# Image guided treatment of liver tumors – experimental MRgHIFU ablation and drug eluting embolic transarterial chemoembolization

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**To Hjalmar, Selma and Erik**

# Content

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*Ulrik Carling – Oslo, January 2020*

## 2. List of papers

Study 1. **Can we ablate liver lesions close to large portal and hepatic veins with MR-guided HIFU? An experimental study in a porcine model**. Carling U, Barkathov L, Reims HM, Storås T, Courivaud F, Airazat AM, Halvorsen PS, Dorenberg E, Edwin B, Hol PK; Euro Radiol. 2019: Feb 8. (Epub before print)

Study 2. **Transarterial chemoembolization of liver metastases from uveal melanoma using irinotecan-loaded beads: treatment response and complications**. Carling U, Dorenberg E, Haugvik SP, Eide NA, Berntzen DT, Edwin B, Dueland S, Røsok B. Cardiovasc Intervent Radiol. 2015 Dec;38(6):1532-41

Study 3. **ALBI and P-ALBI grade in Child-Pugh A patients treated with drug eluting embolic chemoembolization for hepatocellular carcinoma.** Carling U, Røsok B, Line PD, Dorenberg E. Acta Radiol. 2019 Jun;60(6):702-709

## 3. Abbreviations

| | |
|---|---|
| AE | adverse events |
| AFP | alfa-feto protein |
| ALBI | albumin bilirubin grade |
| BCLC | Barcelona clinic liver cancer |
| CBCT | cone beam computed tomography |
| CE | contrast enhanced |
| CRC | colorectal carcinoma |
| CRLM | colorectal liver metastases |
| CT | computed tomography |
| CTCAE | common terminology criteria for adverse events |
| DEBIRI | drug eluting beads loaded with irinotecan |
| DEE | drug eluting embolic |
| DTIC | dacarbazine |
| EASL | European association for the study of the liver |
| ECOG | Eastern cooperative oncology group |
| F | French |
| FLR | future liver remnant |
| HAP | hepatoma arterial embolization score |
| HCC | hepatocellular carcinoma |
| HIFU | high intensity focused ultrasound |
| HKLC | Hong Kong liver cancer |
| IHCC | Intrahepatic cholangiocarcinoma |
| INR | international normalized ratio |
| LD | lactate dehydrogenase |
| MDT | multidisciplinary team |

| | |
|---|---|
| mRECIST | modified response evaluation criteria in solid tumors |
| MRgHIFU | magnetic resonance guided high intensity focused ultrasound |
| MRI | magnetic resonance imaging |
| MUM | metastatic uveal melanoma |
| MWA | microwave ablation |
| NPV | non-perfused volume |
| OS | overall survival |
| P-ALBI | platelet albumin bilirubin grade |
| PES | post-embolic syndrome |
| PET | positron emission tomography |
| PrFS | progression free survival |
| PFS | proton frequency shift |
| PVA | polyvinyl alcohol |
| RCT | randomized controlled trial |
| RE | radioembolization |
| RECIST | response evaluation criteria in solid tumors |
| RFA | radiofrequency ablation |
| SIRT | selective internal radiation therapy |
| T1w | T1 weighted |
| TACE | transarterial chemoembolization |
| TAE | transarterial embolization |
| UM | uveal melanoma |
| US | ultrasound |

## 4. Background

Interventional oncology is a medical field in which tumor treatment is performed with interventional radiology techniques such as image guided ablation, transarterial chemoembolization (TACE) and radioembolization (RE) (1-6). The role of interventional oncology in the treatment of liver tumors is under progress as minimally invasive image guided treatments of liver tumors are in rapid development, and as the treatments can be applied in many various levels of patient care (7). Cancer treatment has traditionally been termed either curative or palliative, however recently life-extending has been proposed as a separate third entity, with the term "palliative" being reserved for later stages of treatment (8). In light of this definition, ablative techniques can be used as an alternative to or in combination with liver surgery with curative intent (9), as well as in the life-extending setting (10). Further, transarterial cancer treatment techniques can be used as neo-adjuvant - given before main treatment (11), adjuvant – given in addition to main treatment (12), life-extending (13, 14) or palliative treatment (15). These different levels of patient care are all under continuous development as surgical, medical, and radiation oncology, and the overlap and interaction between the fields evolves. This multi-modality approach can be illustrated by a patient with liver metastases from colorectal cancer affecting both liver lobes, who is fit for surgery but where the future liver remnant (FLR) is too small to preserve adequate liver function and also contains minor metastatic disease not amendable for resection. After neo-adjuvant chemotherapy, an ultrasound guided percutaneous ablation procedure can be performed of the tumor in the FLR, followed by a fluoroscopy guided percutaneous portal vein embolization for FLR growth, making a liver resection with curative intent possible. For patients with liver tumors this highly dynamic therapeutic landscape calls for a patient specific approach, embodied in the clinical multidisciplinary team (MDT) meeting (16). This individualized patient specific focus, the development of different combinations of treatment alternatives, and the technical development of specific methods poses a challenge for randomized controlled trials (RCT) (7, 17, 18), and strategies used in such trials are sometimes hard to directly translate to the everyday clinical practice. The use of local registries and institutional quality control programs are

therefore of high importance for this field, in addition to RCTs, as in other procedural based fields (19, 20).

This thesis includes three studies in the field of interventional oncology including experimental use of a newly developed ablation method, a clinical study of transarterial treatment of metastatic liver disease, and a study of one of the most studied methods in this medical field – TACE for hepatocellular carcinoma.

### 4.1 The liver and the tumors

The liver is usually considered to consist of two lobes (right and left) which can be further subdivided into 8 segments on the basis of vascular biliary anatomy as described by Dr. Couinaud in 1957 (21). The liver is an important organ as highlighted by that the hepatic blood flow at rest, 1.4 l/min, is the highest of all organs (22). The liver receives blood both from the oxygen rich systemic artery system as well as the veins draining the gastrointestinal (GI) tract and visceral organs through the portal vein system. This give rise to the liver´s unique dual blood inflow of which 20-25% comes from the hepatic artery and 75-80% comes from the portal vein, with oxygen delivery divided relatively equal between the two systems (22). The liver has multiple functions in metabolism, nutrition, protein synthesis, digestion, blood detoxification and purification (23). Important laboratory test for liver function screening includes blood platelet count, (pre-)albumin, bilirubin, international normalized ratio (INR) and enzyme tests including alanine aminotransferase (ALT), serum aspartate (AST), gamma-glutamyl transferase (γGT), alkaline phosphatase (ALP), and lactate dehydrogenase (LD)(24). Impairment of liver function can be seen in patients with liver tumors, either due to the underlying liver disease (25), or due to the tumor burden itself in which case the prognosis is very poor (26, 27). Tumors of the liver can be described as either being primary or secondary. Primary malignant tumors such as hepatocellular carcinoma (HCC) arising from the liver hepatocytes and intrahepatic cholangiocarcinoma (IHCC) derived from intrahepatic bile ducts often develop due to underlying liver or biliary diseases. Secondary malignant tumors, metastases, often arise from colorectal carcinoma (CRC) or more rare tumors such as uveal melanoma (UM).

### *4.1.1 Primary liver cancer – hepatocellular carcinoma*

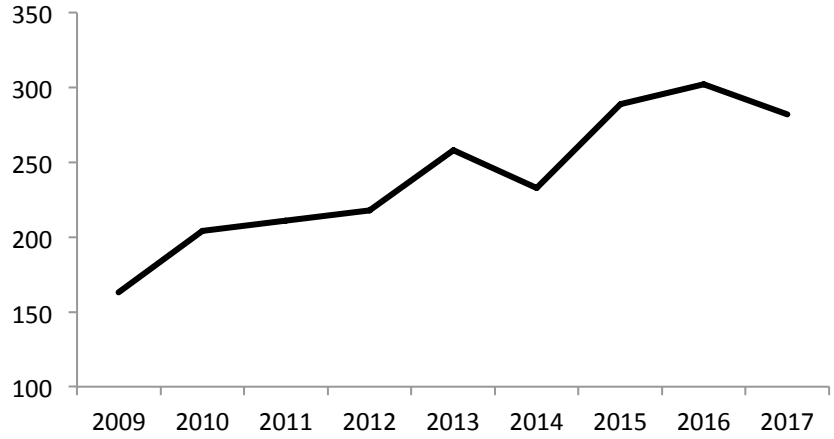
HCC is the sixth most common cancer worldwide, however it is the third to fourth leading cause of cancer related death globally, and the mortality rate almost matches the incidence rate (28). Incidence rates are usually reported for all liver cancer types combined, including HCC and IHCC, however the vast majority of liver cancers are HCC. The peak incidence of HCC is found in areas with endemic hepatitis B virus (HBV) (25) as in Eastern Asia where the age adjusted incidence is 18/100000, accounting for almost 470 000 new cases/year (28). Hepatitis C virus (HCV) is another risk factor for HCC, a common etiology in southern Europe where the HCC incidence is 6.8/100000. Other important risk factors are alcohol induced liver disease and non-alcoholic fatty liver disease (NAFLD) (25, 29, 30). Most cases of HCC develop in patients with liver cirrhosis and less than 20% of HCC cases occur in non-cirrhotic patients in western countries (31, 32). In Norway, the incidence of viral hepatitis has been low and accordingly, the incidence of HCC has been one of the lowest in Europe (28) as well as in the Nordics countries (Table 1). In recent years the HCC incidence has been rising (Figure 1), and in 2017 the age adjusted incidence was 3.5/100000 and 1.9/100000 for men and women, respectively (33), with about 280 new cases. A key characteristic in the Norwegian population has been the relatively high percentage of HCC patients without liver cirrhosis, recently reported to be 44% (34). Even the HCC populations in the Nordic countries seem to differ somewhat as the rate of non-cirrhotic HCC reported from Denmark and Sweden is 20% and 35% (35, 36), respectively.

**Table 1. Age adjusted incidence rates of liver cancer (LC) and colorectal carcinoma (CRC) in the Nordic countries**

| Country | LC* Men | LC* Women | CRC Men | CRC Women |
|---|---|---|---|---|
| **Norway** | 3,5 | 1,7 | 44,4 | 37,0 |
| **Denmark** | 5,7 | 2,1 | 46,0 | 35,7 |
| **Sweden** | 4,8 | 2,0 | 31,6 | 24,9 |
| **Finland** | 5,8 | 2,4 | 28,3 | 20,6 |
| **Iceland** | 4,7 | 1,6 | 32,0 | 24,0 |

Incidence per 100 0000, in 2011-2015.*Liver cancer includes hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Numbers from NORDCAN, Association of the Nordic Cancer Registries, accessed at www-dep.iarc.fr/NORDCAN

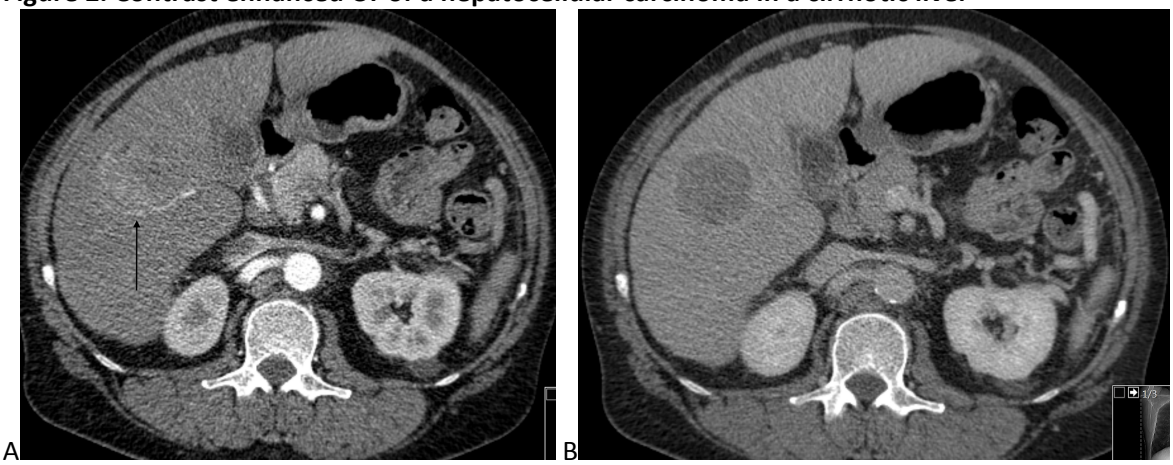
**Figure 1. Incidence of liver cancer in Norway 2009-2017**




Number of new cases was 163 in 2009, rising to 289 in 2015 and being more stable 2015-2017.

HCC receive the majority of the blood supply from the hepatic arterial system (37). Although the underlying factors and clinical presentation differ, HCC tumors share many pathological and radiological characteristics in cirrhotic and non-cirrhotic livers (38, 39). On cross sectional contrast enhanced imaging such as computed tomography (CECT) or magnetic resonance imaging (CE-MRI) the typical HCC tumor shows high contrast uptake in the arterial phase (40) with a contrast washout in later contrast phases (Figure 2). According to the guidelines by the European Association for the Study of the Liver (EASL) (41), this classical appearance is accepted as final diagnosis in a cirrhotic liver, without need for a biopsy or additional serum tumor marker (e.g. alfa-feto protein - AFP).

**Figure 2. Contrast enhanced CT of a hepatocellular carcinoma in a cirrhotic liver**

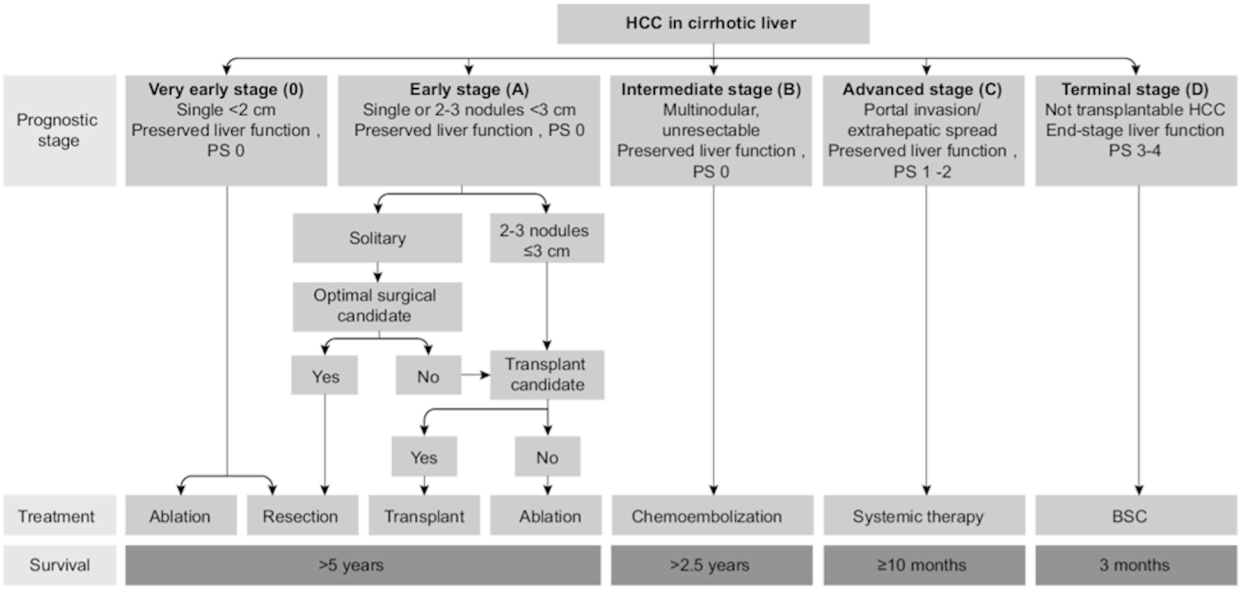


A: Arterial phase contrast enhanced CT with high contrast uptake in the tumor (arrow). B: Venous phase contrast enhanced CT with contrast wash out (arrow). Bulky and nodular surface of the liver indicate cirrhosis.

An important prognostic factor for patients with HCC is the degree of underlying liver disease and hence the reduced liver function, which can limit the therapeutic options as is clearly outlined in current HCC guidelines by the EASL (41). In clinical practice liver function has often been assessed by the Child -Pugh status, initially developed in the 1960s by Drs Child and Turcotte to predict outcome for portal hypertension surgery (42). It was later modified (43), and now includes functional parameters (bilirubin, albumin and INR) and clinical parameters (ascites and encephalopathy). Another system for assessing liver function is the model for end stage liver disease (MELD) score. It was initially developed (44) for patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) and consists of a logarithmic calculation of serum levels of creatinine and albumin, and INR. It has been widely implemented as a prognostic score for patients with liver disease (45), particularly in patients on waiting lists for liver transplantation (46). Due to limitations of both the Child-Pugh score and the MELD score, the ALBI score using only serum levels of Albumin and Bilirubin, and the P-ALBI score, including also platelets, has recently been developed for assessing liver function in HCC patients (47, 48). These objective scores have been evaluated in several studies including patients in different geographical regions, undergoing different treatments for HCC (49-52), but have yet not found their place in clinical decision making. Treatment of HCC also depends on tumor stage which is highlighted in staging systems developed to allocate a patient

to the most appropriate treatment. These systems include the Barcelona Clinic Liver Cancer (BCLC) staging system, the Hong Kong Liver Cancer (HKLC) system, the Okuda system and the Cancer of the Liver Italian Program (CLIP) score (53-56). The BCLC and HKLC systems also include the patients´ performance score in addition to tumor stage and liver function. All the staging systems include Child-Pugh score for assessing liver function, except for the Okuda system in which ascites, serum albumin and bilirubin are used separately. BCLC is the most widely adapted system, and an overview can be seen in Figure 3. It is noteworthy that a distinction between HCC in cirrhotic and non-cirrhotic liver is made in the updated version of the guidelines (41). In the very early stage (BCLC 0) the appropriate treatment would be ablation or resection, and in the early stage (BCLC A) resection, transplantation or ablation. For patients with intermediate stage HCC (BCLC B) the recommended treatment is TACE while systemic treatment is recommended for patients in the advanced stage (BCLC C).

**Figure 3. Barcelona Clinic Liver Cancer (BCLC) staging classification for hepatocellular carcinoma**




Adapted from (41). Preserved liver function = Child Pugh A without ascites, PS = performance score, BSC = best supportive care.

There are many reports where these guidelines are not adhered to. Transplantation criteria for HCC in Norway are extended to patients with a single lesion up to 10 cm or five tumors up to 4 cm of size (57) which is well outside the widely accepted Milan-criteria (58). Similarly, resection has been reported

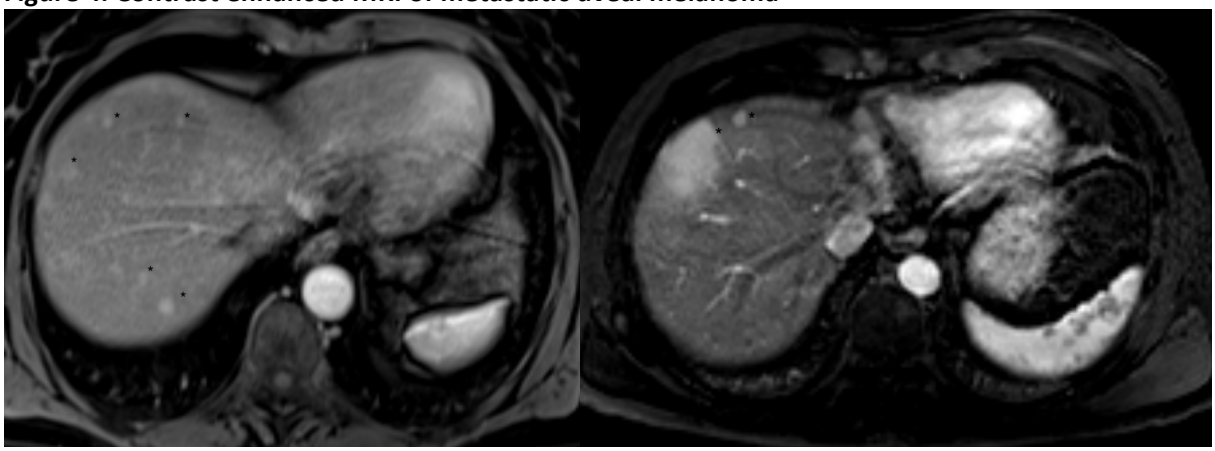
with success in BCLC C patients (59), and TACE has been performed in all the mentioned stages (60, 61). HCC is often diagnosed in a relatively late stage, making treatment with curative intent (e.g. ablation, resection or transplantation) less likely (60, 62), but when these treatments are amendable a 5-year survival rate is reported to be 60-80% in BCLC 0-A (63).

### *4.1.2 Metastatic tumor disease of the liver*

Due to its dual blood flow, the liver is predisposed to be the primary site of hematogenous metastatic disease from the GI tract via the portal system, as in CRLM (64), but also from less common non-GI tract tumors via the arterial system such as metastatic uveal melanoma (65, 66). CRLM is the most common liver tumor as the incidence of CRC is about 4000 cases/year in Norway (33) (Table 1), and about 25-30% of CRC develop liver metastases (67, 68). CRLM and the diagnosis, prognosis and treatment thereof are beyond the scope of this thesis. It should be acknowledged that CRLM is a main challenge for abdominal radiologists, liver surgeons and oncologists (medical and interventional), but first and foremost for the patients themselves. The annual number of liver resections performed at Oslo University Hospital exceeds 300, of which approximately two thirds are performed in patients with CRLM.

Uveal melanoma (UM) is the most common tumor of the eye in adults, but is a rare disease with only 79 reported new cases in Norway in 2017 (33). The predominant metastatic site is the liver and is reported in up to 96% of patients with metastatic uveal melanoma (MUM), and 57-70% have metastases confined to the liver only (65, 69). As in HCC, the blood supply in MUM is mainly arterial and the tumors often show high contrast uptake in the arterial phase on CECT or CE-MRI (Figure 4).

**Figure 4. Contrast enhanced MRI of metastatic uveal melanoma**



T1 weighted contrast enhanced sequences in arterial phase in two patients with metastatic uveal melanoma where liver metastases have high signal intensity (⋆).

The prognosis of MUM is highly dependent on the liver tumor burden (70, 71), and the reported overall survival has traditionally been poor with reports ranging from 2-9 months with a 1-year survival rate as low as 13% (70, 72). In patients amendable to resection a median overall survival of 38 months with 5-year survival rate of 39% has been reported (73) although with a high recurrence rate.

## 4.2 Treatment of liver tumors

Surgical resection and transplantation are the gold standards for curative treatment in patients with liver tumors, but treatment of liver tumors span from invasive surgical techniques including liver transplantation and vascular reconstructions (74, 75) to medical treatment with intravenous systemic chemotherapy (76, 77), immunotherapy (78), and per oral medication, e.g. sorafenib (79). While surgery is a field in massive progress (75, 80, 81), many patients are not amendable (82) for surgical resection or transplantation and minimal invasive image guided treatment options are increasingly important in the treatment of liver tumors.

### *4.2.1 Thermal ablation*

Thermal ablation is usually performed under CT or ultrasound (US) guidance, the latter often in combination with contrast enhancement and more recently with newly developed image fusion tools for optimal visualization (83, 84). There are several methods for ablative therapy of liver tumors (85)

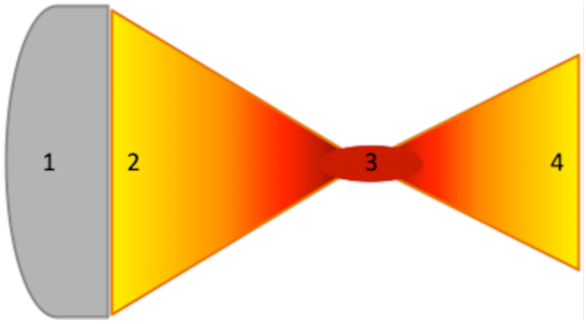
including radiofrequency (RFA), microwave (MWA), laser, cryo, high intensity focused ultrasound (HIFU), irreversible electroporation (IRE), and percutaneous ethanol injection (PEI). RFA, MWA, laser and HIFU are thermal ablation techniques using heat to destroy tissue by creating coagulative necrosis (86, 87). The clinically most used thermal ablative methods for liver tumors are RFA and MWA. In both methods heat is produced by molecular friction but while RFA uses an alternating current, MWA uses an electromagnetic field which is faster and more effective in terms of heat production (86). In RFA and to some extent also in MWA the heat is conducted in the tissue around the needle, and tumor size is therefore a limiting factor for treatment outcome (86, 88-90), as well as adjacent blood flow - denoted "the heat sink effect" (91, 92). RFA has been compared to PEI for treatment of HCC in several studies and have been shown to be superior in terms of response, progression/recurrence free survival, and overall survival (83, 93). Further, RFA has been compared to surgical resection for early stage HCC with good clinical outcomes, and is established as the treatment of choice in non-resectable early stage HCC (41, 94-96). Thermal ablation in combination with chemotherapy increases survival in patients with non-resectable metastatic disease (10). Ablation is also recommended in subsets of patients with metastatic disease in early stages of disease (97), and an ongoing phase III RCT, comparing ablation to resection in metastatic disease (98), may further define the role of ablative therapy in these patients. Due to the potent ablation of MWA, the use of this method is growing, with reports of superiority over RFA (99-101). However a recent RCT comparing RFA and MWA showed very similar, excellent, results for HCC < 4 cm, with a 2-year survival rate around 85% and low complication rates (89). Although overall complication rates are low, these techniques are invasive and may result in complications where bleeding is the most common (83). In addition, needle tract tumor seeding has been reported (102).

#### *4.2.1.1 High intensity focused ultrasound*

High intensity focused ultrasound (HIFU) is a non-invasive ablation modality in which the energy from ultrasound waves is used to produce heat in a desired focal spot (103). The intensity ($W/cm^2$) at the focal spot is up to 10.000 higher than in diagnostic ultrasound, causing frictional heat on the molecular level

(104). The potential biological effects of ultrasound waves were described as early as 1927 (105), however the first clinical report besides earlier neurosurgical endeavors did not come until 1994, in HIFU ablation of the prostate (106). The ultrasound transducer used in HIFU can be either phased array, spherically shaped or combined with interchangeable lenses in order to be able to focus the ultrasound waves without causing non-intended damage on their way (107). The ablations are ellipsoid (with length correlating to diameter) due to the propagation of the ultrasound waves as displayed in Figure 5.

**Figure 5. Schematic sagittal image of high intensity focused ultrasound with propagation of ultrasound waves.**




1= transducer, 2= low energy and temperature in the near-field (e.g. skin level), 3= high energy and temperature in focal point which due to the propagation of the ultrasound waves is oval/ellipsoid shaped, 4= Low energy and temperature in the far-field.

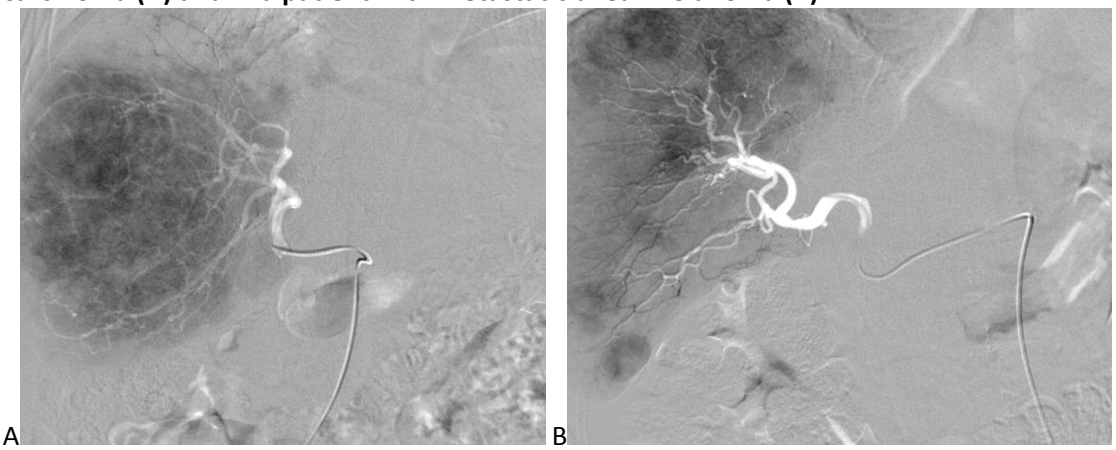
HIFU is used in various clinical scenarios including intracranial ablation of the basal ganglia in tremor and Parkinson´s disease (108), uterine fibroid ablation (109), prostate ablation (110) and pancreatic ablation (111) as well as in hyperthermia induced drug delivery (112). HIFU may be performed either under ultrasound guidance (USgHIFU) or magnetic resonance (MR) guidance (107, 113). In MRgHIFU the MRI and the HIFU systems are interconnected, which allows for the HIFU system to interact with the MR system during the ablations. MR images can thus be obtained during planning, for treatment monitoring (temperature measurements), and for post treatment evaluation (114). Thermometry is possible by the use of temperature sensitive sequences (e.g. proton resonance frequency shift sequences) (115), in near real-time. This unique setup makes it potentially possible to perform multiparametric diagnostics of a liver tumor, non-invasive treatment and initial treatment evaluation in one setting (111, 116). HIFU can ablate sharply delineated volumes (117), and is potentially less sensitive to heat sink than ablative

methods depending on heat conduction (e.g. RFA), and is therefore of particular interest in liver ablation. However, the HIFU ablations are small in size and combinations of several ablations are needed to cover a tumor, which means sessions can be relatively lengthy (118, 119). Further, the liver poses difficulties for HIFU since it is a moving organ (from respiratory and GI tract motion) and partly covered with ribs that are difficult to penetrate with ultrasound (119, 120). Most reports on clinical use of HIFU in liver tumor treatment are from China where USgHIFU has been used for HCC treatment, with reports of adequate feasibility, safety, and treatment outcomes (121-124). In Europe, a current study examines the role of HIFU in reducing blood loss during liver resection (125). Only one single case of clinical treatment in liver tumors is reported from Europe (Rome) using MRgHIFU (126), and MRgHIFU is not in clinical use in treatment of liver tumors yet.

### *4.2.2 Transarterial embolization treatment*

Liver tumors are, as earlier mentioned, usually perfused by vessels derived from the hepatic artery, while normal liver tissue also is perfused by the portal vein. This gives the opportunity to selectively treat tumors by catheterization of the hepatic artery (Figure 6), theoretically sparing normal liver tissue (85).

**Figure 6. Digital subtraction angiogram of the right hepatic artery in a patient with hepatocellular carcinoma (A) and in a patient with metastatic uveal melanoma (B)**



A: Digitally subtracted image showing the hepatic artery in white and a large hepatocellular carcinoma in dark. B: As in A, but multiple oval shaped metastases in dark.

Usual access sites are either the femoral artery in the groin or the radial artery at the wrist. A catheter can be placed either central (non-selective) to treat large parts of the liver (e.g. one whole lobe) or highly

selective, directly in the tumor-feeding arteries. Transarterial therapy includes infusion therapy where cytotoxic drugs are continuously administered via the hepatic artery, and also embolization techniques such as transarterial embolization (TAE), chemoembolization (TACE), immunoembolization and radioembolization (RE). RE or selective internal radiation therapy (SIRT) is a method where radioactive isotope (e.g. yttrium-90; Y-90) tagged glass or resin microspheres (20-60 μm) are deployed in the arterial liver circulation. Y-90 is a beta radiation emitter with short range (<11mm in liver tissue) which gives the opportunity to selectively treat tumors (127). The therapeutic goal is not embolic but dose delivery and the method is used in treatment of both primary and metastatic disease (128-131).

Embolization of liver tumors deprives the tumor of nutrition and oxygen inflow, generating tumor ischemia and cell death (132-134). By regional administration of cytotoxic or -static agents, higher drug concentrations and less side effects can be achieved compared to systemic chemotherapy (135). Embolization therapy for non-resectable HCC was reported 30-40 years ago from USA (136), France (137) and Japan (138), with the latter using gelatin sponge and a combination of mitomycin and adriamycin. The TACE technique still consists of these two parts: embolization, causing ischemia, and delivery of cytotoxic drugs. Combining these two techniques increases the concentration of cytotoxic drug in the tumor, while reducing the plasma concentrations of the drug (139). Conventional TACE (cTACE) has later mainly been performed using lipiodol often in an emulsion with doxorubicin, combined with embolic materials such as gelfoam or particles (138, 140, 141). Drug concentrations and emulsions have varied considerably which has made cTACE relatively difficult to standardize (142), with subsequent difficulty in comparing reported treatment outcomes. With the development of drug eluting embolics (DEE) a more standardized method of TACE has become available (143-145). The embolics are non-biodegradable polymer hydrogel microspheres and for liver therapy the currently most used sizes range from 40 μm to 300 μm (146). The surface of different embolics differ somewhat, but the mechanism of drug loading by ion exchange is similar (147). Embolization with DEEs allows for sustainable high concentrations of therapeutic agents in tumors, while keeping systemic concentrations low (144, 145, 148). DEE-TACE has been investigated in different clinical settings including both primary and metastatic

liver tumors (143), and the most used cytotoxic drugs for DEE-TACE are doxorubicin and irinotecan (149), however also other types of drugs have been successfully loaded onto microspheres (150, 151). Doxorubicin has been used mainly in DEE-TACE for HCC, while irinotecan mainly for metastatic tumors. Complications of TACE include among others liver failure, liver abscess, non-target embolization and vascular mechanical complications such as dissection (152). Further, post embolization syndrome (PES) including abdominal pain, fever and malaise occurs in many patients (153). Comparison of DEE-TACE vs. cTACE in HCC treatment has shown a slightly lower degree of liver toxicity for DEE-TACE (154), however clinical outcome in terms of overall survival has not been significantly different (155, 156). Further, there is still scarce evidence that doxorubicin TACE is better in terms of progression free survival and overall survival than plain embolization, TAE (153, 157-159), and there is also controversy on the use of doxorubicin for HCC treatment (153, 160-162) although it is a well-established clinical routine. See Table 2 for an overview over important RCTs on TACE treatment of HCC. Combinations of transarterial embolization techniques and ablation for HCC have been described (163, 164), however there exists no recommendations on which patients to select for this treatment in current guidelines (41).

**Table 2. Overview over selected randomized controlled trials for transarterial chemoembolization treatment of HCC**

| Primary author (reference) | Year | Method | Number of patients and findings |
|---|---|---|---|
| **LLovet (13)** | 2002 | TACE[1] *vs.* TAE[2] *vs.* BSC[3] | N= 112. TACE improved survival. |
| **Lo (14)** | 2002 | TACE *vs.* BSC | N= 80. TACE improved overall survival. |
| **Lammer (155)** | 2010 | cTACE[4] *vs*. DEE-TACE[5] | N= 212. Equal results on response rate, lower hepatic toxicity for DEE-TACE. |
| **Malagari (157)** | 2010 | DEE-TACE *vs*. TAE | N= 83. Improved response rate with DEE-TACE. |
| **Golfieri (156)** | 2014 | cTACE *vs*. DEE-TACE | N= 177. Equal time to progression and 2 year survival. Less pain after DEE-TACE. |
| **Lencioni (165)** | 2016 | DEE-TACE +/- sorafenib | N= 307. Combination feasible. No prolonged time to progression with combination in BCLC B. |
| **Brown (153)** | 2016 | DEE-TACE *vs.* TAE | N= 101. Equal results on response rate and survival. |
| **Salem (131)** | 2016 | SIRT[6] *vs.* cTACE | N= 179. SIRT improved time to progression in BCLC A+B. |
| **Meyer (166)** | 2017 | DEE-TACE +/- sorafenib | N= 313. No prolonged progression free survival with sorafenib *vs.* placebo. |

[1]Transarterial chemoembolization, [2]transarterial embolization, [3]best supportive care, [4]conventional TACE, [5]drug eluting embolic TACE, [6]selective internal radiation therapy

DEE-TACE with irinotecan has been used in CRLM with increased resection rate in selected patients (167), and has also been effective in patients previously treated with chemotherapy in more advanced stages of disease (168). However, DEE-TACE has so far not been implemented in the standard of care of CRLM patients (169). In treatment of MUM the first reports of DEE-TACE were promising (170, 171), however the role of DEE-TACE in the treatment of metastatic liver tumors is yet to be determined.

## 5. Aim

The overall aim of this thesis is to explore and further develop the use of image guided treatment of liver tumors by examining the possibility of using non-invasive MR guided focused ultrasound for liver ablation and examining the role of transarterial drug eluting embolic chemoembolization (DEE-TACE) for the treatment of liver malignancies. Secondary aim of the thesis is to define an institutional DEE-TACE algorithm for HCC.

### 5.1 Specific aims

For study 1 the aim was to examine the feasibility of ablating normal liver tissue adjacent to large portal and hepatic veins while keeping the vessel wall intact using MRgHIFU. The secondary aim was to compare sonication data for ablations adjacent to hepatic versus portal veins.

For study 2 the aim was to evaluate outcomes, including radiological response and overall survival, and complications of transarterial chemoembolization using drug eluting embolics loaded with irinotecan in patients with liver metastases from UM.

For study 3 the aim of the study was to evaluate outcomes of transarterial chemoembolization using drug eluting embolics loaded with doxorubicin in patients with hepatocellular carcinoma, with respect to recently developed liver function grading systems, the ALBI and P-ALBI grades.

## 6. Material

### 6.1 Animals in study 1

Seven healthy male land swine with a median weight of 21.5 kg (*range 18-28.5 kg*) were included in the study, which was approved by the National Animal Research Authority (project no. 5340). The experiments were performed in the period of 2013- 2014. Animals were in the care of the Department of comparative medicine from the night before the experiments, and held without food approximately 8 hours before induction of anesthesia. The animals were euthanized after final imaging on the day of the procedures.

### 6.2 Patients in study 2 and 3

For the two clinical studies, patients treated at our institution were retrospectively analyzed. The data collecting was made through the institutional clinical and radiological information systems. The retrospective collecting of data and the data analyzes, as well as the publications thereof, were approved by the Data Protection Officer for research at our institution. All patients treated at our institution with

transarterial chemoembolization were discussed at a multi-disciplinary tumor board prior treatment. During the period of inclusion no other transarterial method (e.g. SIRT) was used at our institution for these groups of patients.

In study 2, 14 patients consecutively treated with transarterial chemoembolization for liver metastases from uveal melanoma (MUM) in the period of 2010-2013 were included. The cohort comprised of 6 male and 8 female patients with median age of 64 years (*range 39-74*), and are the only MUM patients treated with this technique in Norway. Tumor burden and survival data of the cohort was compared to a cohort of 14 consecutive patients that had been treated with a standard chemotherapy regimen (dacarbazine - DTIC) in the period 2005-2009 (8 male and 6 females; median age 64 years, *range 24-84*). Data of this cohort was obtained from a local register at the Department of Ophthalmology, Oslo University Hospital, approved by the Data Protection Authority.

In study 3, 49 patients consecutively treated with transarterial chemoembolization for HCC in the period 2009-2015 were included. All patients were Child-Pugh A, and Barcelona Clinic for Liver Cancer (BCLC) stage A-C. The median age was 66 years (*40-range 89*), and 38 (78%) were male. In total during this period there were 53 patients treated with DEE-TACE for HCC, however 4 patients were Child-Pugh B and therefore not included. The patients represent the first patients treated in Norway with this technique.

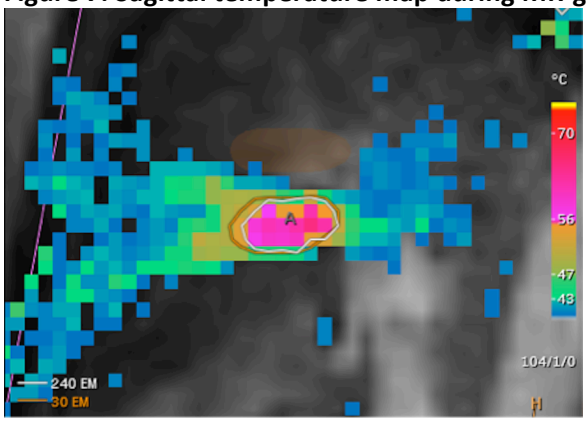
## 7. Methods:

### 7.1 Magnetic resonance guided high intensity focused ultrasound (MRgHIFU) ablation

The HIFU transducer, a phased array 256-channel transducer (Sonalleve, Profound Medical), was integrated in an interchangeable MRI-table. Thereby it was interconnected to a 3.0 T MRI system (Achieva, Philips, software release 2.6.3). The HIFU system was controlled through software designed for clinical uterine fibroid ablation (release R2.1 L2), which limited the maximum acoustical power to 200W. Ablations with this system can be performed in ablation cells with diameter of 4, 8, 12 or 16 mm, and for

large ablations multiple cells needs to be combined. Maximum power (200 W) was used and most ablations were 8 mm in diameter, which are 2 cm in length. In one animal also 4 mm ablations were used. The ablations were planned on coronal, sagittal and axial T1weighted (T1w) images obtained prior to ablations. The ablations were planned adjacent to large (> 5mm) portal and hepatic veins reachable by the HIFU beam. Limitations in ablation planning included air bubbles in skin surface, ribs obstructing the ultrasound waves, limited possibility of tilting the transducer, 12 cm maximum depth from the transducer surface to the focal point and internal air bubbles (GI-tract) in the beam path. Multiple ablation cells were planned adjacent to one another, and each cell was ablated twice to increase the probability of coagulative necrosis in the liver tissue (117). All ablations were aimed directly adjacent to, and to some extent in the vessels. Test ablations of low power (30-60 W) were performed in each cell to ensure feasibility of ablating the cell. Ablations were evaluated by the temperature response visualized by the proton frequency shift (PFS) temperature maps. Temperature measurements were generated with three coronal slices and one sagittal slice at the HIFU focus position (Figure 7).

**Figure 7. Sagittal temperature map during MR-guided high intensity focused ultrasound ablation**




Focal point (purple) with temperature below 70°C, and temperature increase (blue, green, yellow) also in the propagation path of the ultrasound beam (corresponding to Figure 5).

## 7.2 Drug eluting embolic transarterial chemoembolization (DEE-TACE)

### *7.2.1 Study 2 – DEE-TACE in metastatic uveal melanoma*

In this study, drug eluting embolics (size 100-300 µm; DC-Beads™, Biocompatibles UK Ltd, United Kingdom) loaded with irinotecan were used. In patients with bilobar disease, one treatment consisted of

two procedures per lobe, with a total of four procedures. The procedures were performed every second week, alternating between the lobes. In each procedure embolics loaded with 100 mg irinotecan were administered, with a maximum dose of 400 mg per patient. A total of 57 procedures were performed in the 14 patients. In all procedures, arterial femoral access with either a 4 F or 6 F sheet was used. Initial angiographic series were performed in both the celiac trunk and the superior mesenteric artery for evaluation of hepatic artery anatomy through a 4F catheter. Selective catheter position for lobar administration of beads was achieved using microcatheters (Progreat™ 2.7 F, Terumo Medical Corporation, USA), and in some patients segmental catheterizations were necessary to achieve safe and complete lobar treatment due to anatomic variants. In each procedure, beads loaded with irinotecan were mixed with 10-15 ml iodine contrast and injected slowly, following 1-3 ml of intra-arterial lidocaine (10 mg/ml). The endpoint was complete drug administration, unless arterial blood flow ceased before the whole dose had been injected, in which case the procedure would be stopped. An overview angiogram was performed at the end of the procedure. Patients routinely had an intravenous pump to administer 1 mg ketobemidone every eight minutes during the procedure. Other periprocedural drugs included intravenous diazepam and metoclopramide. Postprocedural median hospitalization was one day (range 1-4).

### *7.2.2 Study 3 – DEE-TACE of hepatocellular carcinoma*

In this study, drug eluting embolics (100-300 μm; DC-Beads™, Biocompatibles UK Ltd, United Kingdom) loaded with doxorubicin were used. The standard protocol included one procedure per patient before image evaluation. As in study 2 the procedure was performed through either a 4 F or a 6 F femoral artery access sheath, typically with a 4 F glide-catheter in the proper hepatic artery for initial diagnostic angiograms. On operators´ preference a rotational angiogram with cone beam CT (CBCT) was performed in selected cases. The angiogram was performed with 50% saline diluted iodine contrast, injection rate of 5ml/s and volume of 35 ml. The CBCT was reviewed on a workstation for identification of tumor-feeding arteries. A 3D reconstruction of the intrahepatic arterial tree was made for real-time overlay guidance during fluoroscopy. A microcatheter (Progreat™ 2.7 F, Terumo Medical Corporation, USA) was used for

selective catheterization of the tumor-feeding arteries. A subsegmental catheter position was defined as superselective. The embolics were prepared by the pharmacy in vials of 2 ml loaded with 75 mg doxorubicin. Until august 2012, a second vial of 300-500 µm loaded with 75 mg doxorubicin was used if needed. Later, on the manufacturer's recommendation, only the smaller particles were used, with a maximum of two vials loaded with 75 mg doxorubicin each, 150 mg doxorubicin in total per procedure. The embolization endpoint was stasis of the tumor-feeding arteries and if needed also polyvinyl alcohol (PVA) particles (Contour™, Boston Scientific, USA) were used for additional embolization. Periprocedural drugs included intravenous diazepam and ketobemidone on demand. Median postprocedural hospitalization was two days (range 1-19).

## 7.3 Radiological response

### *7.3.1 Radiological response after ablation*

Contrast enhanced ultrasound (CEUS), CECT or CE-MRI is used for assessing treatment outcomes after tumor ablation in the liver, and lack of contrast enhancement is indicative of successful ablation and treatment response both directly after the procedure and in follow up (83, 172, 173). In study 1, CE-MRI was performed after the final ablation to assess the non-perfused volume (NPV) as measured in 3 planes on the CE-T1w images. CE-T1w images allowed also for evaluation of vessel patency and intrahepatic bleeding. Further, before euthanasia CEUS was performed to additionally evaluate the patency of the vessel adjacent to the ablations.

### *7.3.2 Radiological response after DEE-TACE*

Several methods for evaluating radiological response following transarterial treatment of liver tumors have been developed, where overall the Response Evaluation Criteria in Solid Tumors (RECIST) is the most used (174-178). For HCC treatment the recommended systems are RECIST and the modified version of RECIST (mRECIST), with the latter being the preferred system (41). The main differences between RECIST and mRECIST (Table 3) are different size measurements and the use of contrast enhancement

where in RECIST the longest diameter of the entire lesion is used while in mRECIST size evaluation is based on the largest contrast enhancing part of a lesion (179).

**Table 3. Radiological response to treatment according to Response Evaluation Criteria in Solid Tumors (RECIST) and the modified version, mRECIST**

| Response Outcome | RECIST | mRECIST |
|---|---|---|
| **Complete Response (CR)** | No measurable disease | Disappearance of intratumoral arterial enhancement in all target tumors |
| **Partial Response (PR)** | ≥ 30% decrease in sum of longest diameters | ≥ 30% decrease in sum of longest diameters of arterially enhancing viable tissue in target tumors |
| **Progressive Disease (PD)** | ≥ 20% increase in sum of longest diameter measured on any previous study (must be ≥ 5 mm increase) | ≥ 20% increase in sum of longest diameter of viable target tumor measured on any previous study (must be ≥ 5 mm increase) |
| **Stable Disease (SD)** | Neither PR nor PD | Neither PR nor PD |

In study 2 evaluation of radiological response was performed on CECT obtained about 1.5 months after the treatment was finished (e.g. after four procedures in a patient with bilobar disease). CECT was assessed as according to RECIST 1.1 criteria by the primary author and a co-author with long experience in RECIST classification. Any imaging findings indicative of a complication (i.e. biloma and extensive infarction) were noted. Also, total liver volume measurements pre- and post-treatment were performed. In study 3 the standard protocol was CECT 1 month after the TACE procedure. The CECT was evaluated by two of the co-authors as according to mRECIST. CECT was as in study 2 reviewed for imaging findings indicative of treatment complications.

### 7.4 Histopathological evaluation in study 1 and clinical response in study 2 and 3

Histopathological evaluation in study 1 was performed after the livers were removed and put in 10% formalin. The livers were sliced perpendicular to the anticipated HIFU beam path. The tissue of interest adjacent to the targeted vessels was removed and cut in approximately 3 mm slices, which were processed according to a routine protocol and embedded in paraffin wax. Histological sections from each sample were stained with hematoxylin and eosin and examined by light microscopy by a pathologist with

experience in hepatic histopathology. The histopathological examination focused on assessing necrosis and hemorrhage related to the ablation zone, and included type of vein, distance between vessel and ablation zone, and presence of vein damage.

For both study 2 and 3, overall survival (OS) was used as the main clinical response parameter. In study 2 both OS from time of diagnose and time of treatment was calculated for the patients treated with DEE-TACE and compared to the group that had received systemic treatment with DTIC. In study 3 only OS from treatment start was used. OS analyses in study 3 were censored in patients receiving curative intent treatment (liver transplantation, resection or RFA) after DEE-TACE at the time of that treatment.

### 7.5 Adverse events

Adverse events were not systematically analyzed in study 1. In study 2 complications were assessed as according to the Society of Interventional Radiology (SIR) classification for complications by outcome. In study 3 the SIR classification was used only for reporting periprocedural complications, while symptomatic clinical treatment complications <30 days was assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.1 as according to updated guidelines (180).

### 7.6 Statistical analyses

In study 1, statistical methods were used to compare 8 mm ablations performed adjacent to portal and hepatic veins. Generalized linear mixed models were built with vein type (portal vs. hepatic) as fixed effect, and lesion number as random effect with the variables of interest set as targets. This was performed in an effort to explore the influence of vessel type on the ablations even though the separate ablations within one cluster likely influenced each other. A logistic regression model for heat sink was then extended to a multivariable model.

In study 2 survival data were analyzed using the Kaplan-Meier method with the log rank test for comparison. Laboratory and radiological data were analyzed for potential correlation with survival using

nonparametric Spearman's test for correlation. Mann-Whitney U test was used for comparison between groups. Regression analyses were not performed due to the small number of patients.

In study 3 comparisons between groups were made with the Mann-Whitney test for continuous data and 2x2 tables with Fisher's exact test for categorical data. Survival data were analyzed using the Kaplan-Meier method with the log rank test for comparison of groups. A Cox regression analysis stratified for the median age was performed to test the influence of ALBI and P-ALBI grades on overall survival in multivariate analysis with BCLC class, ECOG status, number of tumors and tumor size.

Analyses were performed in IBM SPSS 21.0-25.0 (IBM Corporation, USA), and for all studies tests were two-sided, confidence intervals were set to 95%, and a p-value $< 0.05$ was defined as statistically significant. Statistical aid was obtained from the Department of Biostatistics at the University of Oslo.

## 8. Summary of results

### 8.1 Study 1

A total of 153 ablations were performed in 81 cells, in a total of 12 lesions; two lesions per animal. Of these, 125 were performed in 8 mm cells, and 28 in 4 mm cells. A total of 79 ablations were aimed at hepatic veins and 74 ablations were aimed at portal veins. On post-ablation MRI imaging there were visible lesions with NPV in all animals on T1w CE-MRI images corresponding to the planning on pre-ablation images. Most vessels adjacent to the lesions had reduced diameter, likely due to compression. In one case, vein occlusion was suspected on MRI and verified on CEUS, whereas CEUS verified patency in two other cases with heavily compressed veins. These three cases were all portal veins. No vessel wall rupture was seen. The histopathological analysis of the 12 lesions revealed hemorrhage and necrosis in all lesions. The median shortest distance to the outer margin of the vessel wall was 0.4 mm (range 0-2.7 mm). Edema around the vessel was seen in almost all the cases, and in some cases also endothelial changes as well as alterations in vessel wall smooth muscle cells were observed. No transections or complete rupture

of the vessel walls were seen. Heat sink was detected by the HIFU system more often in ablations aimed at hepatic veins (*p= 0.045*). A logistic regression model of heat sink showed an odds ratio of 15.0 (*p=0.03*) for heat sink in ablations adjacent to hepatic veins compared to portal veins.

### 8.2 Study 2

Technical success rate defined as complete drug administration (100 mg of irinotecan), was achieved in 50/57 (88%) procedures. In the DEE-TACE group median OS from treatment start was 9.4 months (range 1.7-39) compared to 4.6 months (range 0.5-29.7) in the DTIC group (*p=0.23*). Survival following DEE-TACE was correlated to the pretreatment liver tumor burden, and also higher pretreatment LD levels were prognostic of shorter survival. Changes of LD, and total liver volume after treatment also correlated with one another as well as survival, indicating that the higher rise in LD and the more liver volume increase, the shorter survival. Radiological response was assessed for 13 of the DEE-TACE patients with median 12 lesions (range 2-102). On first follow-up imaging, none of the patients obtained a complete or partial response, and 11/13 (85%) had progressive disease. Nine patients (69%) had one or more new lesions in the liver. There were cases where target lesions were delineated and had decreased contrast enhancement, indicative of successful treatment, while at the same time new lesions had developed. Major complications were mainly PES and liver dysfunction where 4 patients had a total liver volume increasing between 62.5% and 311% and deteriorating laboratory liver function tests. Further, one patient died 10 days after a fourth TACE-procedure.

### 8.3 Study 3

Of the 49 Child-Pugh A patients in this study there were 21 patients with ALBI grade 1 and 29 patients with P-ALBI grade 1. There was one ALBI grade 3 patient and three P-ALBI grade 3 patients. There were no significant differences between patients with ALBI grade 1 and 2, or P-ALBI grade 1 and 2 in terms of tumor and treatment characteristics. Technical success of the first DEE-TACE procedure was 96.0% in 49 procedures. Overall objective response (complete + partial response) at one-month follow-up was observed in 34/46 (74%), with three patients missing from analysis. Nine of the 49 patients went on to

treatment with curative intent with a median overall survival of 75 months. After censoring these patients the median overall survival of the whole cohort was 14.9 months (*1.7-62.0*), with a significant (p=0.003) difference between P-ALBI grade 1 and 2 patients. When stratifying for response according to mRECIST there were significant differences in overall survival between both ALBI grade 1 and 2 (*p=0.02*), and P-ALBI grade 1 and 2 (p<0.001). Overall survival with respect to BCLC stage revealed significant differences in survival between ALBI grade 1 and 2 (26.9 *vs.* 12.8 months; *p=0.002*), and P-ALBI grade 1 and 2 (26.7 *vs.* 12.8 months; *p=0.007*) in BCLC B, while not in BCLC C (ALBI: *p=0.63*; P-ALBI: *p=0.055*). Cox regression analyses of overall survival for BCLC B and C patients stratified for the median age revealed significant hazard ratios of 2-3 for ALBI grade 2, P-ALBI grade 2, and tumors larger than 8 cm. Adverse events occurred in 13 patients and were mainly PES, but also included infection, abscess and hepatic dysfunction. In these 13 patients there was an overrepresentation of patients with additional bland embolization (*p= 0.02)*. There were no significant differences in total number of adverse events with respect to ALBI and P-ALBI grade, but hepatic failure (n= 3) only occurred in ALBI and P-ALBI grade 2 patients, and 4 of 5 cases of post embolization syndrome needing hospitalization occurred in patients with both ALBI 1 and P-ALBI 1.

## 9. Discussion

Image guided treatment of liver tumors and interventional oncology is a field in enormous development. In this thesis different aspects of the field are explored, spanning from technical aspects to patient selection. The numbers of subjects in the three studies included in this thesis are limited, and therefore findings and subsequent conclusions should be viewed with this in mind. However all three papers are in areas were research still is warranted and they therefore have a value within their respective fields, and the thesis thus contributes to further develop the interventional oncology field as a whole.

### 9.1 Study 1- experimental perivascular MRgHIFU ablation

In this study the feasibility of ablating liver tissue close to major hepatic and portal veins using MRgHIFU was demonstrated. This indicates that tumors close to major hepatic vessels potentially can be successfully

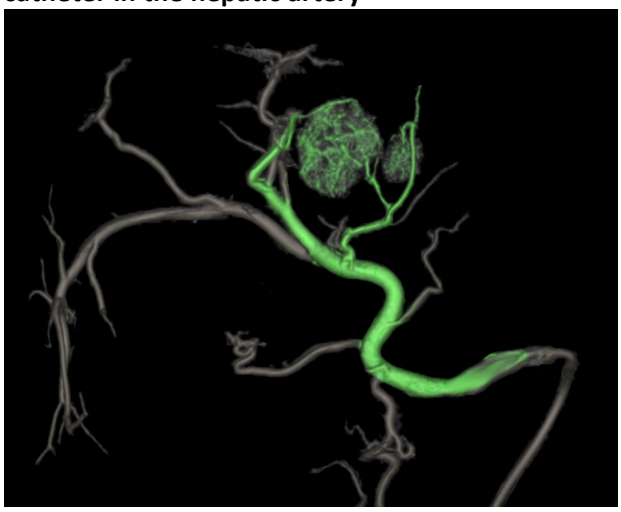
treated with this modality without severe vessel damage. However, as described in the study, about 30% of the ablations rendered non-significant heating as termed by the HIFU system, and 30% of the ablations were displaced from the focus, with median 4 mm (for the 8 mm ablations). This displacement may or may not be clinically relevant, however these findings indicate that high-precision ablation close to major vessels in the liver can be challenging. Target tracking is an important issue in MRgHIFU ablation (181), and recent suggestions for improvement of targeting during lengthy procedures include new fast imaging sequences for temperature and displacement measurements (182). Large ongoing projects include entire new frameworks for continuous target tracking (183) and development of new hardware for motion compensated MRgHIFU ablation (184), potentially allowing for ablation during respiration or respiratory gated ablation. Limitations of the MRgHIFU system used in our study included limited angulation of the HIFU transducer, limited focus depth (12 cm from transducer membrane) and lack of possibility to shut down parts of the transducer. These limitations made planning ablations close to large vessels difficult as dense (e.g. ribs) or gas filled (e.g. lungs, bowel, stomach) structures had to be avoided. This in parts explains the lengthy procedures. Recent hardware updates address some of these limitations, where it is now possible to shut down parts of the transducer, facilitating intercostal ablation, however with a loss of acoustic power. To make MRgHIFU a true alternative to invasive liver ablation, focus depth and angulation needs not to be limited since deep perivascular tumors would be where HIFU could definitely be the preferred ablative tool. In theory this modality could be used for diagnosis and non-invasive treatment in the same setting, however there are definitive obstacles to overcome before this scenario can be reality. The FUSIMO (Focused Ultrasound Surgery in Moving Organs) and the following TRANS-FUSIMO are large EU-funded projects aiming to develop MRgHIFU to a valid clinical option in liver tumor ablation (185).

### 9.2 Study 2 and study 3 - DEE-TACE of liver tumors

The clinical studies 2 and 3 represent the first Norwegian studies in TACE treatment for liver tumors. The patients included in these retrospective analyses are among the first consecutive patients treated with this

modality in Norway in the years 2009-2015. The DEE-TACE treatments in studies 2 and 3 differ in technique such as catheter position, number of procedures, embolization endpoint and type of cytotoxic drug delivered (e.g. irinotecan in study 2 and doxorubicin in study 3). In study 2 a lobar embolization approach was used, as super-selective catheterization of the multiple tumor-feeding arteries usually is not achievable in multifocal metastatic disease (186-189). However, as anatomy varies also segmental catheterization was performed in selected cases to ensure safe embolization. The protocol for bilobar disease with treating both lobes twice, alternating between the lobes with procedures 2 weeks apart was adapted from the recommended schedule for CRLM treatment as per manufacturer instructions and as published by Lencioni *et al* (188). In HCC, the number of tumors usually is lower than in metastatic disease, making a more selective approach achievable. Selective catheterization of tumor-feeding arteries was therefore aimed for in study 3, explaining why only two patients were treated in a lobar fashion. The embolization endpoint also differed in these two studies as drug delivery of irinotecan was aimed for in study 2, whereas drug delivery of doxorubicin and stasis was aimed for in study 3. This means that tumors in study 3 were bland embolized using PVA particles (not loaded with drug) if there was continuous flow in the tumor-feeding arteries after the maximum of 150 mg doxorubicin had been administered. An important aspect of HCC embolization is the selective catheterization of tumor-feeding arteries as this gives the opportunity for more selective tumor treatment, thereby sparing normal liver parenchyma. Visualization of feeding arteries is therefore more important in HCC treatment than in lobar metastatic treatment. Rotational angiography with CBCT improves detection of tumor-feeding arteries and can be used to facilitate a more selective treatment (190), as shown in Figure 8.

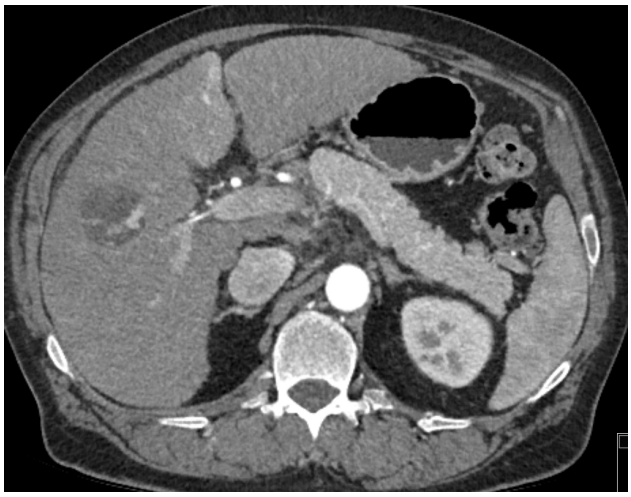
**Figure 8. Image from 3D volume rendering of cone beam CT obtained by rotational angiogram with a catheter in the hepatic artery**



Two hepatocellular tumors with the tumor-feeding arteries (TFA), as well as the arterial route from catheter tip to the TFA are highlighted in green.

Radiological response was assessed after median 4 procedures in study 2, while after one procedure in study 3, as reflected by the different treatment protocols for metastatic disease and HCC. Apart from different number of procedures before first imaging evaluation in the two studies, radiological response was assessed differently as RECIST 1.1 was used in study 2 and mRECIST was used in study 3. It is well described that the residual arterial contrast enhancement after TACE is an important prognostic tool in HCC (41, 177, 191), for which mRECIST has been developed (179), Figure 9. However while mRECIST is the preferred radiological response system in HCC (41), this is more controversial in metastatic disease (174). In study 2 most patients had progressive disease due to new lesions, and therefore would have been categorized as progressive disease also if mRECIST (table 3) had been used.

**Figure 9. Contrast enhanced CT in arterial phase after DEE-TACE treatment of a hepatocellular carcinoma**



Small residual arterial contrast enhancement indicates partial response according to the modified RECIST criteria (same patient as in Figure 2).

Retrospective recording of adverse events (AE) is challenging, as minor (e.g. CTCAE 1-2, SIR classification A-B) complications and AE are likely to be missed. Therefore only clinically significant AE and complications were recorded in both studies. The SIR classification has been developed as a general method for reporting complications following an interventional radiology procedure, however due to its limitations it has recently been updated (192), and current guidelines by the Society of Interventional Radiology (SIR) issued in 2017 recommend using either the new SIR adverse event classification or the CTCAE, as used in study 3.

Overall survival is the most definite endpoint following oncological treatments, and the gold standard of outcome measurements (180). However as patients are often treated by several modalities in different sequences, overall survival is not always an optimal parameter for assessing specific treatment efficacy, and surrogate measurements are time to progression (TTP) or progression free survival (PrFS) using radiological response at defined time points (180). In our material TTP and PrFS were less relevant in study 2 as progression occurred in most patients at first evaluation (after median 1.5 months). In study 3 the impact of liver function as per the new liver function staging systems ALBI and P-ALBI was examined and therefore OS was an adequate endpoint as liver function impacts OS. However TTP and PrFS would have given additional information, but due to different routines at the referring hospitals

standardized imaging follow-up for all the patients was not possible to obtain and these analyses were therefore omitted.

### *9.2.1 Study 2 - DEE-TACE in metastatic uveal melanoma*

Metastatic uveal melanoma has poor prognosis. In 2009, at the time for the initiation of DEE-TACE using irinotecan at our institution, the treatment alternative in unresectable patients was limited to systemic treatment with dacarbazine (DTIC). Irinotecan is not a drug usually used for systemic treatment of metastatic uveal melanoma, however there were also very limited data supporting the use of doxorubicin for these patients at that time. As a study on DEE-TACE loaded with irinotecan was published in 2009 reporting encouraging results (170), it was decided to adapt this approach. Unfortunately, our findings did not warrant a change of practice, although the overall survival was about twice as long for DEE-TACE compared to DTIC. This difference did not reach statistical significance, possibly due to the low number of patients, however there were differences in biomarkers (liver tumor burden, and serum levels of LD) favoring the DEE-TACE group and several patients who received DEE-TACE also received other treatments after DEE-TACE. Due to low response rate/rapid progression in combination with the observed complications, we concluded that treatment with irinotecan DEE-TACE alone was not justified. At the time of the study on DEE-TACE, promising systemic treatments including immunotherapy were investigated and as the number of patients with MUM is low, patients were rather allocated to these new treatments. Unfortunately, to date no systemic treatment of MUM has made a major impact on OS in these patients (193-195). To our knowledge no other studies on DEE-TACE using irinotecan for MUM have been published following our paper. In 2015 a blinded RCT on immunoembolization using granulocyte–macrophage colony-stimulating factor (GM-CSF) *versus* bland embolization was published with a significant benefit of immunoembolization in terms of OS in patients with large hepatic tumor burden, however the PrFS and OS in the whole cohort did not differ significantly. In 2017, Martin *et al* published their results on doxorubicin loaded DEE-TACE (196, 197). In that cohort 65% of the patients had extrahepatic disease, and the OS was 5.4 months. Although it was reported limited decline in quality of

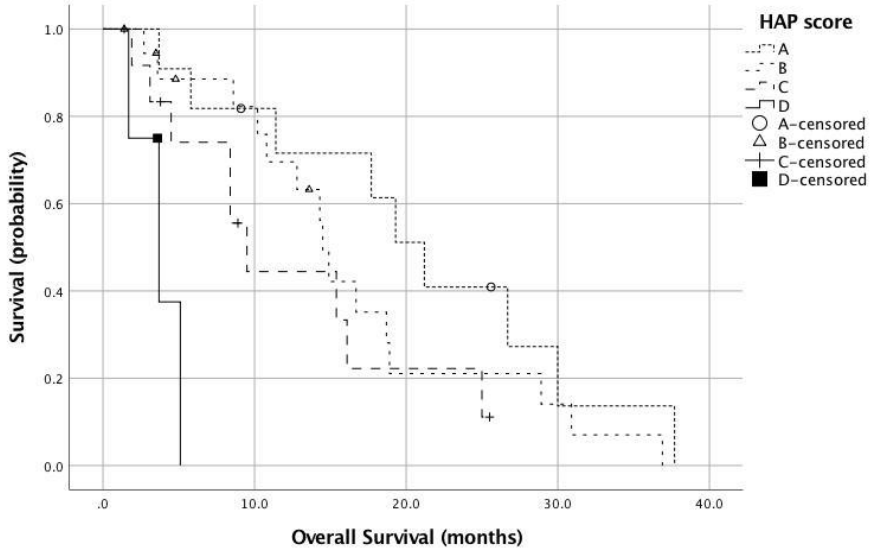
life and limited number of adverse events this modality is not likely to change clinical practice. In accordance with our study, the authors reported response in targeted lesions while 75% had new lesions on first imaging evaluation (at median 2.5 months). This shows that a combination of liver directed therapy such as DEE-TACE and an effective systemic treatment is an unmet need. Recently, an interesting study on the use of combination of immunotherapy and radioembolization with Y-90 was published, although retrospective and with a limited number of patients (n = 11) (198). The PrFS was 15.4 months and OS was 17 months, and a phase I study exploring this combination therapy is currently recruiting patients (Clinical Trials: NCT02913417).

### *9.2.2 Study 3 - DEE-TACE in hepatocellular carcinoma and treatment algorithm proposal*

The findings in study 3 indicate that the newly developed liver function grades, ALBI and P-ALBI, might be used as prognostic markers for Child Pugh A HCC patients treated with DEE-TACE, and can thereby offer a possibility for refined patient selection. This finding is in line with other studies on HCC across different treatment modalities (50-52, 199). It should be emphasized that our findings indicate that these liver function grades may be used as prognostic markers in the Norwegian population, which as earlier mentioned has differed from many other geographical areas due to the relatively high rate of non-cirrhotic HCC patients. In our study P-ALBI grade was more consistent in stratifying survival, however in larger cohorts in other treatment modalities the superiority of P-ALBI over ALBI has not been shown (52, 199). Although effective as prognostic markers, the inclusion of these grades in the pre-treatment patient work up needs more research. As we observed in our study and also highlighted in staging systems such as the BCLC system, the prognosis of HCC patients depends on both liver function and tumor burden. Combining ALBI/P-ALBI grades with tumor burden is therefore warranted. A study including ALBI-grade in the BCLC system instead of Child-Pugh status (200) showed similar overall prognostic performance compared to Child-Pugh based BCLC, but the role of these new function grades has yet to be determined.

As earlier discussed, according to the BCLC system TACE should be offered to intermediate stage, BCLC B, patients. However this group of patients is relatively heterogenic in terms of liver function and tumor burden and therefore efforts to further improve stratification within BCLC B have been made (201). Separate scores have also been developed and an example is the hepatoma arterial embolization (HAP) prognostic score (202). It was developed in the United Kingdom in 2013, and has recently been validated in a large randomized trial (166). The HAP-score includes tumor size, AFP, albumin and bilirubin, resulting in a score A-D, where score D has been shown to have the shortest survival. The HAP score and other scoring systems (203) have not gained widespread recognition due to difficulties in applying these scores in other populations than where they were developed. However, when applying the HAP score to our 2009-2015 cohort (N= 48, 5 missing due to no pre-TACE AFP), there are four groups characterized by slightly different survival curves (Figure 10). This trend needs to be validated in a larger cohort, but HAP might be a useful tool for identifying patients who are less likely to benefit from TACE treatment also in our population.

**Figure 10. Overall survival after DEE-TACE in HCC patients (n=48,) treated 2009-2015**




Median overall survival in months; HAP score A: 21.2 (3.7-37.7), B: 14.5 (2.7-36.9), C: 9.5 (1.9-25.0), D: 3.7 (1.7-5.1); p= 0.002.

Contraindications for TACE in HCC patients are relatively few (152). Although it has been advocated for a 10 cm upper limit in the past, no definite size limit exists as long as the tumor can be treated selectively, and a relatively good performance score and liver function can be maintained. Typical limits for TACE treatment are patients with a performance score of ECOG > 2 and Child-Pugh score > 8 (score C), although treatment of Child-Pugh C patients has been reported with acceptable results (204). Several factors need to be considered when assessing if a patient is suited for TACE treatment. Prognostic factors such as liver function and tumor burden are mentioned above, but other important prognostic factors include vascular invasion (typically portal vein thrombus) and extrahepatic disease (50, 205, 206). A patient with either vascular invasion or extrahepatic disease is classified as BCLC stage C and is not a TACE candidate in the BCLC system. However, a large registry study has shown that the overall most common first line treatment for HCC is TACE, and that about 50% of patients receiving TACE are BCLC C patients (61). BCLC C patients were also included in study 3 and might have influenced the overall survival of 15 months in the study. Expert panels have acknowledged that a subgroup of BCLC C patients (e.g. segmental portal vein thrombus while Child-Pugh A) could benefit from TACE (141, 152, 201, 207), and that TACE may safely be performed in these patients (208). This approach is also endorsed in the HKLC staging system (54). Also, in patients with extrahepatic spread, the hepatic lesion is still a main prognostic factor and could be considered for treatment if eligible (153, 205). In a recent study a subset of patients with extra hepatic disease had improved survival after TACE compared to systemic treatment (209). As in BCLC stage B there have been efforts in refining the BCLC stage C in order to identify patients who could benefit from TACE and a scoring system named BCLC C HCC prognostic (BCHP) score has been developed (210). The score comprises of the above mentioned prognostic factors and in that study a subgroup of BCLC C patients with an overall survival of 28 months following DEE-TACE was identified. This underlines that improved tools for patient selection is of high importance.

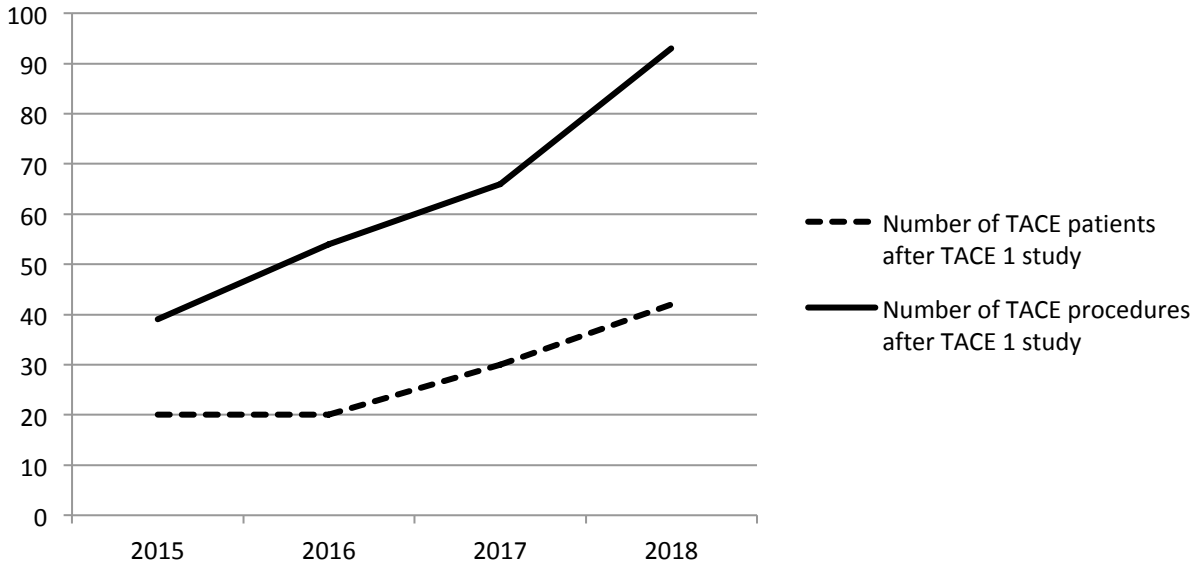
Even though TACE for HCC is a well-described treatment method, the above mentioned different prognostic factors make generalization of HCC patients difficult, thereby making strict detailed procedure

guidelines for TACE difficult and most guidelines leave procedure details up to the performing interventionist. There are several methodological issues to be considered: What is the optimal embolization agent? Is cytotoxic drug needed or is bland embolization sufficient? What drug should be used? What endpoint should be aimed for (stasis of tumor-feeding arteries *versus* drug delivery) and should additional bland embolization be used? How many treatments should be given? These different aspects of the method itself are under ongoing debate, and there is no one-size-fits-all solution. At the time of inclusion in study 3 the patients were routinely scheduled for one procedure before image evaluation. Further, stasis of the tumor-feeding arteries was used as embolization endpoint. In order to obtain stasis in one procedure extra bland embolization was performed in 14 (29%) patients. As mentioned in study 3 patients treated with additional PVA were overrepresented in the patients with complications. Whether this was related to additional PVA or related to tumor characteristics cannot be answered due to the small number of patients. In a study by Malagari *et al* (211) abscess formation was seen in cases (2.5%) where additional bland embolization was used, and therefore the authors recommend repeat procedure rather than trying to obtain stasis in one procedure in large hypervascular tumors. In the RCT by Brown et al (153) only 1 abscess (1%) was observed using a relatively aggressive embolization protocol, however the largest PVA particle used was only 100 μm. In a retrospective study it was found that full stasis is related to inferior outcomes compared to sub-stasis (212). However the particles used in that study were relatively large (majority of PVA was 355-500 μm), and it has been shown that poorer outcome and more complications can be related to larger (>300 μm) particles (213). The data on endpoints and use of additional bland embolization is otherwise relatively scarce and in expert panel guidelines whether to use additional bland embolization or not to obtain stasis is left to the decision of the interventionist (207, 214). It is clear that tumor ischemia plays a significant role in the treatment (153, 157). However hypoxia and ischemia can also induce neo-angiogenesis through vascular endothelial growth factor (VEG-F) pathways, and might promote a more aggressive tumor growth/spread (215, 216). In light of this, combination therapy using a systemic VEG-F inhibitor (sorafenib) and DEE-TACE has been explored. Although acceptable safety has been shown in two RCTs, the clinical effect has not been proven (165, 166).

Doxorubicin is the most used drug in DEE-TACE, however the efficacy of the drug has been questioned (153, 162), especially in a hypoxic milieu (161) and recently idarubicin has undergone initial clinical evaluation with promising results regarding safety and response (217). It is essential that a drug used in TACE have beneficial intratumoral pharmacokinetics and is effective under hypoxic conditions (218-220).

In the 2009-2015 cohort in study 3, only 31% of the patients underwent more than one procedure. This relatively low rate might have influenced the overall survival, although the objective response rate of 74% was acceptable when compared to other studies (153, 155, 157, 166). Radiological response is an important factor for prognosis (221) and should guide on demand retreatment as proposed in a score for decision on retreatment, the ART score (222). The importance of retreatment is highlighted in current guidelines and as long as no significant reduction in performance score or liver function occurs it is recommended to perform at least two TACE procedures before evaluating a patient as a "non-responder" (141, 223). Further, untreatable progression post TACE (so-called "unTACEable" progression) is related to radiological tumor progression, deterioration of liver function or performance status (41), where in a recent study intrahepatic tumor progression was the most common reason while the liver function and performance status more often were preserved (224). This is important as most of these patients can be considered for alternative treatments, and it is essential to consider the liver function when evaluating a patient for TACE retreatment. ALBI/P-ALBI grades might be more sensitive than Child Pugh score in this setting (225). Since 2015, after the period of inclusion in study 3, we have seen an increase in number of new patients treated/year and also number of treatments per patient (Figure 11).

**Figure 11. Number of patients and procedures per year after study 3 (TACE 1) in years 2015-2018**




Both number of patients and procedures has more than doubled in the time interval.

In the period 2015-2018, 65% had more than one treatment, and the mean number of treatments in the recent years has been 2-3 treatments per patient. These changes are probably multi-factorial including that patients are scheduled for retreatment directly after the first procedure if not the entire tumor was treated in the first session, a more stringent imaging follow up of the patients, and a more active role of the interventional radiologists in the MDT meetings. Other, more technical, changes includes routine use of CBCT at the first TACE procedure, and sometimes during retreatment procedures for visualizing tumor-feeding arteries, and the introduction of smaller microcatheters (2.0 F) allowing for even more selective catheterization. The impact of these modifications of the treatment protocol on the treatment outcomes needs continuous evaluation. A proposal of an institutional algorithm for DEE-TACE treatment in HCC patients can be seen in Table 4.

**Table 4. Proposal for an institutional algorithm for DEE-TACE treatment of hepatocellular carcinoma**

| | |
|---|---|
| **Indications** | Transarterial chemoembolization (TACE) is the recommended treatment for patients with asymptomatic and large/multifocal HCC without macrovascular invasion or extrahepatic metastasis (i.e. intermediate HCC, BCLC[1] stage B). Can be utilized as:<br><br>1. Definite treatment in unresectable (incl. transplantation and ablation) patients.<br><br>2. Bridge to definite treatment (ablation, resection or transplantation). If need for volume expansion, lobar SIRT[2] is an option. Combined portal vein embolization and TACE can be performed safely sequentially in a course over time. |
| **Patient selection** | Several factors weigh in and patient selection is on individual basis.<br>*Liver function:*<br>Preferably Child Pugh (CP) A-B7 patients without ascites - compensated liver cirrhosis. Ascites is not a contraindication *per se*. CP C patients can also be considered in carefully selected cases with good performance score and where defined tumors with distinct tumor-feeding arteries allow for super-selective embolization. P-ALBI/ALBI[3] grades give additional information on the prognosis; grade 3 is not a contraindication per se.<br>*Number and size of tumors:*<br>No defined upper limit regarding size or number of lesions, but an extensive tumor burden with massive replacement of both entire lobes is non-eligible. In large number of tumors, especially one sided, SIRT should be considered.<br>*Vascular invasion and extrahepatic spread:*<br>Generally predictors of poor prognosis, but TACE can be considered in cases with limited portal vein and/or liver vein occlusion, especially where liver function is preserved. TACE is an option in patients with limited extrahepatic disease, where the extrahepatic disease is unlikely to limit life expectancy significantly more than liver tumor. In these cases systemic treatment should be considered in addition. |
| **Procedure** | *Catheterization:*<br>As selective as possible. Cone beam CT is recommended. Lobar treatment should be avoided in patients with comprised liver function. Balloon occluding flow diversion may be used if super-selective catheterization is not possible.<br>*Embolic:*<br>Drug eluting embolics no larger than 300 µm loaded with doxorubicin (50 mg/ml), usually 150 mg. Lower loading doses (33 mg/ml) in smaller tumor load (e.g. re-treatment in earlier lesions with partial response) can be considered. |

| | |
|---|---|
| | *Additional embolization:*<br>If two procedures are planned, first procedure could give maximum dose without additional embolization. Larger PVA particles than 150-250 µm should be avoided if not in special cases (e.g. arterio-portal fistulas, large intratumoral bleeding, very high flow and super-selective catheter position).<br>*Additional ablation:* In selected cases additional thermal ablation can be considered.<br>*Additional systemic treatment:*<br>Should be considered in patients with advanced disease (as according to BCLC C) with macrovascular invasion or extra hepatic disease. |
| **Follow-up and retreatment** | *Imaging:*<br>If all target tumors are treated and stasis in feeding arteries → three-phase contrast enhanced CT at 4 weeks post-TACE. Potential retreatment candidates are scanned after 3, 6, and 12 months.<br>*Retreatment:* Tumors not fully treated either due to multi-focality, size (>5cm) or large number of feeding arteries → new procedure after 2-3 weeks (after return to basis level of liver enzymes). Retreatment after image evaluation should be on demand if residual tumor enhancement, as long as no severe deterioration in overall performance status or liver function. Patients with progressive disease should be considered for an alternative treatment (e.g. SIRT, systemic treatment). |

[1]Barcelona clinic liver cancer staging system, [2]selective internal radiation therapy, [3]scores based on serum levels of platelets, albumin and bilirubin

### 9.3 Future aspects

Ablative and embolic therapies are options for liver tumor treatment by themselves or in combination. Combination therapy might be superior in selected cases, and a recent meta-analysis showed that the combination of TACE and ablation of HCC resulted in the best tumor response and longest survival when compared to transarterial techniques alone, however concluding that the existing level of evidence is low to moderate (226). Non-invasive ablation such as MRgHIFU has the potential of further expanding the number of patients that are able to be treated, however improvements of targeting and reach of the ultrasound beam are needed. Embolotherapy in HCC will further evolve, with refined particles and drugs being used, where the last years have shown a trend in using smaller particles, down to 40 µm of size (227, 228), and recently radiopaque particles have been introduced (229). The role of radioembolization

needs to be further established and in HCC patients it can be argued that this technique should be used before considering TACE since it does not occlude the vessels needed for TACE. An important part of future research is the development of refined tools for stratification of HCC patients, allowing for a more precise patient selection. This will be even more important when more effective treatments hopefully are available for treatment of advanced disease (i.e. immunotherapy), and combinations of interventional radiology techniques and systemic immunotherapy needs to be explored in the near future.

### 9.4 Conclusions

Image guided treatments are under continuous development and are important tools in individualized regimes of liver tumor treatment. It is feasible to ablate liver tissue close to large veins using MRgHIFU, and this method might become a clinical valid option in liver tumors close to large vessels not amendable for other surgical or ablative techniques. The role of DEE-TACE in MUM treatment is questionable, but further development of systemic therapy warrants interest for combinations of transarterial and systemic treatment. The role of DEE-TACE in HCC treatment in Norway is increasing with an increasing number of patients treated, and DEE-TACE can be used both in a neo-adjuvant and a palliative setting. For prognostication new liver function grading systems can be of importance also in our population and further studies should explore the use of these grades also in monitoring patients during follow up after TACE treatment.

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