Advancements in minimally invasive image-guided liver therapies

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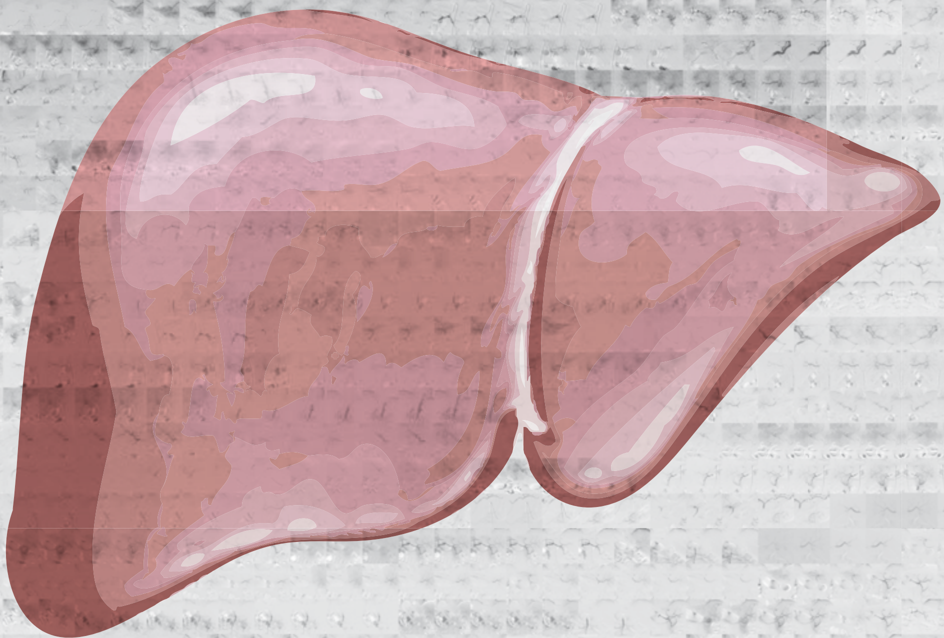
Chapter 12

General discussion and future perspectives



INTRODUCTION

When thinking about ways to cure cancer, the human brain is tempted to oversimplify. The idea that we will one day find the perfect solution to treat cancer is appealing and conceivable, but unlikely given the historical facts. In the past, doctors (mostly surgeons) believed we might be able to eradicate cancer by radical surgery. Yet, despite the tremendous contribution surgery has made to improve the life-expectancy of cancer patients on a whole, even aggressive surgery provides little chance of a cure in metastatic cancer. For long, people have been hopeful that chemotherapy would provide a definitive solution to metastatic cancer. In the past century, a multitude of clinical trials have been conducted in many different cancer types, often with ever-intensified regimes of combination chemotherapy. We now know that chemotherapy provides a cure in some and palliation in many patients, but there still are many cancer patients that are desperately in need of better therapies. Over recent years we have turned our hopes on targeted molecular therapies, propelled by the successes in unraveling the genetics of oncogenesis. Despite the many promising trials that have been conducted over recent years, there is a lesson to be learned from the past. It is very likely that we will see some spectacular breakthroughs in cancer treatment in the coming years, but it is unlikely that targeted or molecular drugs will solve it all. The battle against cancer will need to be fought along many lines of medical research. Some inventions will have a tremendous impact on the life of cancer patients, whereas other research will only have limited effect. Yet, the only way we stand a chance to defeat cancer is by trying in many different ways. By bringing together the ingenuity and efforts of many, we will change the perspective of cancer patients of the future. This thesis is a contribution, albeit small, to the fight against cancer. This thesis focuses on patients with hepatic malignancies.

PART 1. RADIOFREQUENCY ABLATION

Improvements in outcomes after percutaneous ablation may be achieved in different ways. Identifying and selecting those patients that will benefit most from RFA is an important first step. The study presented in **Chapter 2** demonstrates that the survival rate between patients from distinct geographical regions may differ as a result of differences in baseline parameters and patient selection. As demonstrated in this study, tumor size >3cm and tumor number >1 are independent risk factors for recurrence (csHR = 1.568; 95% CI: 1.083-2.271 and 1.494; 95%CI: 1.031-2.163 respectively). This finding is consistent with previous reports in the literature (1-3). As shown in our study, patients from a Northern-European country have a higher cumulative incidence of death despite lower recurrence rates. This underlines the importance of factors such as the etiology of underlying liver disease and disease stage at the time of treatment.

Further advances in the field of RFA may be achieved through improvements in tumour targeting. As discussed in **Chapter 3**, co-registration of US and CT/MRI images can be performed using manual, semi-automatic or automatic co-registration. Our phantom study with the GE Logiq E9 navigation software demonstrated that the accuracy of automatic co-registration is inferior to manual co-registration and semi-automatic co-registration. The mean registration mismatch was ≤ 2.5mm for both manual and semi-automatic co-registration in our study. This is consistent with other phantom studies using similar image fusion technology (4). Unfortunately, the accuracy of co-registration is lower in a clinical setting as a result of factors such as the deformability of tissue, breathing and movement. New image fusion technology should compensate for such factors as well as provide ways to obtain easier and faster image fusion.

A third way to improve the outcome after RFA is through the combination of ablation with other therapies, such as TACE, radioembolization or systemic treatment (see below). Also, other ablation techniques may prove to be a solution to the limitations of RFA, as they are less (microwave ablation) or non-dependent (irreversible electroporation) on thermal conductivity of tissue.

In **Chapter 4**, we investigated the use of TACE as an adjuvant treatment to RFA in HCC >3cm. Unfortunately, the combination of RFA with adjuvant drug eluting bead-TACE was associated with low rates of local tumor control and survival. The 3-year local tumor progression free-survival and overall survival after combined treatment was 17.9% and 59.4% respectively. This compares unfavorable with results obtained with RFA with neo-adjuvant TACE, but comparison of results is problematic, as the different studies have been conducted in distinctly different patient cohorts.

PART 2. TRANSARTERIAL LIVER THERAPIES

TACE is generally considered as a palliative treatment, as complete tumor necrosis is often not achieved. Incomplete tumor necrosis may be a result of incomplete tumor treatment or incomplete response to treatment. Better imaging techniques have led to lower rates of incomplete tumor treatment. The use of cone-beam computed tomography (CBCT) and computed tomography hepatic arteriography (CTHA) enable improved identification of all arteries with blood supply to a tumor. Previous studies have shown that the use of these imaging modalities results in improved outcomes (5-7). In **Chapter**

5, we demonstrated that catheter-directed contrast-enhanced ultrasound (CCEUS) provides similar multi-planar information on tumor enhancement as CTHA without exposing a patient to iodinated contrast media or additional radiation. Unfortunately, practical limitations have hampered the implementation of CCEUS into routine clinical practice.

Radioembolization is generally used to treat patients with advanced stages of disease. In large tumors, delivering a tumoricidal radiation dose to the entire tumor is challenging. As demonstrated in **Chapter 6**, in patients with unresectable hepatocellular carcinoma up to 37% of patients may have extra-hepatic vascular tumor supply. Identifying extra-hepatic feeders is essential to ensure complete tumor treatment and improve outcomes. Other studies have reported extrahepatic arterial tumor supply in 17-30.8% (8-11). In these studies, angiography and CBCT were used to identify extrahepatic tumor supply. In our study, we used CTHA and this may have led to better detection of extrahepatic feeders as CTHA has better spatial resolution and a larger field of view. Furthermore, the superior image quality of CTHA proved to be essential in enabling safe radioemboliza-tion through the right inferior phrenic artery. In **Chapter 7**, we demonstrated the superiority of CTHA over angiography and Tc99m-macroaggregated albumin single photon emission computed tomography with integrated computed tomography (Tc99m-MAA SPECT/CT) in the detection of the falciform artery. Despite this and other studies on the superior image quality of CTHA, this imaging modality has not been widely adopted outside of Japan, mainly because of the higher costs compared to CBCT. Further studies will need to investigate whether the higher costs of CTHA are counterbalanced by the superior image quality.

CTHA was also used to develop artery-specific SPECT/CT partition modeling in radioembolization, as described in **Chapter 8**. This technique allows individualized patient treatment with a reduced risk of under-treatment of tumor areas. Based on dose calculations using integrated CTHA, we estimated that a target volume dose of >90 Gy is associated with complete radiological response. Other studies have suggested that radiation doses of at least 100-120 Gy are required for complete response. Yet, estimating the relationship between radiation dose and response is complicated by the fact that distribution of microspheres in inhomogeneous and tissue radiation dose can only be measured indirectly. Better insight in dose-response relationships in radioembolization may be provided by post-treatment imaging with positron emission tomography (PET) or with the use of new generation microspheres.

PHP is a novel minimally invasive treatment for patients with hepatic malignancies. **Chapter 9** provides an overview on the currently available literature on PHP. The recognition of PHP as a first line therapy for patient with hepatic metastases from ocular melanoma is growing, but further research is needed in order to optimize treatment protocols and reduce systemic toxicity. In **Chapter 10**, we demonstrated that the second generation Delcath hemofiltration system has a higher and more consistent chemotherapy filtration rate compared to earlier generation filters. In the future, new detoxification filters factory tuned to high affinity for specific chemotherapeutics may further reduce systemic exposure to chemotherapeutic drugs or enable more effective treatment with other drugs than melphalan chloride.

PART 3. PATIENT MANAGEMENT

New biochemical drugs and technological discoveries with great promise for the future are often at the center of the attention of researchers and funding agencies. This may divert the attention away from research projects that may seem less innovative and exciting. Nevertheless, projects that investigate everyday practise may have an important impact on the wellbeing of patients. In **Chapter 11**, we demonstrated that both patient safety and satisfaction improve significantly when patients are seen in an interventional radiology outpatient clinic prior to an intervention. With the increasing number and complexity of procedures, it is important that interventional radiologists take greater responsibility over the peri-procedural management of patient undergoing minimally invasive image-guided therapies.

FUTURE PERSPECTIVES

Percutaneous RFA offers important advantages over surgery. It is associated with lower morbidity and mortality rates, shorter hospital stays and lower costs. Yet, recurrence rates after RFA tend to be higher than after surgery, especially in larger tumors. Future research should aim to reduce recurrence rates after percutaneous ablation to make it a therapy that is as effective as surgery. Other ablation techniques, such as microwave ablation or irreversible electroporation, have been developed in order to overcome the limitations of RFA, but so far studies have failed to provide evidence that these newer ablation methods are superior to RFA. Limitations that apply to RFA often also apply to other percutaneous ablation techniques.

An important limitation of percutaneous ablation is the absence of histological confirmation of treatment success. Whereas the surgeon will get confirmation from the pathologist whether a tumor has been removed successfully with sufficient margins, the interventional radiologists relies on post-procedural imaging. We therefore need better ways to assess tumor necrosis and ablation margins with medical imaging. Our research team is currently investigating post-processing software that allows fusion of pre- and post-ablation cross-sectional images to better define ablation margins. With the use of such software, we may be able to identify patients that are likely to have microscopic residual tumor. Patients with increased risk of incomplete tumor ablation may then be re-ablated before recurrence actually occurs.

Another important cause of recurrence after percutaneous ablation may be the presence of micro-metastases. These frequently occur in close proximity to the primary tumor, but may not be coagulated during the ablation. Our research group has initiated a research project to investigate segmental radioembolization as an adjuvant treatment to RFA. Findings in experimental animal studies have demonstrated increased tumor necrosis and improved animal survival after combined treatment with RFA and radiation therapy when compared with either therapy alone (12,13). Preliminary clinical studies in primary lung malignancies have confirmed the synergistic effects of these therapies (14). Potential causes for the synergy include the sensitization of viable tumor cells to subsequent radiation owing to the increased oxygenation resulting from hyperthermia-induced increased blood flow to the tumor (15). Another possible mechanism, which has been seen in animal tumor models, is a radiation-induced inhibition of repair and recovery and increased free radical formation (16). It is unknown what radiation dose should be used when combining RFA with adjuvant radioembolization. This will be investigated in a dose-finding study that is financially supported with a research grant from Health Holland and the Maag Lever Darm stichting.

Conclusions

1. Midterm recurrence and death rates after radiofrequency ablation (RFA) differ between hepatocellular carcinoma (HCC) patients in South-East Asian and Northern-European populations as a result of differences in baseline patient characteristics and patient selection.
2. The accuracy of manual and semi-automatic co-registration of ultrasound (US) and computed tomography (CT) images is better than that of automatic co-registration, based on experiments with the General Electric Logiq E9 navigation platform in a phantom.
3. Local tumor progression-free survival rates after combined RFA and drug-eluting bead transarterial chemoembolization (DEB-TACE) for HCC >3 are low compared to the results reported after combination therapy of conventional transarterial chemoembolization (TACE) followed by RFA.

4. Catheter-directed CEUS is a potentially valuable imaging tool in adjunction to DSA when performing TACE and may provide similar information as catheter-directed computed tomography hepatic arteriography (CTHA).
5. Delivery of Y90 microspheres through the right inferior phremic artery (IPA) is feasible and safe with the use of CTHA in addition to digital subtraction angiography and Tc-99m macroaggregated albumin (MAA) single photon emission computed tomography/integrated computed tomography (SPECT/CT).
6. The hepatic falciform artery detection rate of CTHA is superior to that of DSA and 99mTc-MAA SPECT/CT.
7. Image-guided personalized predictive dosimetry by artery-specific SPECT/CT partition modeling achieves high clinical success rates for safe and effective Y90 radioembolization.
8. Percutaneous hepatic perfusion should be considered as a first line treatment in patients with liver metastases from ocular melanoma
9. The Delcath Systems' second generation (GEN2) hemofiltration system has a higher melphalan filter efficiency compared to the first generation filters and a more consistent performance.
10. Patient safety and satisfaction improve significantly if patients receive consultation and screening in an interventional radiology (IR) outpatient clinic prior to elective IR procedures.

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