GENERAL SUMMARY

In Chapter 2.1 the long-term results and prognostic factors of radiofrequency ablation (RFA) for unresectable colorectal liver metastases (CRLM) in a single center with >10-years of experience were retrospectively analysed. One-hundred patients with unresectable histologically proven CRLM (sizes 0.2–8.3cm; mean 2.4cm) underwent a total of 126 RFA sessions (237 lesions). Mean follow-up time was 29.0 months (range 6-93 months). No direct procedure-related deaths were observed; two patients died in the first two weeks after RFA due to a massive myocardial infarction and pulmonary embolism respectively. Major complications were present in 11 patients (hemorrhage 1, abscess 4, cholangitis 1, gastric perforation 1, skin burns 2, lung embolus 1, pleural effusion 1). Local RFA-site recurrence was 12.7% (n=30/237) (for tumor-diameters <3cm, 3-5cm and >5cm this was respectively 5.6%(n=8/143), 19.5%(n=15/77) and 41.2%(n=7/17)). Centrally located lesions recurred more often than peripheral ones (21.4%(n=21/98)) versus 6.5%(n=9/139); p=0.009)). Including additional treatments for recurring lesions when feasible, patient and lesion based local control reached 54% and 93%. Mean survival-time from RFA was 56 (95%CI 45-67) months. Overall 1, 3, 5 and 8 year-survival from RFA was 93%, 77%, 36% and 24%. RFA for unresectable CRLM was concluded to represent a safe and effective treatment option, which can provide long-term survival-benefit comparable to surgical resection. Factors determining success were lesion-size, number and location of lesions.

In Chapter 2.2 we retrospectively analysed the safety and efficacy of RFA versus microwave ablation (MWA) in the treatment of unresectable CRLM in proximity to large vessels and/or major bile ducts. A database search was performed to include patients with unresectable histologically proven and/or 18F-FDG PET avid CRLM who were treated with RFA or MWA between January 2001 and September 2014 in a single centre. All lesions that were considered to have a peribiliary and/or perivascular location were included. Two-hundred and forty-three patients with 774 unresectable CRLM were ablated. One-hundred and twenty-two patients (78 male; 44 female) had at least one perivascular or peribiliary lesion (n=199). Primary efficacy rate of RFA was superior to MWA after 3 and 12 months follow-up (P =0.010 and P =0.022); however, after multivariate analysis this difference was non-significant at 12 months (P =0.078) and vanished after repeat ablations (P =0.39). More CTCAE (Common Terminology Criteria for Adverse Events) grade III complications occurred after MWA versus RFA (18.8% vs. 7.9%; P=0.094); biliary complications were especially common after peribiliary MWA (P=0.002). We concluded, RFA and MWA can be considered safe treatment options that appear to have equal efficacy for unresectable perivascular CRLM. Thermal ablation in the vicinity of major bile ducts seems effective although major complications can occur. Given the similar efficacy rate and lower complication
rate it is advised to use RFA instead of MWA for lesions that are located in the vicinity of the main bile ducts.

In **chapter 2.3** we assessed safety and outcome of RFA and MWA as compared to systemic chemotherapy and partial hepatectomy (PH) in the treatment of CRLM. MEDLINE, Embase, and Cochrane Library were searched, and systematic reviews of randomized trials, controlled studies, comparative observational studies with multivariate analysis and/or matching were included. Guidelines from Clearinghouse and International Network Guidelines were included and reviewed according to the AGREE-II instrument. The search resulted in 3504 records; 315 articles were selected for full text review; 45 were included: 8 systematic reviews, 2 randomized studies, 23 comparative observational studies, 2 guideline-articles and 10 case series; in addition 13 guidelines were evaluated. RFA plus systemic chemotherapy was superior to chemo alone. PH was superior to RFA alone but not to RFA + PH or, for patients with multiple small CRLM, to MWA. Compared to PH, RFA was associated with fewer complications, but MWA was not. This meta-analysis accentuates the clinical benefit of thermal ablation over chemo alone for unresectable small CRLM. Ablation for unresectable CRLM seems inferior to PH for resectable lesions, although the superior safety profile combined with the apparent selection bias stress the need to conduct a randomized controlled trial for small resectable and ablative CRLM.

In **chapter 3.1** we retrospectively evaluated the results regarding survival and recurrences after RFA treatment in patients with CRLM. We concentrated particularly on local site recurrences after thermal ablation and re-treatment. 132 patients were included in this analyses that were treated from July 2000 to December 2010. All patients had metastases confined to the liver only or in combination with potentially curable extrahepatic disease. In 64 patients, RFA was combined with resection. The patients had a total number of 390 lesions, of which 290 were ablated. A median of three tumors were treated per patient. Median survival was 41 months, with a 3- and 5-year survival of respectively 60% and 30.8%. Following initial RFA, 30.8% of the patients developed a local site recurrence (LSR) in 14.1% of the ablated lesions. This is comparable to results from previous literature. Local recurrence occurred in 39 patients and was strongly related to lesion size; 9% in lesions <3cm up to 45% in lesions >5cm. LSR was not a predictor for overall survival (39 months for patients with LSR and 44 months without a LSR, p=0.75). Retreatment was performed in 26/39 patients, of whom eight remained disease-free after a median follow-up of 34 months. The reason not to treat a LSR was the presence of extensive intra- or extrahepatic disease. These patients were referred to the medical oncologist. Local recurrence on its own was never a reason to deter from renewed local treatment. These study findings suggest that RFA can be applied to CRLM of ≤3cm with curative intent. In the absence
of extensive intra- and/or extrahepatic disease, repeated treatment of local recurrences should be considered and is often successful.

In chapter 3.2 our aim was to assess criteria for FDG PET-CT image interpretation following RFA, and to define a timetable for follow-up. The main area of concern regarding RFA of CRLM is the risk of developing a LSR. Follow-up imaging plays a key role in the detection of recurrent disease, especially because treatment of recurrences can provide complete tumor remission. Reported accuracy of FDG PET-CT in detecting LSR is high compared to morphological imaging alone, but no internationally accepted criteria for image interpretation have been defined. Patients who underwent RFA for colorectal liver metastases between 2005 and 2011, with FDG PET-CT follow-up within one year after treatment were included. Results of repeat FDG PET-CT scans were evaluated until a LSR was diagnosed. One hundred-seventy scans were obtained of 79 patients (179 lesions), 57 scans (72%) were obtained within 6 months of treatment. Thirty patients developed local recurrence; 29 (97%) within 1 year. Focal uptake in the ablation zone is always considered a LSR. Rim-shaped FDG uptake around an ablated area can disappear spontaneously within 5 months and therefore is not pathognomonic for a LSR. Only 2% of lesions of <1 cm and 4% of <2 cm showed a LSR. Since the majority of local site recurrences are diagnosed within one year after RFA, regular follow-up using FDG PET-CT within this time-period is advised, so repeated treatment can be commenced. Rim-shaped uptake may be present until 4–6 months after ablation, complicating evaluation. The additive value of follow-up lesions <2 cm may be limited, although follow-up FDG PET-CT is also useful to detect new CRLM. Future larger, preferably prospective randomised trials, are necessary to establish a survival benefit of an intensive follow-up regime after ablative treatment.

In chapter 4.1 we evaluated the feasibility of combining transcatheter computed tomography (CT) arterial portography (CTAP) or transcatheter CT hepatic arteriography (CTHA) with percutaneous liver ablation for optimized and repeated tumor exposure. Accurate intraprocedural targeting, monitoring, and control of ablation play a critical role in the success of percutaneous ablation. At the present time, CT is one of the most widely used imaging modalities for percutaneous ablation because it enables acquisition of three-dimensional images of the tumor in relation to the surrounding structures, the needle electrodes, and the ablation zone. CT fluoroscopy enables two-dimensional dynamic and real-time image-guided probe placement. However, in many cases, tumor tissue and ablation zones are barely visible on nonenhanced CT. During CT-guided thermal ablation, the delineation of tumor tissue and the induced coagulation zone is often limited to a time window after the application of intravenous contrast material. Consequently, having reached the maximum dose of intravenous contrast material after one or two injections, repetitive monitoring during the intervention is restricted and in most centers limited to injection before the procedure (treatment planning). Study
participants were 20 patients (13 men and 7 women; mean age, 59.4 y; range, 40–76 y) with unresectable liver-only malignancies; 14 with colorectal liver metastases (29 lesions), 5 with hepatocellular carcinoma (7 lesions), and 1 with intrahepatic cholangiocarcinoma (2 lesions), that were obscure on nonenhanced CT. A catheter was placed within the superior mesenteric artery (CT arterial portography) or in the hepatic artery (CT hepatic arteriography). CT arterial portography or CT hepatic arteriography was repeatedly performed after injecting 30–60 mL 1:2 diluted contrast material to plan, guide, and evaluate ablation. The operator confidence levels and the liver-to-lesion attenuation differences were assessed as well as needle-to-target mismatch distance, technical success, and technique effectiveness after 3 months. Technical success rate was 100%; there were no major complications. Compared to conventional unenhanced CT, operator confidence increased significantly for CTAP/CTHA cases (p < 0.001). The liver-to-lesion attenuation-differences between unenhanced CT, contrast-enhanced CT and CT arterial portography or CT hepatic arteriography were statistically significant (mean attenuation-difference 5HU vs. 28HU vs. 70HU; p < 0.001). Mean needle-to-target mismatch-distance was 2.4±1.2 mm (range 0-12.0mm). Primary technique effectiveness at 3 months was 87% (33/38 lesions). We concluded that in patients with technically unresectable liver-only malignancies, single-session CTAP/CTHA guided percutaneous tumor ablation enables repeated contrast-enhanced imaging and real-time contrast-enhanced CT fluoroscopy and hereby improves lesion conspicuity.

CTAP guided percutaneous liver tumor ablation has proven feasible and accurate to treat liver metastases from colorectal origin that are obscure on ultrasound and unenhanced CT. However, distinguishing local recurrence from post-ablation scars can still be difficult. In chapter 4.2 we reported nine patients with post-ablation recurrences, in whom CTHA allowed differentiation of recurring or residual vital tumor tissue with post-ablation scar tissue. In 9/9 cases the LSR presented as a typical ring-enhancing lesion with an interruption at the interface with the abutting non-enhancing post-ablation scar, which we called the incomplete ring sign. The recurring lesions were all successfully retreated using RFA (4 patients), MWA (3 patients) or IRE (2 patients). In one patient a new lesion, which was already detected on pre-procedural F18-FDG PET-CT, was also clearly visible using CTHA. Using CTHA it is possible to plan and guide percutaneous retreatment and confirm technical success without oversized re-ablations or jeopardizing patients renal function.

Chapter 5.1 describes the first clinical experiences with a novel bipolar plan-parallel expandable system for large-size liver tumors. Although radiofrequency ablation (RFA) is a promising method for local treatment of liver malignancies, with conventional monopolar systems recurrence rates for large size tumors (≥ 3.5cm) remain high. Eight consecutive patients with either unresectable CRLM (6 patients), carcinoid liver metastases (1 patient) and hepatocellular carcinoma (HCC) of ≥ 3.5cm were treated
with bipolar RFA during laparotomy with ultrasound guidance. Early and late, major and minor complications were recorded. Local success was determined on 3-8 months follow-up CT scans of the upper abdomen. Nine CRLM, one carcinoid liver metastases and one HCC (3.5–6.6cm) were ablated with bipolar RFA. Average ablation time was 16 minutes (range 6-29 min.). Two patients developed a large liver abscess which required re-laparotomy. In both cases bowel surgery during the same session probably caused bacterial spill. There were no mortalities. The patients were released from hospital between 5 and 29 days after the procedure (median 12 days). The 6-12 months follow-up PET-CT scans showed signs for marginal RFA-site tumor recurrence in two patients with CRLM (2/11 lesions). Preliminary results suggest bipolar RFA to be a relatively safe, fast and feasible technique which seems to improve local control for large size hepatic tumor ablations.

Chapter 5.2 describes our initial clinical experience with bipolar RFA for symptomatic giant hepatic hemangiomas (HCG). Hemangioma is the most common benign solid liver tumor. Lesions >4 cm have been referred to as giant hemangiomas. Although most hemangiomas are asymptomatic, larger lesions may produce a variety of symptoms and treatment is favourable. Four consecutive patients with a large-volume, symptomatic HCG of >10 cm were treated with bipolar RFA during laparotomy with ultrasound guidance. Complications were carefully noted. Clinical and radiological effectiveness were evaluated comparing baseline with 3 and 6 months follow-up of symptom assessments and upper abdominal magnetic resonance imaging (MRI) or CT. RFA was successfully performed for all four giant hemangiomas. No major complications were observed. Peri-procedural shrinking was remarkable and intermediate term volume reduction ranged from 58-92% after 6 months. Symptom relief after 6 months was complete in two patients and considerable in the other two. To conclude, bipolar RFA seems to represent a promising technique for the treatment of symptomatic large-volume giant hemangiomas of the liver and should be considered an alternative to surgical resection.

In patients that require treatment for GCH RFA has been suggested to represent a safe and effective alternative to invasive surgery. In our recent report (chapter 5.2) bipolar RFA, using two expandable needle electrodes, was uneventfully performed in patients with large GCH (>10cm). In chapter 5.3 we present two cases in which bipolar RFA of very large symptomatic GCH (15.7 and 25.0cm ) was complicated by heme pigment-induced acute kidney injury due to massive intravascular hemolysis caused by heat. In both patients the urine showed a red-brown discoloration directly after the ablation. They became anuric and presented with progressive dyspnea, tachypnea and tachycardia, requiring hemodialysis for a period of one month in one case. Lab results revealed heme pigment induced acute kidney injury. Both patients fully recovered and both showed a complete relieve of symptoms at 3 months following the procedure.
RFA for large GCHs can cause heme pigment induced acute kidney injury due to massive intravascular hemolysis. The presented cases suggest that caution is warranted and advocate an upper limit regarding the volume of GCHs that can be safely ablated.