Advancements of interventional oncology treatments for early stage hepatocellular carcinoma

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Chapter 10

Summary, general discussion and future perspectives

SUMMARY

Hepatocellular carcinoma (HCC) is witnessing a rise in its incidence, predominantly attributable to the aging population. The implementation of screening programs among high-risk populations has led to improved detection in an early phase. However, since the underlying liver cirrhosis remains incurable, the cause of tumor genesis is not being addressed, and a risk of developing new intrahepatic lesions after initial treatment remains present. Accurate minimally invasive treatment of Barcelona Clinic Liver Cancer (BCLC) early stage disease therefore serves two main purposes. First, it aims to offer an equally efficacious alternative to surgical resection for patients unable to undergo surgery due to portal hypertension caused by the underlying cirrhosis. Secondly, these interventions strive for optimal local control of the disease, while extending the window of opportunity for potential liver transplantation in eligible patients. This thesis contributes to pushing the boundaries for patient tailored and optimal minimally invasive management of early stage HCC.

Part 1 of this thesis focusses on the optimization of thermal ablation (TA) techniques, with the ultimate goal of enhancing their effectiveness in the treatment of early stage HCC lesions >2 cm. In *Part 2*, minimally invasive combination therapies are studied, tailored for early stage HCC lesions of 2 - 5 cm. Lastly, *Part 3* is directed to the long term outcomes after trans-arterial radioembolization (TARE) treatment for HCC.

Part 1: Thermal ablation: reproducibility and ablation margins

In *Chapter 2,* a comparative assessment of two commercially available microwave ablation (MWA) systems was conducted, focusing on the dimensions and sphericity of the ablation zones. These experiments were carried out in ex-vivo porcine liver specimens. Analysis of the ablation zones using high-field MRI showed differences in ablation size and sphericity between the two MWA systems at similar ablation settings. Notably, the Emprint ablation system demonstrated more uniform and predictable ablation zones across repeated measurements. Consistency in the size and shape of ablation zones is of high importance in the context of treatment planning and, ultimately, the prevention of local recurrences.

The confirmation of technical success is of great value in averting local recurrences. *Chapter 3* provides a comprehensive overview of the existing literature on ablation margin quantification methods. A total of 75 studies were included in a systematic review, 58 of which being clinical trials. In most clinical trials, target ablation margins were set at ≥ 5 mm, which is in accordance with clinical practice guidelines. Among all studies, 21 used co-registration software for minimal ablation margin (MAM) quantification. Both rigid and non-rigid registration techniques were utilized almost equally, whilst most applications incorporated semi-automatic segmentation tools. Furthermore, ten studies that explored

tissue shrinkage after TA were included, revealing a considerable variation in their findings. It is important to note that the vast majority of evidence is derived from retrospective data analysis. There is need for prospective data concerning ablation margin quantification and its correlation with local recurrences.

In *Chapter 4* commercially available non-rigid registration software was used for retrospective ablation margin quantification in 25 patients who had undergone TA of HCC lesion(s). In 7 of these patients, registration quality between diagnostic and post-ablation imaging was insufficient for quantitative analysis of ablation margins. Local recurrences were observed in eight out of the 18 remaining patients with a median follow-up time of 9.5 months. The results indicated that negative ablation margins strongly correlated with the occurrence of local tumor progression, as the average minimal ablation margin was -8.44 mm (SD 4.27) in patients who developed local recurrences, against -0.30 mm (SD: 2.00) in patients who did not. Interestingly, all patients with an ablation margin >0 mm did not develop local recurrent disease. The findings indicate that tissue shrinkage after ablation is an important factor to take into account, since not all patients with negative ablation margins developed local recurrences. It is important to stress the low eligibility to the study of the initial cohort (25/78 patients), due to its retrospective nature and differences in patient positioning between diagnostic and post-ablation imaging. To surpass the limitations faced in the retrospective study, the IAMCOMPLETE study protocol was designed, which incorporates a standardized pre- and post-ablation scanning protocol.

Chapter 5 describes the results of the prospective IAMCOMPLETE study, in which feasibility of rigid co-registration and ablation margin quantification was analyzed. In a study cohort of 20 patients (male: 13; mean age : 67.1 ± 10.8 [SD]; Child-Pugh A: n=12, B: n=8; BCLC stages very early: n=8, early: n=12, intermediate: n=2) , pre- and post- ablation contrast enhanced CT scans were acquired under general anesthesia and with a pre-oxygenated breath hold. This approach yielded a successful image registration in 16/20 patients (80%) and in 84% of all tumors. High inter- and intra-observer agreement rates for tumor segmentation were found, with a dice similarity coefficient of 0.815 and 0.830, respectively. The average MAM was 0.63 mm (SD: 3.589). Noteworthy, an average MAM of -4.0 mm was found in the two cases in which local recurrences developed and margins of the ablation procedure could be quantified. In this study the potential influence of tissue shrinkage was also suspected, since only 2/9 lesions with a negative MAM developed local recurrent HCC within one year.

Part 2: Combined treatment regimens for early stage HCC

Chapter 6 presents the findings of a retrospective cohort study on the combined treatment approach involving TA and transarterial chemoembolization (TACE) in 38 patients (male: n=34; median age 68.5 (range: 40-84); liver cirrhosis: n=33; BCLC early stage HCC: n=21,

intermediate stage: n=17, adjuvant TACE: n=27, neoadjuvant TACE: n=11). In this study the clinical outcomes in terms of overall survival (OS), time to progression (TTP), and local tumor progression (LTP) of both neoadjuvant and adjuvant use of TACE were examined. The median time to LTP was 23.6 months among patients subjected to neoadjuvant TACE whereas the median time to LTP in those treated with adjuvant TACE was 8.1 months ($p = 0.19$). Although no significant results were found, the trend suggests a better local control was obtained in patients treated with neoadjuvant TACE. This is in line with the current most common application of combined TACE and TA as described in literature. The median OS was 52.7 months for the entire cohort and no statistically significant differences between adjuvant and neoadjuvant TACE were found.

The HORA EST HCC study protocol is introduced in *Chapter 7*. In this multicenter, dose escalation cohort study, patients with HCC lesions of 2-5 cm underwent a combined treatment regimen involving TA and adjuvant holmium-166 (^{166}Ho) TARE. The hypothesis of this study was that hyperemia occurs in the direct proximity after ablation, which would allow for preferential accumulation of TARE using holmium-166 microspheres. The primary objective of this trial was to determine the optimal radiation dose to the treatment volume, ensuring a tissue absorbed radiation dose of 120 Gy to the target volume, encompassing the immediate periphery of the ablation zone.

In *Chapter 8* the results of the HORA EST HCC study are presented. In this prospective trial, 12 patients were treated with TA and holmium-166 TARE (male: 10; median age: 66.5 (IQR [64.3-71.7]); median tumor diameter: 2.7 cm (IQR [2.1-4.0])) A preferential accumulation of ^{166}Ho microspheres was observed within the target volume. After 2 patients had received 60 Gy of ^{166}Ho to the treatment volume the dose was escalated to 90 Gy for subsequent patients. The study ascertained that a treatment volume dose of 90 Gy was required to achieve the desired absorbed dose of 120 Gy within the target volume (median absorbed dose: 138 Gy (IQR: [127-145])). Remarkably, none of the 12 patients who underwent this treatment protocol developed local recurrences within 1 year of follow up, highlighting its promising efficacy in preventing tumor recurrence.

Part 3: TARE beyond early stage HCC

Chapter 9 describes the long-term results after TARE in a multi-center cohort comprising three academic medical centers, focusing on the long-term liver-related complications of TARE in patients who had not developed TARE induced liver disease (REILD). In total, 85 patients were included, 16 of whom developed REILD. Of the remaining 69 patients, 38 developed liver decompensation with Child-Pugh ≥ B7. A significant difference in OS was found between patients who developed REILD versus patients who did not; 16 vs 31 months respectively. In comparison to a matched control group of patients who underwent systemic

treatment with sorafenib, a higher incidence of liver decompensation was observed as late complication after TARE; 62% vs 27%. Nevertheless, it is worth noting that the OS after TARE was significantly longer than after sorafenib; 16 vs 8 months. Notably, the Albumin-Bilirubin (ALBI) score emerged as an independent predictive factor for the development of liver decompensation and OS.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The role of interventional oncology has grown tremendously over the last decade, which has led to it being a fully accepted and integrated discipline in oncologic care pathways [1]. Interventional oncology often offers effective, minimally invasive local therapies with low complication rates and shorter hospital stays [2]. This provides clear advantages over surgery and systemic therapies, as both are related with a high burden on the individual patient as well as healthcare costs. The increased use of interventional oncology is reflected in all recent HCC guidelines. TA is the treatment of choice in HCC lesions <2 cm, as the oncological outcomes are equal to those of surgery but at lower complication rates and costs [3, 4]. In the recent update of the Barcelona Clinic Liver Cancer (BCLC) staging system trans-arterial therapies, such as trans-arterial chemoembolization (TACE) and TARE, are recognized as effective alternative regimens for early stage HCC patients not eligible for surgery or ablation. Also in more advanced stages, TACE and TARE have been recognized as effective palliative treatments. Continuous technological advancement and the execution of larger and well-designed clinical trials studying the effect of treatment improvements, as well as head-to-head comparisons with other therapies, ameliorate and may further define the position of these therapies.

Thermal ablation

TA is the main treatment modality that has been discussed in this thesis. Advancements in treatment techniques have led to adoption of TA as first line treatment for HCC lesions <2 cm. For larger lesions, there is a clinically unmet need for a validated tool or technique that reduces the risk of local recurrences, that hampers further implementation in HCC guidelines. The workflow of TA consists of several steps, as can be seen in figure 1. Each step allows for the use of different techniques that could influence the treatment outcome of TA.

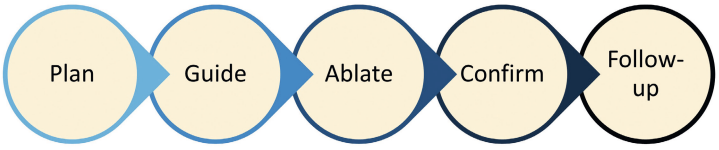

Figure 1 *Workflow of TA.*

Consistency in ablation zone sizes is of great importance for accurate treatment planning. Chapter 2 of this thesis presented the potential variety observed in ablation zones created by two different MWA systems, and even by a single ablation system in repeated measurements. The findings of this study reflect clinical practice, as ablation zone sizes and shapes can highly vary among patients. There are computational models that predict ablation zone sizes and shapes, while taking into account patient- and tissue specific factors [5]. Although the

use of these models would be very helpful, the research is currently in a premature phase and needs further development and validation before it can be used in clinical practice for treatment planning.

Image guidance can be provided by ultrasound, fusion of ultrasound-CT or ultrasound-MR, CT with intravenous contrast, CT with direct contrast agent infusion in the hepatic artery, and cone-beam CT. The image guiding modality should be chosen that provides the highest level of control over the needle position in respect to the tumor location, which can differ per treatment. Besides different imaging modalities, advanced needle guidance systems are currently available, for instance using optical or electromagnetic tracking, or even robotic assistance [6]. These systems contribute to the standardization of the procedure, which often translates to low tumor recurrence rates [7-9]. Moreover, as it increases reproducibility, those systems could contribute to shorter learning curves [10].

Confirmation of treatment success has been the most investigated topic in this thesis. Key in defining technical success of TA is the verification of ablation margins by using registration of pre- and post-ablation images, as has been demonstrated in *Chapters 4 and 5*. Besides the research presented in this thesis, multiple other articles have demonstrated poor reproducibility of eyeballing on pre-and post-ablation scans in the assessment of technical success, and the potential of quantifying the MAM [11, 12]. Interestingly, introducing a more objectified way to quantify a treatment outcome goes hand in hand with introducing the quantification paradox. By being able to measure an outcome, a complex problem is reduced to a single value, which is analyzed in terms of accuracy. In ablation margin quantification, the level of treatment success is often reflected by the smallest distance between a single point on a tumor surface and its closest border of an ablation zone: the MAM. This single value may be influenced by factors such as accuracy of tumor segmentation and image registration, but also factors such as liver deformation or tissue shrinkage during ablation, as can be read in *Chapter 5.* Further research should focus on advanced algorithms that allow for image registration with highest accuracy, and to different quantitative outcome measure that correlate mostly with treatment outcome. This research would be of great importance for further advancing TA practice. However, bringing an image registration tool to clinical practice today would enable a shift from side-by-side eyeballing to an overlay of images, which is likely to directly impact patient care. Although mostly supported by retrospective data, literature is unambiguous in the finding that image registration would improve the assessment of technical treatment success [13].

Prospective clinical trials are necessary to further prove the benefit of ablation margin quantification in clinical practice. Ideally, a cut-off minimal ablation zone value would be found that correlates with a low risk of local tumor recurrence. This requires a robust analysis

workflow that needs optimization of pre- and post ablation imaging protocols for accurate and automatic segmentation of tumor and ablation zone [14]. Moreover, image registration of pre- and post ablation images should further be optimized, which should probably be (partly) AI powered and use a combination of rigid and non-rigid registration [14, 15]. Large clinical trials are needed, such as the PROMETHEUS study which is coordinated by the LUMC, to further investigate how quantitative ablation margin values correlate to treatment outcome. [16, 17].

The growing role of real world data studies, such as CIEMAR and IMAGIO [18], and large clinical trials in the field of TA could create large datasets of TA imaging and patient data. By using large data sets for the training of AI models, a more patient tailored treatment approach could be developed. Depending on patient and tumor specific factors, the a priori probability of local recurrence after treatment varies among patients. Besides the lesion size and ablation margins obtained, treatment of recurrent cancer, perivascular tumor localizations, non-smooth tumor surfaces, high alpha-fetoprotein levels and higher Child-Pugh liver cirrhosis status are associated with more aggressive recurrences [19]. Further personalization of TA treatment therefore seems needed, although limited literature on this topic is currently available. Future research could learn from large data sets and answer questions like: *Do different tumor subtypes require different ablation margins? Do all TA patients need the same follow-up protocol? Could peri-procedural imaging protocols be optimized for better delineation of HCC lesions with non-smooth tumor borders? Is it possible to simulate the ablation zone pre-procedurally based on patient-specific parameters? Which patients would benefit most from (neo)adjuvant treatment?*

TARE

TARE has had a bumpy ride in making its way to clinical practice guidelines of HCC, and may be the best example to emphasize the value of the patient-tailored use of a minimally invasive treatment. After failing to meet superiority over the multi-kinase inhibitor sorafenib for advanced HCC (SARAH and SIRveNIB trials), the expectations for this treatment may have been tempered. However, since the first correlation of tumor absorbed radiation dose with treatment outcome was found, a large research field developed in terms of personalized dosimetry, with studies describing treatments with tumor absorbed doses of over hundreds of grays [20]. In a retrospective analysis of the SARAH trail, the predicted absorbed tumor dose at time of the Tc-99m labeled aggregated macro-albumin (^{99m}Tc-MAA) SPECT/CT scan during the work-up procedure turned out to be the only independent predictor of survival: 14.1 months in patients receiving >100 Gy ^{90}Y to the tumor vs 6.1 months in patients receiving a lower tumor dose [21]. Recently, it was prospectively confirmed in the DOSISPHERE-01 trial that personalized dosimetry yielded a higher objective response rate in patients targeted ≥205 Gy of glass microspheres to the tumors [22].

Over the last few years, clinical guidelines have been developed demonstrating the use of TARE for different applications: radiation segmentectomy for smaller lesions, lobectomy procedures for larger lesions and to induce hypertrophy of the future liver remnant prior to hemi-hepatectomy, and whole liver treatment [23]. In general, the trend has shifted more to the use of TARE in limited parts of the liver for intermediate or early stage HCC rather than whole liver treatment in advanced stages. This is in line with the findings of *Chapter 9* of this thesis, which discusses the late onset of liver decompensation after the use of TARE in a population with mainly intermediate and advanced stage HCC. In line with the findings of this study, more papers describe the ALBI score as early predictor of liver decompensation onset after TARE [24, 25]. Since better systemic treatment options, such as combined atezolizumab and bevacizumab, are now available, patient selection for TARE in more advanced disease stages is of even greater importance. This emphasizes the role of treatment planning based on the scout procedure. In general, selective catheterization of the tumor(s) and leaving a part of the liver untreated is a prerequisite for a successful therapy. The ^{99m}Tc-MAA scout procedure should demonstrate sufficient dose accumulation in the tumors that enable a high tumor dose while limiting the dose to the healthy liver parenchyma. This also means that a patient with an insufficient tumor absorbed dose as predicted by the SPECT-CT scan after the ^{99m}Tc-MAA-procedure should be brought back to the tumor board meeting to reconsider the choice of therapy. Future research could contribute to this decision by further defining threshold values that predict successful or unsuccessful treatment for the different radioembolization products and treatment approaches. Moreover, a patient tailored work up currently requires information from diagnostic imaging, SPECT/CT, and cone-beam CT. The development of a scout procedure with PET-tracer would allow for a contrast enhanced PET/CT scan with optimal image registration between anatomical and nuclear imaging at a superior resolution. Especially in challenging cases, this would contribute to improved dose planning and thus to treatment outcome.

In the HORA EST HCC trial, TARE has been used as adjuvant therapy after TA. Since the design of that study, the RASER and LEGACY studies have demonstrated high efficacy of TARE segmentectomy in equally sized lesions with local control rates similar to those after TA [26, 27]. These findings have led to the positioning of TARE as therapy for early stage HCC lesions ≤8 cm in the BCLC guidelines for patients ineligible to surgery or TA [28]. Despite the promising results so far, superiority over TA or surgical resection for these patients has not been investigated. Years of combined TA with TACE did not lead to full adoption in clinical guidelines, despite several studies that were performed. In *Chapter 8* the results of the HORA EST HCC trial showed that ^{166}Ho microspheres could be delivered in high concentrations to the area at risk for tumor recurrences after TA. Future research should focus on how to incorporate the excellent results of high dosed radiation segmentectomy in the combined treatment regimen of TA and TARE to further reduce local recurrence rates. The current

protocol could be altered in such way that small treatment volumes receive a higher average radiation dose than larger treatment volumes. Moreover, since the individual treatment outcomes of TA and TARE have improved over time, one could debate whether a combined treatment regimen in tumors <3 cm would be (cost-)effective. Therefore, inclusion criteria should shift from 2-5 cm to 3-6 cm lesions.

CONCLUSION

Early stage HCC remains a complex field with numerous sophisticated treatment options. Consequently, a 'one size fits all' approach is unlikely to be applicable. On the one hand conducting extensive studies with harmonized treatment protocols is crucial for head-to-head comparisons of outcomes within patient cohorts. At the same time, this wealth of data is essential for developing a nuanced understanding of which patients would benefit most from what treatment on an individual level. We should be aware not to treat all TA patients with an adjuvant treatment in order to prevent one tumor recurrence, which could have been predicted on by better use of imaging parameters and patient data.

Historically, progress in cancer therapy has been marked by incremental advancements rather than a quest for a singular "magic bullet" solution. The introduction of groundbreaking anti-cancer drugs or surgical techniques has often been met with initial enthusiasm, only to reveal limitations in their effectiveness over time. Nevertheless, these individual therapies have made meaningful contributions to the treatment of cancer patients. Interventional oncology is a relatively young field that experiences rapid and successive technological advancements. It is only logical to expect the growth and developments of the field to continue, playing a pivotal role in addressing future healthcare challenges, which is particularly relevant in the context of a healthcare system under pressure of an aging population and limited resources.

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