

## Online 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  $\leq 2$ , ASA  $\leq 3$  and CCI  $\leq 8$ ); 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  $\leq 2$  patients, for ECOG  $\geq 3$  patients the risks of surgery, thermal ablation and IRE do not outweigh the benefits[5-8]; in select patients with limited disease ( $\leq 3$  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  $\geq 3$  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  $\leq 3$  patients, for ASA 4 patients the risks of surgery, thermal ablation and IRE do not outweigh the benefits; in select patients with limited disease ( $\leq 3$  CRLM) SBRT can be considered for ASA 4 patients[8-13].

*Based on several studies ASA  $\geq 4$  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  $\geq 40\%$ . 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  $\leq 4$  and for patients with CCI 5-8 if the procedure is considered non-complex (minor hepatectomy +/- ablations); for patients with a CCI  $\geq 9$  the risks of surgery, thermal ablation and IRE do not outweigh the benefits; in select patients with limited disease ( $\leq 3$  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 downstaging 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 unresectable 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  $\leq 3$ cm, 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 ( $\leq 1\%$ ) 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  $\leq 3$ cm, if the location of the CRLM is *deep-seated* (e.g. resection would require major hepatectomy), at the prerequisite that ECOG is  $\leq 2$ , ASA is  $\leq 3$  and CCI is  $\leq 8$ )[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  $\leq 3$ cm, and can be considered for CRLM 3-5cm when (further)

downsizing systemic therapy is unfeasible, at the prerequisite that CCI  $\leq 8$ , ASA is  $\leq 3$  and ECOG is  $\leq 2$ [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 nr 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  $\leq 3$ cm, and 3-5cm if further downsizing systemic therapy is unfeasible, at the prerequisite that CCI is  $\leq 8$ , ASA is  $\leq 3$  and ECOG is  $\leq 2$ [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 ( $\leq 3$  CRLM) if an ablative dose can be delivered without jeopardizing liver function and other organs or structures at risk, at the prerequisite that ECOG is  $\leq 3$ , ASA is  $\leq 4$  and CCI is  $\leq 10$ [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 ( $\geq 3$ ) within a single lobe when at least one of these CRLM is deep-seated, even when potentially ablatable, at the prerequisite that CCI is  $\leq 8$ , ASA is  $\leq 3$  and ECOG is  $\leq 2$ [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  $\leq 3\text{cm}$  ( $\geq 6$  CRLM in total and  $\geq 3$  deep-seated CRLM in both lobes separately) what treatment is appropriate: chip-and-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 ( $< 10\text{mm}$ ) 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  $> 5\text{cm}$ , 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 to deliver an ablative dose without jeopardizing liver function and adjacent organs or structures at risk[51,60].

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