DISCUSSION AND FUTURE PERSPECTIVES
Interventional oncology (abbreviated IO) is a subspecialty field of interventional radiology that deals with the diagnosis and treatment of cancer and cancer-related problems using targeted minimally invasive procedures performed under image guidance. Interventional oncologists nowadays play a major role in multidisciplinary cancer teams where they provide innovative solutions to improve combined therapies and to treat complications. IO represents the fastest growing subspecialty in the field of oncology. Given the minimally invasive nature of the treatments that are generally associated with less pain, fewer side effects, faster recovery, shorter hospitalization times and lower costs, this seems justified. Interventional oncology has settled as a separate pillar of modern oncology and employs X-ray, ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) to help guide miniaturized instruments (e.g. biopsy needles, ablation electrodes, intravascular catheters) to allow targeted and precise treatment of solid tumors located in various organs of the human body, including but not limited to the liver, kidneys, lungs, and bones.

Over the past decade, especially radiofrequency ablation (RFA) and microwave ablation (MWA) have evolved into important therapeutic tools for the treatment of non-resectable primary and secondary liver tumors. The clinical benefit of thermal ablation is represented in several clinical studies and nowadays the techniques are widely adopted in international guidelines for the radical treatment of relatively small lesions. These reports underline the safety, feasibility and efficacy of this new and modern concept in treating liver tumors. Ablation has proven its clinical impact in hepatocellular carcinoma and replaced surgery for the majority of patients with very-early and early stage disease with nowadays even higher evidence grades compared to surgery \(^1\). The adoption of thermal ablation for colorectal liver metastases has been a lengthier and more challenging process, and the interventional radiology and oncology societies have only themselves to blame. With merely one high-quality randomized controlled trial (the EORTC-CLOCC trial \(^2\)), which even had to be downgraded from a phase III to a phase II trial due to slow accrual, the evidence was circumstantial and potentially biased for over 15 years. The recently presented long-term results leave little room for debate with an 8-year overall survival rate of 8.9% for chemotherapy alone versus 35.9% for RFA plus chemotherapy \(^3\). Given the survival-plateau at 8-years, many patients with potentially ablatable disease, that were treated with systemic chemotherapy alone, seem to have been deprived of their last realistic chance for cure as a result (8-year progression free survival 2.0% versus 22.3%, for the chemotherapy alone versus the RFA plus chemotherapy group). Various other attempts in history demonstrate the difficulties in setting-up and completing well-designed comparative studies for local therapies. Nonetheless, even though intuitively improved methods are rapidly introduced and adopted into general practice, this does not deprive us from our job to provide evidence at an early stage that these developments are true advances with less
complications and/or superior oncological outcome preferably in terms of complications, cost-effectiveness and quality-adjusted life years. For less common diseases or conditions we should prefer multicenter collaborations or accept the unavoidable lack of evidence and hence extrapolate data from comparable and more frequently encountered conditions in order to move forward and reach the highest achievable evidence levels.

**CURRENT TREATMENT GUIDELINES FOR COLORECTAL LIVER METASTASES**

Surgical resection represents the historical standard and treatment of first choice with 5-year OS reaching 35-60%. To eliminate unresectable metastases, several ablative strategies have emerged. Thermal ablation techniques employing RFA and MWA have slowly worked their way into common clinical practice and international guidelines. Thermal ablation for small liver lesions has an excellent safety profile with a low complication rate for smaller liver tumors. However, the issue of local site recurrence after thermal ablation has prohibited widespread adoption of the technique for resectable lesions. In the last few years, thermal ablation techniques have substantially improved with primary efficacy rates (complete ablation after the first procedure) for lesions ≤3cm now reaching 92-100% \(^4\). These results are comparable to the efficacy rate after surgical resection (negative margins) for similar-sized lesions. The relative ease to percutaneously re-ablate potential site recurrences, nowadays often in the setting of a one-day admission under conscious sedation, has downgraded the relevance of LSR with local control rates (assisted technique effectiveness) approaching 100% for lesions ≤3cm. As mentioned above, the recently presented long-term results from the EORTC CLOCC-trial (ASCO 2015) show a clear survival benefit of RFA plus systemic chemotherapy over chemotherapy alone for unresectable CRLM: 8-year OS 35.9% versus 8.9% (p=0.01; HR 0.58; 95%CI 0.38-0.88) \(^3\). The superior safety profile, the competitive oncological outcome and the suggested lower overall costs of thermal ablation over surgical resection, stress the need to conduct a randomized controlled trial for patients with small resectable and ablatable colorectal liver metastases.

For decades systemic treatment with 5-fluorouracil based regimens was considered standard of care for patients with advanced metastatic colorectal cancer, improving OS from 6 months to 10–12 months. The development of chemotherapeutic agents such as oxaliplatin and irinotecan has substantially improved OS to a median of up to 24 months. Sequential treatment with all available cytotoxic agents, as well as the introduction of Epidermal Growth Factor receptor (EGFR) and Vascular Endothelial Growth Factor (VEGF) binding monoclonal antibodies have further increased overall survival \(^5\)\(^-\)\(^8\).
Discussion and future perspectives

The high relapse rate after curative resection of CRLM, and the efficacy of modern systemic treatment in the metastatic setting, have prompted investigators to perform studies to evaluate the potential role of systemic chemotherapy combined with liver resection. The purpose of both adjuvant and neo-adjuvant chemotherapy is to treat microscopic disease that is not addressed by surgery. This microscopic disease may be promoting the high relapse rate that is observed after liver surgery. Notably, current literature suggests that timing of additional chemotherapy (adjuvant versus neo-adjuvant) seems to have no influence on outcome \(^9\). The role of perioperative chemotherapy in case of resectable CRLM was established in a randomized controlled trial \(^10\). In the mature OS analysis of this trial there was no significant effect on OS after a median follow up of 7 years \(^11\).

**FOCAL THERAPY FOR COLORECTAL METASTASES – EXPANDING THE HORIZON**

The multidisciplinary VUmc hepato-pancreatico-biliary (HPB) research group is conducting (and/or participating in) several ongoing and future studies regarding focal therapy for patients with colorectal cancer liver metastases that will further define borders and hopefully expand these patients horizons.

**The CHARISMA trial**

In the past, several clinical risk scores (CRS) for the outcome of patients with CRLM have been published. In 1999, Fong et al. described the most widely used CRS \(^12\). This prognostic scoring system has been verified by independent investigators \(^13\). Several authors have proposed the concept of stratification by CRS in relation to the effects of a multimodal treatment strategy on OS. These authors suggest that patients with a high risk score have a worse prognosis and might therefore benefit more from chemotherapy compared to patients with a low risk score \(^14, 15\).

**Table 1:** Fong’s clinical risk score for tumor recurrence (CRS)

<table>
<thead>
<tr>
<th>Points</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Node-positivity primary</td>
</tr>
<tr>
<td>1</td>
<td>&lt;12 months disease free interval</td>
</tr>
<tr>
<td>1</td>
<td>&gt;1 liver tumors</td>
</tr>
<tr>
<td>1</td>
<td>Largest tumor &gt;5cm</td>
</tr>
<tr>
<td>1</td>
<td>CEA &gt;200 ng/mL</td>
</tr>
<tr>
<td>Score 0-5</td>
<td>*at time of diagnosis liver metastases</td>
</tr>
</tbody>
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*at time of diagnosis liver metastases
As described earlier, efforts to improve outcome of liver surgery by combining the resection with chemotherapy have failed to demonstrate definite OS benefit. This may partly be due to the fact that these studies involve strict protocol inclusion criteria. Consequently, patients with a high clinical risk score - which might benefit the most from chemotherapy - are often underrepresented in these studies. Since genuine survival benefit has not yet been demonstrated, could this low impact of chemotherapy on survival then be explained by the relatively low risk profile of the patients included in these trials?

The currently ongoing Dutch CHARISMA trial will evaluate the effect on OS of neo-adjuvant chemotherapy in patients with primary resectable CRLM and a high CRS (Fong) of 3–5, thereby bearing a poor prognosis. The primary aim of this study is to compare OS in high-risk patients with resectable liver metastases randomized for treatment with chemotherapy, consisting of capecitabine and oxaliplatin (XELOX), followed by surgery versus surgery alone.

The correlation between lesion-size and outcome in terms of both local failure and overall survival after thermal ablation is strong and well established. Likewise, neo-adjuvant chemotherapy may downstage patients to less-invasive surgical resections and reduce peri-operative complications in selected patient groups. Given the high objective response rate of first line oxaliplatin based chemotherapy (> 80%), and anticipating on the results of the CHARISMA study, there is a rationale to give neo-adjuvant chemotherapy prior to thermal ablation and surgical resection in patients with more extensive disease and/or a higher clinical risk score (CRS >4).

**The ORCHESTRA trial**

Several studies have reported a worse outcome for patients with hepatic and extrahepatic disease. Nevertheless, retrospective series have shown that long term survival can be achieved in this specific group. One meta-analysis that included 1152 patients with simultaneous extrahepatic disease showed long term survival after radical resection of both the hepatic and the extrahepatic lesions. Although controversial, an increasing subset of patients are offered surgical resection, stereotactic ablative radiotherapy or thermal ablation of pulmonary metastases with similar results regarding outcome according to series using either multivariate analysis or case matching. After complete resection of extrahepatic metastatic sites 5 year survival rates of 40-68% can be achieved. Approximately 5-10% of the colorectal cancer patients will have metastases in both liver and lungs. In selected patients combined resection of lung and liver metastasis is feasible and 5 year survival rates of 30-60% have been reported. One has to realize that these reports concern a specifically selected group of patients and 5-year survival rates are therefore highly biased. For patients with >1 extrahepatic site or with involvement of the celiac axis lymph nodes or the
Discussion and future perspectives

adrenal gland, prognosis is cumbersome and focal tumor eradication seems unbeneficial over systemic chemotherapy alone. Whether maximum debulking for patients with more extensive extrahepatic metastatic colorectal carcinoma improves survival will hopefully be shown in the currently ongoing ORCHESTRA trial.

The COLDFIRE-1 and 2 trials

Although thermal ablation has improved survival rates for patients with CRLM, factors like size and location limit its use and effectiveness. With RFA, the rate of complete tumor necrosis falls below 50% when vessels larger than 3mm abut the tumor as a consequence of the heat-sink effect. Similarly, limitations around safety have been demonstrated for lesions close to vital structures like major bile ducts and vessels due to the risk of thermal damage.

Irreversible electroporation (IRE) is a novel ablation modality that may overcome some of the limitations of ablative therapies. It is based on a pulsating current created between multiple needle electrodes placed around the target lesion. The electric pulses alter the transmembrane potential of biologic cells. If the duration of the applied electrical pulses is below the charging time of the outer cell membrane, an interaction of the electric field with subcellular structures occurs. This interaction results in permanent permeabilization of the cell membrane, which disrupts cell homeostasis and ultimately leads to cell death. The irreversibly damaged cells are left in situ and are removed by the immune system. Two main factors stimulate research into IRE as an ablation modality. Since the mechanism of cell death is predominantly nonthermal, connective tissue structure is preserved, so there is no damage to associated blood vessels and bile ducts. For the same reason, treatment efficacy is not impeded by heat-sink. This allows for treatment of liver tumors deemed unresectable or ineligible for other focal ablation techniques due to localization near these structures.

The capability of IRE to destroy CRLM in humans was recently demonstrated by the VUmc research group in the COLDFIRE-1 pilot-study. In this study resectable CRLM were treated with IRE and resected one hour later. The investigators were able to demonstrate cell death of the ablated tumors within one hour after ablation, with intact larger vascular and ductal structures within the ablation zone. The first studies investigating hepatic IRE on clinical indication also yield promising results. A systematic review found an overall complication rate of 16%, which is similar to RFA. Complete tumor eradication was achieved in 67-100%, and this percentage was even higher for tumors < 3cm. However, since most studies are retrospective with short-term follow-up using heterogeneous study populations and design, the value of the current evidence can be considered limited.

The primary aim of the currently ongoing COLDFIRE-2 study is to investigate the efficacy of IRE for CRLM that are unsuitable for resection and thermal ablation due
to the vicinity of vulnerable structures such as bile ducts, vessels and bowel. Other outcomes are safety and accuracy of contrast-enhanced computed tomography (ceCT) and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) CT in the detection of local tumor progression.

The COLLISION trial

Numerous studies have demonstrated a superior safety profile in addition to lower direct and indirect costs of thermal ablation over surgical resection. Despite this, the 5-year OS (range 15-62%) 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. Because the groups are by definition confounded by indication these results should be interpreted with care. 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 VUmc center for image guided tumor ablation (CIGTA) has designed a two-arm phase-III randomized controlled trial comparing surgical resection (standard of care) to thermal ablation (experimental arm) for resectable and ablatable CRLM ≤3cm.

The primary objective of the COLLISION trial is to prove non-inferiority of thermal ablation compared to hepatic resection in patients with at least one resectable and ablatable CRLM (≤3cm) and no extrahepatic disease. COLLISION is a future single-blind prospective multi-center phase-III randomized controlled trial. We hypothesize that thermal ablation is non-inferior to surgery for the selected patient groups in terms of the primary objective (overall survival). Patients with ≥1 resectable and ablatable CRLM (≤3cm), no extrahepatic disease, a good performance status (WHO 0-2) and a low-risk clinical risk score (CRS 0-2; Fong et al.) are considered eligible. Supplementary resections for resectable lesions >3cm and thermal ablations for unresectable CRLM ≤3cm are allowed with a maximum number of CRLM of 10. Eligible patients will be stratified into low-, intermediate- and high disease burden after assessment by an expert panel. 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 ≤3cm ablatable. Eligibility needs to be reconfirmed during the surgical procedure. Hereafter, patients will be randomized to undergo surgical resection of the target lesions (allowing thermal ablation for additional unresectable lesions) or thermal ablation (allowing resection for additional unablatable lesions). Patients will remain unaware of the appointed treatment arm and the actual treatment of their target.
lesions (single-blind). Postprocedural care will be identical between the two groups with the exemption that hepatic recurrences (either local site recurrence or new lesions) suitable for both resection and ablation will again be treated with the technique used to treat the initial target lesion(s). Conferring to national guidelines follow-up will include 18F-FDG-PET-CT scans, laboratory tests including tumor markers (CEA) and quality of life questionnaires. Patients with recurrences that are considered unsuitable for additional focal therapy will be re-referred to their medical oncologist to assess additional systemic chemotherapy. In the event of chemotherapeutic down-staging hereafter, focal therapy can be reconsidered. The primary endpoint is overall survival (intention-to-treat analysis). Main secondary endpoints are overall disease-free survival, time to progression, time to local progression, primary and assisted technique efficacy, procedural morbidity and mortality, length of hospital stay, assessment of pain and quality of life, cost-effectiveness ratio and quality-adjusted life years.
Figure 1: Flowchart of the COLLISION trial – Colorectal liver metastases: surgery versus thermal ablation - a phase III single-blind prospective randomized controlled trial.
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