMALL NON COMPARATIVE CASE SERIES & EXPERT OPINIONS

3. AMERICAN SOCIETY of ANESTHESIOLOGISTS (ASA) SCORE: Curative-intent local therapy for CRLM is appropriate for ASA ≤3 patients, for ASA 4 patients the risks of surgery, thermal ablation and IRE do not outweigh the benefits; in select patients with limited disease (≤3 CRLM) SBRT can be considered for ASA 4 patients.[8-13]

Based on several studies ASA ≥4 was associated with a higher mortality (15.3 – 43.2%) and severe morbidity (37.5%).

EVIDENCE LEVEL LOW-MODERATE: SEVERAL RETROSPECTIVE COMPARATIVE CASE SERIES AND LARGER REGISTRY RESULTS

4. UNDERLYING LIVER DISEASE (ICD-10): Curative-intent local therapy for CRLM is appropriate for no or mild underlying liver disease; for severe underlying liver disease the risks do not outweigh the benefits.[14,15]

The overall surgical risk of mortality for patients with severe underlying liver disease is ≥40%. The limited data available specifically for liver surgery suggest that the risk is even higher. Hence, curative intent local therapy should not be performed for patients with severe underlying liver disease.

EVIDENCE LEVEL LOW: RETROSPECTIVE COMPARATIVE CASE SERIES AND REGISTRY RESULTS

5. CHARLSON COMORBIDITY INDEX (CCI): Curative-intent local therapy for CRLM is appropriate for patients with CCI ≤4 and for patients with CCI 5-8 if the procedure is considered non-complex (minor hepatectomy +/- ablations); for patients with a CCI ≥9 the risks of surgery, thermal ablation and IRE do not outweigh the benefits; in select patients with limited disease (≤3 CRLM) SBRT can be considered if CCI is 9-10.[8-10,16,17]

Based on our literature review the 3-month mortality after surgery is 3.4-7.2% for CCI 0-2, 18.5% for CCI 3-4 and 33.8% for CCI 5-8.

EVIDENCE LEVEL LOW-MODERATE: SEVERAL RETROSPECTIVE COMPARATIVE CASE SERIES AND LARGER REGISTRY RESULTS

Based on a limited number of studies, liver SBRT, which does not require anesthesia or conscious sedation, seems to be safe and locally effective in select patients with a poor performance

EVIDENCE LEVEL LOW: SMALL NON COMPARATIVE CASE SERIES & EXPERT OPINIONS

DISEASE CHARACTERISTICS

6. STAGE IVa DISEASE: Upfront curative intent local treatment without peri-procedural systemic therapy is the appropriate therapy if the procedure is considered *non-complex* (minor hepatectomy and/or ablations).[18,19]

The results from the large phase III RCT, where the addition of perioperative chemotherapy (FOLFOX4) over surgery alone for patient with resectable CRLM was assessed, found a marginal difference in disease-free survival and concluded that the primary endpoint was met. However, when analyzing the long term results no overall survival benefit was found. The majority of guidelines state that, because the initial primary endpoint was met, periprocedural systemic therapy should be offered. Others, including the Dutch IKNL guidelines, believe that disease-free survival should merely be regarded as a surrogate endpoint for overall survival and, even though the study was questionably underpowered to detect a difference in OS, favor using the harder endpoint OS over its surrogate DFS in this study.

EVIDENCE LEVEL: RCT (HIGH)

7. STAGE IVb DISEASE: Upfront curative intent local treatment without peri-procedural systemic therapy is the appropriate therapy if the surgical procedure, with or without ablative treatment, is considered *complex* (major hepatectomy +/- ablations), with the following two exemptions where 4-6 cycles of induction systemic therapy are indicated: (a) if downsizing systemic therapy is likely to reduce the surgical risk or (b) in case of early metachronous disease developed within 6 months following primary tumor diagnosis (test of tumor biology).[20-23]

Tanaka et al. reported fewer extended hepatectomies after neoadjuvant chemotherapy. Expert and consensus articles advice peri-procedural chemotherapy for early metachronous disease.

EVIDENCE LEVEL: SEVERAL RETROSPECTIVE COMPARATIVE CASE SERIES AND LARGER REGISTRY RESULTS (LOW)

8. STAGE IVc DISEASE: In patients, unsuitable for curative intent surgery and/or ablation due to number, size and location of CRLM, with potentially downstagable disease, induction systemic therapy is appropriate until: a) curative intent local treatment has become possible or (b) when further downsizing will not (further) decrease procedural risk.[24-29]

Several studies (systematic review, RCTs and retrospective cohort) found significantly increased resectability after induction chemotherapy.

EVIDENCE LEVEL: RCTs and SYSTEMATIC REVIEWS (HIGH)

9. STAGE IVd DISEASE: For liver-only colorectal metastases, the term permanently unsuitable for curative intent local treatment should be reserved for (a) patients who remain ineligible for radical intent local therapy following induction systemic therapy, (b) patients with upfront contra-indications for radical intent local therapy and contra-indications to receive systemic therapy and (c) patients with a poor general health status who do not qualify for any local therapy (SBRT, local ablation and surgery).[30]

In the ongoing CAIRO-5 trial, that compares different systemic therapy regimens for unresectable liver only CRLM patients, a considerable percentage of patients with CRLM originally deemed 'permanently unresectable' were converted to resectable and/or ablatable disease after induction chemotherapy.

EVIDENCE LEVEL: OBSERVATION FROM RCT, (MODERATE)

10. PROGNOSTIC BIOMARKERS: At the prerequisite that the primary tumor plus any locoregional lymph nodes are (or will be) radically resected (or treated with radical intent otherwise), curative intent local treatment can currently not be (dis)qualified or classified to specific local treatment groups based on the following parameters: primary tumor location, synchronous versus metachronous disease, previous (neo)adjuvant therapies for locoregional disease, the best objectified response to systemic treatment, (y)p/cT-stage and (y)p/cN-stage, RAS or BRAF wildtypes or mutations, microsatellite (in)stability, consensus molecular subtypes, clinical risk score (CRS by Fong et al.) and the modified CRS, CEA or other tumor marker quantities, the presence and quantity of circulating tumor cells and DNA.[31-36]

The majority of the abovementioned parameters, biomarkers or validated scoring systems have proven to be important prognostic biomarkers correlated with survival, and for some (such as RAS mutation) several studies recommend wider resection and/or ablation margins to prevent recurrence / local tumor progression. However, currently these parameters cannot be used as predictive markers, because they cannot preclude patients from local treatment nor categorize them into a specific local treatment group.

EVIDENCE LEVEL: NO EVIDENCE

11. FUTURE LIVER REMNANT (FLR) VOLUME AND/OR FUNCTION: If the FLR volume and/or function is sufficient, curative-intent local therapy for CRLM is appropriate, regardless of the total number of CRLM; patients cannot be disqualified based on the total number of CRLM alone.[37,38]

Multiple studies have shown long-term disease-free and overall survival after local treatment of CRLM in patients with a high number of CRLM and all suggest superiority of local therapy over chemotherapy alone.

EVIDENCE LEVEL: SEVERAL RETROSPECTIVE COMPARATIVE CASE SERIES (LOW)

TUMOR CHARACTERISTICS

12. Partial hepatectomy is the appropriate local treatment method for patients with resectable CRLM >3cm, at the prerequisite that ECOG is ≤2, ASA is ≤3 and CCI is ≤8.[39,40]

Partial hepatectomy is the historical gold standard. Multiple prospective and retrospective series and large scale prospective registries, systematic reviews and meta-analyses have shown a superior overall survival of hepatectomy over systemic therapy alone. Furthermore, long-term disease-free and overall survival and even cure can be established in a substantial proportion of resectable liver only CRLM patients.

EVIDENCE LEVEL 'PARTIAL HEPATECTOMY SUPERIOR TO SYSTEMIC THERAPY ALONE': (HISTORICAL STANDARD / LOW - MODERATE)

13. Partial hepatectomy is the appropriate local treatment method for patients with resectable *exophytic* or *perihilar* CRLM ≤3cm, at the prerequisite that ECOG is ≤2, ASA is ≤3 and CCI is ≤8.[39,40]

Partial hepatectomy is the historical gold standard. Multiple prospective and retrospective series and large scale prospective registries, systematic reviews and meta-analyses have shown a superior overall survival of hepatectomy over systemic therapy alone. Furthermore, long-term disease-free and overall survival and even cure can be established in a substantial proportion of resectable liver only CRLM patients.

EVIDENCE LEVEL 'PARTIAL HEPATECTOMY SUPERIOR TO SYSTEMIC THERAPY ALONE': (HISTORICAL STANDARD / LOW - MODERATE)

14. Partial hepatectomy is the appropriate local treatment method for patients with resectable *superficial or shallow* CRLM ≤3cm, at the prerequisite that the general health condition is good (ECOG ≤1, ASA ≤3 and CCI ≤4).[39-44]

Partial hepatectomy is the historical gold standard. Multiple prospective and retrospective series and large scale prospective registries, systematic reviews and meta-analyses have shown a superior overall survival of hepatectomy over systemic therapy alone. Furthermore, long-term disease-free and overall survival and even cure can be established in a substantial proportion of resectable liver only CRLM patients.

EVIDENCE LEVEL 'PARTIAL HEPATECTOMY SUPERIOR TO SYSTEMIC THERAPY ALONE': (HISTORICAL STANDARD / LOW - MODERATE)

Multiple retrospective series, systematic reviews and meta-analyses have shown a superior overall survival of partial hepatectomy over thermal ablation for liver only CRLM. However, given the high risk of residual bias when comparing ablation for unresecatble disease and partial hepatectomy for resectable disease and given several recent series with comparable outcome, the evidence level from these analyses were downgraded.

EVIDENCE LEVEL 'PARTIAL HEPATECTOMY SUPERIOR TO THERMAL ABLATION': (LOW)

15. Thermal ablation can be considered for patients with resectable *superficial or shallow* CRLM ≤3cm, if the general health condition is poor (ECOG 2 and ASA 3 or CCI 5-8).[8,45]

Patients with a high ECOG, ASA and/or CCI score have a high risk for postoperative mortality and morbidity as mentioned earlier. Abundant series / registries and several systematic reviews and meta-analyses have shown that thermal ablation alone has a very low mortality (≤1%) and low complication rate, even though often performed in patients with suboptimal general health conditions. Given the current clinical equipoise of partial hepatectomy and thermal ablation for small-size CRLM in patients with an optimal general health condition, thermal ablation seems more appropriate in patients with suboptimal general health condition. In other words, the risk-benefit ratio favors thermal ablation over partial hepatectomy in patients with a suboptimal general health status.

EVIDENCE LEVEL: EXPERT OPINION (LOW)

16. Thermal ablation is the appropriate local treatment method for patients with resectable and thermally ablatable CRLM ≤3cm, if the location of the CRLM is *deep-seated* (e.g. resection would require major hepatectomy), at the prerequisite that ECOG is ≤2, ASA is ≤3 and CCI is ≤8).[46]

There is no literature available comparing major hepatectomy to thermal ablation. In the COLLISION trial expert panel the majority of the panelists do routinely disagree to randomize these patients. The argumentation being that these patients should be offered ablation due to its lower complication rate, sparing of parenchyma and the good local control rate of thermal ablation. Given the current clinical equipoise of partial hepatectomy and thermal ablation for easily resectable small-size CRLM, thermal ablation seems more appropriate than major hepatectomy for deep-seated CRLM. In other words, the risk-benefit ratio favors thermal ablation over partial hepatectomy in these patients.

EVIDENCE LEVEL: EXPERT OPINION (LOW)

17. Thermal ablation is the appropriate local treatment method for patients with unresectable and thermally ablatable CRLM ≤3cm, and can be considered for CRLM 3-5cm when (further) downsizing systemic therapy is unfeasible, at the prerequisite that CCI ≤8, ASA is ≤3 and ECOG is ≤2.[21,37,41-44,47]

The long term results of the phase II EORTC CLOCC trial found a superior DFS and OS with the addition of thermal ablation compared to chemotherapy alone in unresectable CRLM, however due to serious indirectness (substantial no. of patients also had resections) and serious imprecision (trial was stopped early, before reaching sample size) the evidence level was downgraded from very high to moderate.

EVIDENCE LEVEL: DOWNGRADED RCT (MODERATE TO HIGH)

18. Irreversible electroporation (IRE) can be considered for patients with unresectable and not thermally ablatable *perihilar* or *perivascular* CRLM ≤3cm, and 3-5cm if further downsizing systemic therapy is unfeasible, at the prerequisite that CCI is ≤8, ASA is ≤3 and ECOG is ≤2.[48-50]

Multiple prospective and retrospective studies and a systematic review have found IRE to be a feasible and effective treatment method for unresectable and not thermally ablatable CRLM. The ESMO guidelines have adopted the ablative therapy for CRLM unsuitable for surgery and thermal ablation in 2016. The final results of the prospective COLDFIRE-2 trial are currently under review pending minor residual revisions at the Journal of Clinical Oncology (JCO) and in that phase-2 effectiveness-threshold the primary endpoint was met: 68.0% of patients were alive without local tumor progression at 1-year post-IRE.

EVIDENCE LEVEL LOW: PROSPECTIVE AND RETROSPECTIVE COHORT STUDIES

19. Stereotactic ablative radiotherapy (SBRT) can be considered for patients with limited disease burden (≤3 CRLM) if an ablative dose can be delivered without jeopardizing liver function and other organs or structures at risk, at the perquisite that ECOG is ≤3, ASA is ≤4 and CCI is ≤10.[51-54]

Based on a limited number of studies, liver SBRT, which does not require anesthesia or conscious sedation, seems to be safe and locally effective in select patients with a poor performance status.

EVIDENCE LEVEL LOW: SMALL NON COMPARATIVE CASE SERIES & EXPERT OPINIONS

20. Hemihepatectomy is the appropriate local treatment method for multiple CRLM (≥3) within a single lobe when at least one of these CRLM is deep-seated, even when potentially ablatable, at the prerequisite that CCI is ≤8, ASA is ≤3 and ECOG is ≤2.[39,40]

There is no literature available comparing major hepatectomy to multiple single-lobe thermal ablations. In the COLLISION trial expert panel the majority of the panelists do routinely disagree to randomize these patients. They should be offered (major) hepatectomy. The abovementioned argument to favor thermal ablation over major hepatectomy for deep-seated CRLM given its low complication rate and good local control is less apparent when multiple tumors have to be ablated within a single lobe. In other words, the risk-benefit ratio does not favor multiple unilobar thermal ablations over hemihepatectomy in this subgroup.

EVIDENCE LEVEL VERY LOW: SMALL NON COMPARATIVE CASE SERIES & EXPERT OPINIONS

21. When considering fit patients with multiple *scattered* and *bilobar* CRLM ≤3cm (≥6 CRLM in total and ≥3 deep-seated CRLM in both lobes separately) what treatment is appropriate: *chipand-burn* wedge resection(s) of all exophytic, superficial and shallow CRLM and thermal ablation of all deep-seated CRLM; or a *2-stage-hepatectomy*: stage 1: wedge resection(s) of all superficial CRLM and thermal ablations of all deep-seated CRLM in 1 lobe and (following contralateral liver augmentation) stage 2: contralateral hemihepatectomy.[55,56]

Score 1-3: chip-and-burn

Score 4-6: equipoise

Score 7-9: 2-stage-hepatectomy

A systematic review on two-stage hepatectomy showed median OS of 37 months, this is comparable to the results of a study on single-stage resection + MWA showing a median OS of 38-42 months)

EVIDENCE LEVEL LOW: NON COMPARATIVE CASE SERIES & EXPERT OPINIONS

TREATMENT CHARACTERISTICS

22. Anatomical contra-indications for partial hepatectomy are: (a) inability to obtain R0 margins, (b) inability to leave a sufficient FLR volume and/or function, (c) inability to preserve the dual blood supply and the venous and biliary drainage from the FLR and (d) inaccessibility of the abdominal cavity due to excessive abdominal adhesions.[18,50,57,58]

Definition adheres to several previously published attempts to postulate resectability criteria.

23. Anatomical contra-indications for thermal ablation are: (a) peri-tumoral vicinity (<10mm) of the common, left or right hepatic bile duct or (b) peri-hepatic critical structures that cannot be distanced using surgical or interventional dissection methods, (c) the abutment or encasement of the single remaining major portal or systemic vein following surgery and (d) an invasion of the free wall of the inferior caval vein. The maximum size is 3cm, although thermal ablation can be considered for 3-5cm unresectable CRLM after failure to (further) downsize them with systemic therapy.[59]

Definition adheres to the quality improvement guidelines published by CIRSE.

24. Contra-indications for irreversible electroporation are: CRLM >5cm, ventricular arrhythmias, cardiac stimulation devices and congestive heart failure.

Definition adheres to the standardized protocol published in JVIR 2020: Irreversible electroporation for hepatic tumors: protocol standardization using the modified Delphi technique. Ruarus et al. JVIR 2020

25. Contra-indications for stereotactic body radiotherapy (SBRT) are: >3 CRLM and inability do deliver an ablative dose without jeopardizing liver function and adjacent organs or structures at risk.[51,60]

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APPENDIX 2.1

Definitions

Eastern Cooperative Oncology Group (ECOG) performance status

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

American Society of Anesthesiologists (ASA) performance status

ASA I	A normal healthy patient
ASA II	A patient with mild systemic disease. Mild diseases only without substantive functional limitations.
ASA III	A patient with severe systemic disease. Substantive functional limitations; One or more moderate to severe diseases.
ASA IV	A patient with severe systemic disease that is a constant threat to life.
ASA V	A moribund patient who is not expected to survive without the operation
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes

Underlying liver disease

Mild liver disease = chronic hepatitis (or cirrhosis without portal hypertension)

Severe liver disease = cirrhosis and portal hypertension with or without variceal bleeding history

Charlson Comorbidity Index (CCI)

Variable	Definition	Points
Myocardial infarction	History of definite or probable MI (EKG changes and/or enzyme changes)	1
Congestive heart failure	Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents	1
Peripheral vascular disease	Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm)	1
Cerebrovascular accident or transient ischemic attack	History of a cerebrovascular accident with minor or no residua and transient ischemic attacks	1
Dementia	Chronic cognitive deficit	1
Chronic obstructive pulmonary disease	-	1
Connective tissue disease	-	1
Peptic ulcer disease	Any history of treatment for ulcer disease or history of ulcer bleeding	1
Mild liver disease*	Mild = chronic hepatitis (or cirrhosis without portal hypertension)	1
Uncomplicated diabetes*	-	1
Hemiplegia	-	2
Moderate to severe chronic kidney disease	Severe = on dialysis, status post kidney transplant, uremia, moderate = creatinine >3 mg/dL (0.27 mmol/L)	2
Diabetes with end-organ damage*	-	2
Localized solid tumor**	-	2
Leukemia	-	2
Lymphoma		2
Moderate to severe liver disease*	Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history	3
Metastatic cancer**	-	6
AIDS	-	6

Plus 1 point for every decade age 50 years and over, maximum 4 points.

* liver disease and diabetes inputs are mutually exclusive (e.g. do not give points for both "mild liver disease" and "moderate or severe liver disease").

** Other than the colorectal cancer for which the patient is currently being assessed (the comorbidity score is for co-existing diseases)

General health status

Very poor general health status:	ECOG ≥3, ASA ≥4 and/or CCI ≥9
Poor general health status:	ECOG 2 *and* ASA 3 or CCI 5-8
Good general health status:	ECOG ≤2, ASA ≤3 and CCI ≤4

Fong Clinical Risk Score (CRS)

Validated prognostic score for CRLM

Node-positive primary	1 point
Disease -free interval from primary to metastases <12 months	1 point
Number of hepatic tumors >1	1 point
Largest hepatic tumor >5cm	1 point
carcinoembryonic antigen level >200 ng/ml	1 point

0-2 points low risk

3-5 points high risk

Note: CRS is defined only once, at the time of detection of the CRLM

Hepatectomy

No consensus exists regarding the definition of a major hepatectomy and more specifically the minimum number of segments removed. Because this is off topic for the current study, we avoided the 'number of segments removed' discussion and classified resection types into minor versus major, hereby adhering to both the Dutch DHBA guidelines and the COLLISION trial research protocol.

A standard definition of major hepatectomy: resection of four or more liver segments. Srinevas K. Reddy et al. HPB 2011; Redefining major hepatic resection for colorectal liver metastases: Analysis of 1111 liver resections. Gareth Morris-Stiff et al. Int J Surg 2016; Implementation and first results of a mandatory, nationwide audit on liver surgery; Implementation and first results of a mandatory, nationwide audit on liver surgery. Leonie R. van der Werf et al. HPB 2016.

Minor hepatectomy: wedge resection, segmentectomy, left lateral sectionectomy, right posterior bisectionectomy, residual healthy liver volume >40%, ≤1 hepatic vein involved and inferior caval vein free from tumor.

Major hepatectomy: (extended) hemihepatectomy, left medial sectionectomy (sIV), right anterior sectionectomy (sV/VIII), central bisegmentectomy (sIV/V /VIII), residual healthy liver volume ≤40%, or biliary or vascular reconstruction(s) required.

Future liver remnant

Future liver remnant volume is defined as the ratio of the remnant functioning liver volume (FLR) to the total functional liver volume (TFLV). The TLV is calculated using the following formula: total liver volume (TLV) – tumor volume (TV) = TFLV. Future liver remnant function is calculated using 99mTcmebrofenin hepatobiliary scintigraphy. There is currently no consensus whether to prefer FLR volume, FLR function or both and hence this is up to local expertise and will be disregarded in our paper as it is off-topic.

Early metachronous disease

Occurrence of CRLM within 6 months after diagnosis of the primary cancer in patients without metastases at the time of diagnosis of the primary tumor, at the prerequisite that adequate crosssectional imaging for staging purposes was performed at baseline.

Perihilar CRLM

'Involvement (direct abutment, ingrowth or encasement) of the central bile ducts' here means resection would require biliary reconstruction surgery if resected. Peritumoral vicinity (<10 mm) of the central bile ducts here means thermal ablation is contraindicated.

Perivascular CRLM

‘Involvement (direct abutment, ingrowth or encasement) of major blood vessels’ here means resection would require vascular reconstruction and thermal ablation would entail risk of vascular thrombosis, occlusion and / or life-threatening hemorrhage.

‘Peritumoral vicinity of major blood vessels’ here means thermal ablation is not contra-indicated, but tumors are at risk for heat-sink induced incomplete ablations.

The following location definitions *only apply to* small-size CRLM (≤3cm)!

Exophytic CRLM:	The center or at least a substantial part of the tumor lies beyond the confines of the liver.
Superficial CRLM:	Tumors located at the surface of the liver that require minor hepatectomy.
Shallow CRLM:	Tumors located sub-surface or at shallow depths that require minor hepatectomy.
Deep-seated CRLM:	Deep-seated CRLM that, by definition, require major hepatectomy.

APPENDIX 3.1

Table 2: Guidelines from Clearinghouse and International Network Guidelines reviewed according to the AGREE-II* instrument.

	7	8	9	10	11	12	13	14	Domain score
ACR 2014	2	1	3	6	3	2	1	1	22.9
ASCRS 2012 (colon)	6	3	2	2	3	3	2	1	29.2
ASCRS 2013 (rectum)	6	1.5	2	2	3	2.5	2	1	25
CCO 2012	6	7	2,5	1.5	2.5	6	7	7	65.6
ESMO 2012	1	1	1.5	3	1.5	2	1	2	10.4
ESMO 2014	1	1	2	1.5	2.5	2	1	2	10.4
ESMO 2013	1	1	1.5	1.5	2	2.5	1	2.5	10.4
IKNL 2014	4	3.5	3.5	5.5	5.5	6	5	5	62.5
KCE 2014	6.5	3	7	6	6	7	6.5	7	85.4
NCCN 2015 (colon)	4.5	2	1.5	4.5	3.5	2	1.5	7	38.5
NCCN 2015 (rectum)	4.5	2	1.5	4.5	4	2.5	1.5	7	40.6
NICE 2011	7	7	7	6	7	7	5.5	6	92.7
SIGN 2011	4.5	3.5	3.5	4	5.5	5	5	4	56.3

*** A quality score is calculated for each of the six AGREE II domains. The six domain scores are independent and should not be aggregated into a single quality score. Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. Although the domain scores are useful for comparing guidelines and will inform whether a guideline should be recommended for use, the Consortium has not set minimum domain scores or patterns of scores across domains to differentiate between high quality and poor quality guidelines. These decisions should be made by the user and guided by the context in which AGREE II is being used.**

Table 2 (online appendix). Guidelines from Clearinghouse and International Network Guidelines reviewed according to the AGREE-II instrument.

Table 3 (online appendix). Search-strategies.

Available on: https://link.springer.com/article/10.1007/s00270-018-1959-3

Table 4 (online appendix). List of excluded studies.

Available on: ttps://link.springer.com/article/10.1007/s00270-018-1959-3

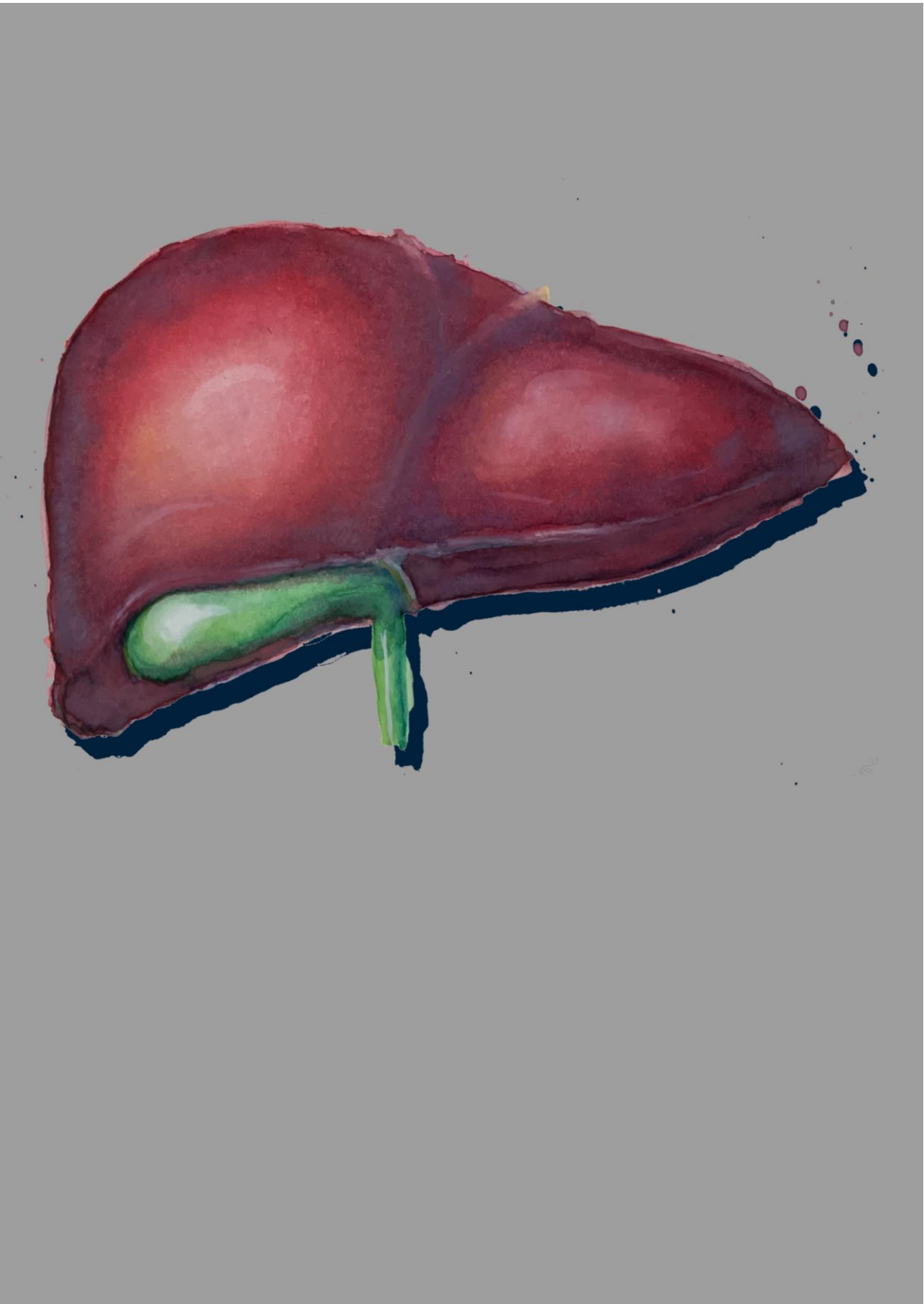
APPENDIX 8.5

		Univariable Analysis		Multivariable Analysis	
		HR (CI)	*p*-Value	HR (CI)	*p*-Value
Repeat local treatment	Repeat resection	Reference	0.959	Reference	0.397
	Repeat thermal ablation	1.023 (0.426–2.454)		1.486 (0.594–3.714)	
Patient-Related Factors					
Gender	Male	Reference	0.655		
	Female	1.233 (0.492–3.089)			
Age (years)		1.006 (0.970–1.044)	0.730		
ASA physical status	1	Reference	0.263		
	2	1.713 (0.230–12.747)			
	3	0.645 (0.067–6.208)			
Comorbidities	None	Reference	0.776		
	Minimal	1.288 (0.568–2.919)			
	Major	0.857 (0.191–3.838)			
BMI (kg/cm²)		1.065 (0.979–1.159)	0.141		
Primary tumor location	Rectum	Reference	0.715		
	Colon left-sided	0.678 (0.268–1.720)			
	Colon right-sided	0.819 (0.297–2.262)			
Factors Regarding Initial Local Treatment of CRLM					
Initial CRLM diagnosis	Synchronous	Reference	**0.002**	Reference	0.077
	Metachronous	3.964 (1.643–9.560)		2.391 (0.909–6.284)	
Number of tumors	1	Reference	0.898		
	2–5	1.273 (0.454–3.574)			
	>5	1.150 (0.365–3.625)			
Size of largest metastasis (mm)	Small (1–30)	Reference	0.353		
	Intermediate (31–50)	0.399 (0.114–1.390)			
	Large (>50)	*			
Extrahepatic disease	No	Reference	0.545		
	Yes	0.538 (0.072–4.004)			
Type of procedure	Resection	Reference	0.950		
	Thermal ablation	1.018 (0.401–2.585)			
	Resection and thermal ablation	0.693 (0.264–1.820)			
	IRE	*			
	SBRT	*			
Factors Regarding Repeat Local Treatment of CRLM					
Time between initial treatment and diagnosis recurrence (months)		1.029 (1.010–1.049)	**0.003**	1.032 (1.012–1.052)	**0.001**
Number of tumors	1	Reference	**0.016**	Reference	0.194
	2–5	0.292 (0.126–0.677)		0.431 (0.173–1.072)	
	>5	*		*	
Size of metastasis (mm)	Small (1–30)	Reference	0.525		
	Intermediate (31–50)	1.914 (0.624–5.871)			
	Large (>50)	*			
Chemotherapy	No	Reference	0.264		
	Yes	0.592 (0.236–1.485)			
Margin size	<5mm	Reference	0.652		
	>5mm	0.717 (0.169–3.042)			

Table S1. Univariable and multivariable cox regression analysis to detect potential confounders associated with local tumor progression-free survival (LTPFS). After removal of initial CRLM diagnosis and number of recurrent metastasis, and adjusting for the confounder time between initial treatment and diagnosis recurrence, corrected HR of repeat local treatment was 1.486 (95% CI, 0.594–3.714; p = 0.397). HR = hazard ratio, CI = 95% confidence interval, ASA = American Society of Anesthesiologists score, BMI = body mass index, * = insufficient subgroup size for each treatment group.

		Univariable Analysis		Multivariable Analysis	
		HR (CI)	*p*-Value	HR (CI)	*p*-Value
Repeat local treatment	Repeat resection	Reference	0.660	Reference	0.942
	Repeat thermal ablation	1.139 (0.637–2.038)		1.024 (0.545–1.922)	
Patient-Related Factors					
Gender	Male	Reference	0.834		
	Female	1.052 (0.655–1.691)			
Age (years)		0.982 (0.962–1.003)	0.092	0.986 (0.964–1.009)	0.239
ASA physical status	1	Reference	0.470		
	2	1.425 (0.570–3.562)			
	3	1.748 (0.664–4.607)			
Comorbidities	None	Reference	0.649		
	Minimal	1.015 (0.648–1.590)			
	Major	1.344 (0.707–2.554)			
BMI (kg/cm²)		0.971 (0.919–1.027)	0.305		
Primary tumor location	Rectum	Reference	0.877		
	Colon left-sided	1.008 (0.606–1.677)			
	Colon right-sided	1.134 (0.643–2.000)			
Factors Regarding Initial Local Treatment of CRLM					
Initial CRLM diagnosis	Synchronous	Reference	0.089	Reference	0.199
	Metachronous	0.691 (0.452–1.058)		0.731 (0.453–1.179)	
Number of tumors	1	Reference	0.311		
	2–5	1.077 (0.645–1.798)			
	>5	1.504 (0.843–2.684)			
Size of largest metastasis (mm)	Small (1–30)	Reference	0.189		
	Intermediate (31–50)	0.630 (0.379–1.046)			
	Large (>50)	0.731 (0.291–1.840)			
Extrahepatic disease	No	Reference	0.238		
	Yes	0.577 (0.232–1.437)			
Type of procedure	Resection	Reference	0.824		
	Thermal ablation	1.203 (0.717–2.017)			
	Resection and thermal ablation	0.889 (0.529–1.496)			
	IRE	1.108 (0.263–4.668)			
	SBRT	0.698 (0.095–5.153)			
Factors Regarding Repeat Local Treatment of CRLM					
Time between initial treatment and diagnosis recurrence (months)		0.980 (0.963–0.998)	0.032	0.973 (0.951–0.995)	0.016
Number of tumors	1	Reference	0.235		
	2–5	1.422 (0.934–2.164)			
	>5	1.852 (0.254–13.511)			
Size of largest metastasis (mm)	Small (1–30)	Reference	0.008	Reference	0.002
	Intermediate (31–50)	1.533 (0.839–2.803)		1.959 (1.054–3.641)	
	Large (>50)	8.469 (1.982–36.183)		10.409 (2.266–47.816)	
Chemotherapy	No	Reference	0.158		
	Yes	0.707 (0.437–1.144)			

Table S2. Univariable and multivariable cox regression analysis to detect potential confounders associated with distant progression-free survival (DPFS). After removal of age and initial CRLM diagnosis, and adjusting for the confounders size of largest recurrent metastasis and time between initial treatment and diagnosis recurrence, corrected HR of repeat local treatment was 1.024 (95% CI, 0.545–1.922; p = 0.942). HR = hazard ratio, CI = 95% confidence interval, ASA = American Society of Anesthesiologists score, BMI = body mass index.



LIST OF PUBLICATIONS

The full list of published papers, ordered by the year of publication.

1. Ruarus AH, Vroomen L, Puijk RS, Scheffer HJ, Faes TJC, Meijerink MR. Conductivity Rise During Irreversible Electroporation: True Permeabilization or Heat? Cardiovasc Intervent Radiol. 2018;41(8):1257-66.

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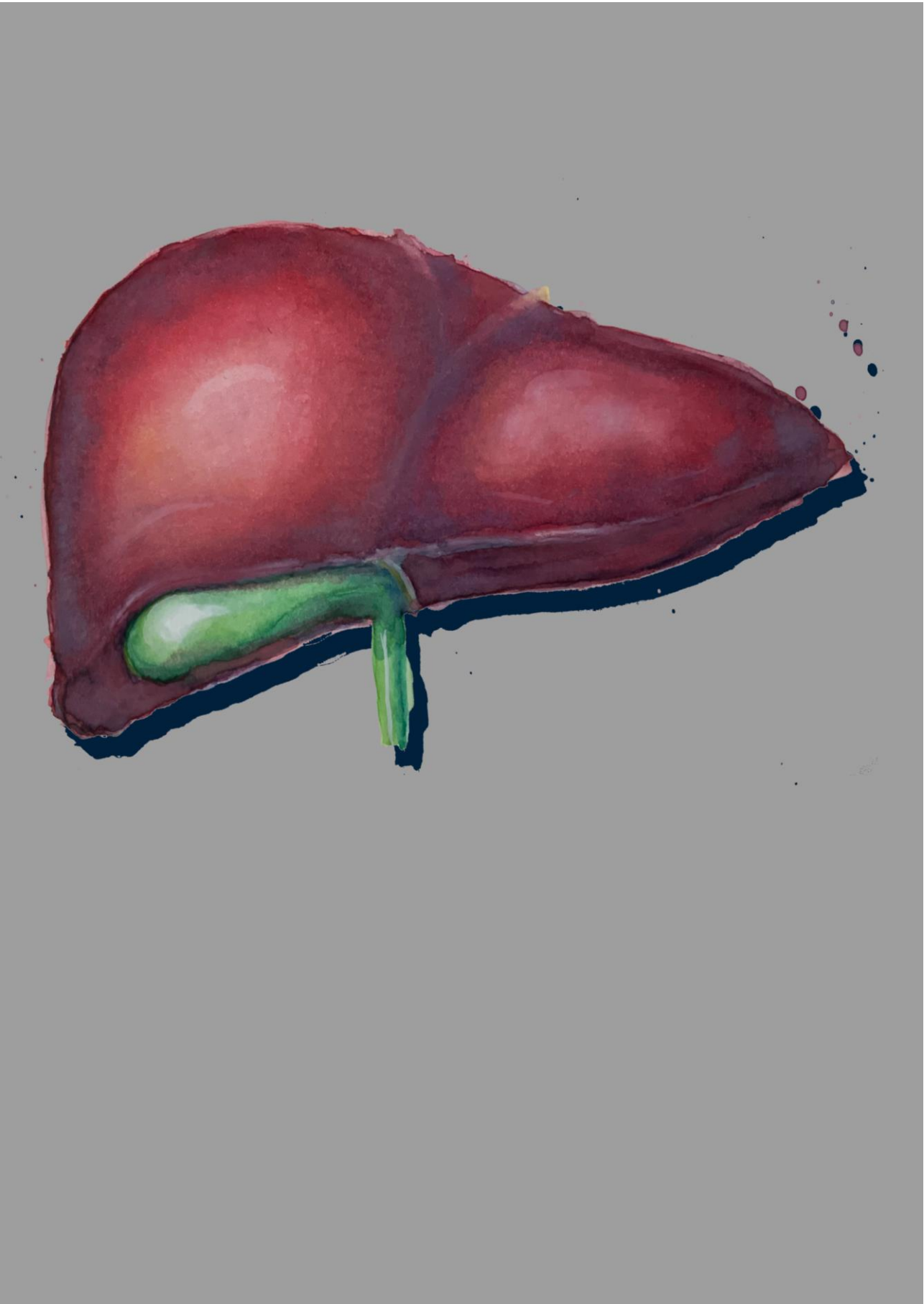

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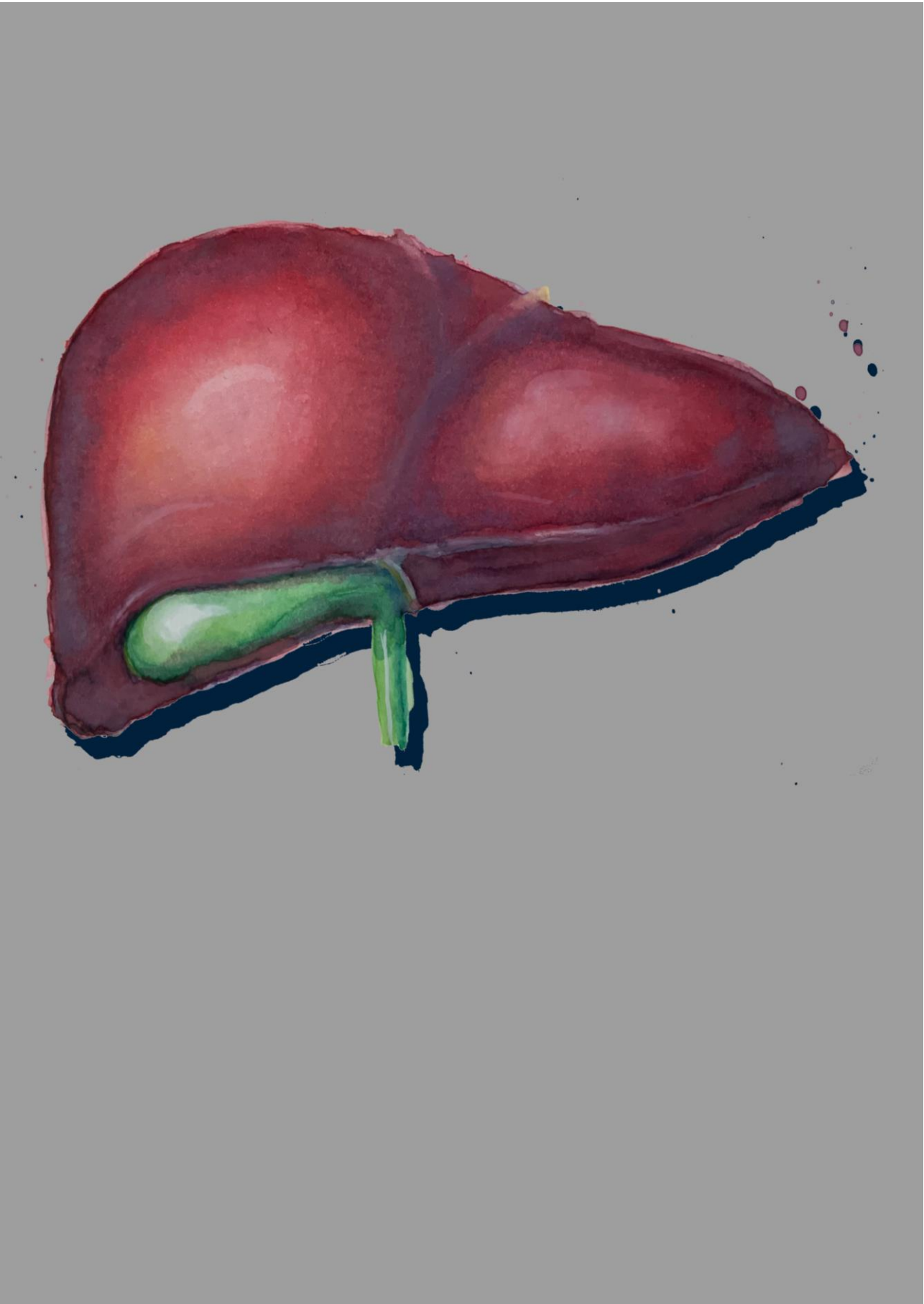

CURRICULUM VITAE AND AWARDS

Robbert Staffan Puijk was born on 30th of July 1988 in Zeist, the Netherlands, as the oldest of a family with two children. After primary school he went to the RSG ‘t Slingerbos in Harderwijk, where he obtained his VWO-level high school certificate in 2006. Directly hereafter Robbert started his medical training at the University Medical Center in Utrecht. During medical school, he worked as a student tutor anatomy at the Utrecht University and performed a clinical internship at the University Malaya Medical Centre in Kuala Lumpur. After medical school he gained clinical experience as a surgical resident-not-in-training at the Diakonessenhuis hospital and UMCU in Utrecht. During this period he developed his affinity with (interventional) radiology.

In 2017, Robbert started his PhD trajectory at the dept. of Radiology and Nuclear Medicine, subdivision of Interventional Radiology & Interventional Oncology at the Amsterdam University Medical Centers (AUMC), location VUMC. During this period, he was the co-initiator and coordinator of the international randomized ‘COLLISION’ trial, the prospective Amsterdam CORE registry (AmCORE) and the international SIO-DATECAN consensus guidelines project. To date he is (co-)author of 32 papers in the field of Interventional Oncology. Robbert and his supervisor prof. dr. M.R. Meijerink have been awarded the CVIR Editors' Medal 2019 for their paper ‘Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis’. In 2023, Robbert has been awarded the CVIR Editors’ Medal for his paper ‘Improved outcomes of thermal ablation for colorectal liver metastases: a 10-year analysis from the prospective Amsterdam CORE registry (AmCORE)’. Besides these two prestigious awards, Robbert was able to present his research output at multiple (inter)national gatherings with faculty invitations at the ADIO, AMIOS, CIRSE, ECIO, MIOLive, SIO, and Spectrum conferences over the past years.

In May 2020, Robbert started working as a resident Radiology and Nuclear Medicine at the OLVG hospital in Amsterdam. In 2023 he started his integrated Interventional Radiology residency program at the Amsterdam UMC and OLVG hospital.

Bibliography

Prizes

- CVIR Editors' Medal 2023, CIRSE 2023, Copenhagen, Denmark
- CVIR Editors' Medal 2019, CIRSE 2019, Barcelona, Spain
- Distinguished oral abstract, SIO 2019, Boston, USA

Presentations as invited speaker (Faculty)

- Thermal liver ablation, Spectrum 2024, Miami, USA
- Workshop on thermal liver ablation, Spectrum 2023, Miami, USA
- Presenter IRE pancreas, ADIO 2022, Athens, Greece
- Workshop on thermal liver ablation, CIRSE 2022, Barcelona, Spain
- Session moderator on image-guided therapies, CIRSE 2022, Barcelona, Spain
- Presenter guidelines time-to-event endpoints, ECIO 2022, Vienna, Austria
- Presenter COLLISION interim results, MIOLive 2022, Rome, Italy (virtual)
- Presenter COLLISION interim results, Spectrum, Miami Beach, USA
- Presenter Imaging to Define Ablation, SIO 2021, San Francisco, USA (virtual)
- COLLISION trial study design, AMIOS 2018, Amsterdam, the Netherlands

Abstract presentations

- 10y analysis of thermal ablation for CRLM, SIO 2022, San Francisco, USA
- COLLISION interim results, NVIR 2022, Utrecht, NL
- CTHA-guidance in percutaneous thermal ablation, CIRSE 2021 (virtual)
- CTHA-guidance in percutaneous thermal ablation, SIR 2020, Seattle, USA (virtual)
- CTHA-guidance in percutaneous thermal ablation, SIO 2020, New Orleans, USA
- Anesthetic management during percutaneous MWA, SIO 2019, Boston, USA
- Systematic Review and Meta-Analysis, CIRSE 2018, Lisbon, Portugal

“Coming together is a beginning.
Keeping together is progress.
Working together is success.”

Henry Ford (1863-1947)