Development of a Hybrid Stereotactic Guidance System For Percutaneous Liver Tumour Ablation

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Biomedical Engineering
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Abstract

Stereotactic Image-Guided Surgical Navigation Systems (IGSNSs) support percutaneous procedures by using medical imaging and tracking information, to assist the surgeons in the preprocedural planning and intraprocedural steps. This thesis describes the development of a stereotactic IGSNS for percutaneous liver tumour ablation, the goal of which is to assist positioning the tip of the ablation applicator accurately to ensure complete tumour coverage. The main system improvement is the employment of a mini stereotactic patient-attach aiming device that is used as a pointer to ensure needle tip position prior needle insertion. The thesis chapters describe the development and validation of the components of the stereotactic IGSNS. An anthropomorphic phantom development for validation and training is also presented. We hypothesize that the combination of spatial tracking, real-time ultrasound, mechanical stabilization provided by the mini-stereotactic device and image-to-image registration will improve the targeting accuracy for the focal treatment and reduce the needle repositioning.

Keywords: Image-Guided procedures, Liver ablation, Ultrasound, Computer tomography, Virtual reality, Minimally invasive surgery, Rigid image registrations, Phantom development
Lay Summary

Liver cancer is one of the most common cancers around the world. One common treatment, besides surgical resection or liver transplantations, is tumour ablation. Liver tumour ablation consists in eliminating all the malignant cells of the tumour, without having to extract a part of the organ. This procedure can be done via open surgeries (the liver is exposed prior to inserting the ablation needle) or percutaneously (the ablation needle is inserted through a small incision on the skin). In either case, for the liver tumour ablation procedure to be considered successful, the needle tip needs to be placed at the center of the tumour, so that the ablation zone covers the entire volume of the tumour. A Stereotactic Image-Guided Surgical Navigation System (IGSNS) is a platform that assists surgeons during percutaneous procedures. Stereotactic IGSNSs use medical images such as ultrasound or computer tomography to visualize structures and organs and to navigate the surgeons during these procedures. In this thesis, the development of a Stereotactic IGSNS for percutaneous tumour ablation is presented. The main improvement of our Stereotactic IGSNS is the employment of a mini patient-attach needle guider that is used as a pointer. The needle guider projects a virtual line to show the needle path before insertion, ensuring an accurate needle tip position thus a successful treatment. The thesis also presents an algorithm to perform “image-to-image” registration, which is used to fuse two medical images (e.g., ultrasound and computer tomography) and ensure proper visualization of all the liver structures in a unique map. Finally, the design of a liver phantom that can be used for testing and training in the IGSNS is presented. We hypothesize that the combination of the registration of medical images and the mechanical stabilization provided by the mini needle guider will improve the process of ablation treatment and reduce needle repositioning during the procedure.
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<tr>
<td>2D</td>
<td>Two-dimensional</td>
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<tr>
<td>3D</td>
<td>Three-dimensional</td>
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<tr>
<td>AC</td>
<td>Alternating Current</td>
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<tr>
<td>ASR</td>
<td>Age Standardized Rate</td>
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<td>BCLC</td>
<td>Barcelona Clinic Liver Cancer</td>
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<tr>
<td>CAD</td>
<td>Computer-Aided Design</td>
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<tr>
<td>CCD</td>
<td>Charge-Coupled Device</td>
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<tr>
<td>CEUS</td>
<td>Contrast-enhanced Ultrasound</td>
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<td>CT</td>
<td>Computer Tomography</td>
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<tr>
<td>DC</td>
<td>Direct Current</td>
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<tr>
<td>DOF</td>
<td>Degrees of Freedom</td>
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<tr>
<td>EASL</td>
<td>European Association for the Study of the Liver</td>
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<tr>
<td>EM</td>
<td>Electromagnetic</td>
</tr>
<tr>
<td>EMTS</td>
<td>Electromagnetic Tracking System</td>
</tr>
<tr>
<td>FG</td>
<td>Field Generator</td>
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<td>FOV</td>
<td>Field of View</td>
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<td>FRE</td>
<td>Fiducial Registration Error</td>
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<td>FT</td>
<td>Freeze-thaw</td>
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<td>HCC</td>
<td>Hepatocellular Carcinoma</td>
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<tr>
<td>HD</td>
<td>High Definition</td>
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<tr>
<td>HV</td>
<td>Hepatic Vein</td>
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<tr>
<td>ICP</td>
<td>Iterative Closest Point</td>
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<tr>
<td>IF</td>
<td>Image Fusion</td>
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<tr>
<td>IGSNS</td>
<td>Image-Guided Surgical Navigation System</td>
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<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>IRE</td>
<td>Irreversible Electroporation</td>
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<tr>
<td>IVC</td>
<td>Inferior Vena Cava</td>
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<tr>
<td>LED</td>
<td>Light-Emitting Diode</td>
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<tr>
<td>LT</td>
<td>Liver Transplant</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>MWA</td>
<td>Microwave Ablation</td>
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<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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<td>OTS</td>
<td>Optical Tracking System</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>RF</td>
<td>Radiofrequency</td>
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<tr>
<td>RMS</td>
<td>Root-mean-square</td>
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<tr>
<td>ROI</td>
<td>Region of Interest</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>Ph-P1</td>
<td>Phantom experiment position 1</td>
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<td>Ph-P2</td>
<td>Phantom experiment position 2</td>
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<tr>
<td>PLA</td>
<td>Polylactic Acid</td>
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<td>PV</td>
<td>Portal Vein</td>
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<td>PVA-c</td>
<td>Polyvinyl Alcohol Cryogel</td>
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<tr>
<td>PVC</td>
<td>Polyvinyl Chloride</td>
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<tr>
<td>PVDF</td>
<td>Plastic Polyvinylidene Difluoride</td>
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<tr>
<td>Px</td>
<td>Patient</td>
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<tr>
<td>PZT</td>
<td>Lead-zirconate-titanate</td>
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<tr>
<td>TARE</td>
<td>Transarterial Radioembolization</td>
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<tr>
<td>TRE</td>
<td>Target Registration Error</td>
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<tr>
<td>US</td>
<td>Ultrasound</td>
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Chapter 1

Introduction

A percutaneous liver tumour ablation procedure is a minimally invasive surgery, performed via a small incision through the patient’s skin. For this procedure to be considered successful, the ablation needle tip needs to be positioned at the centre of the tumour mass to ensure complete tumour coverage by the treatment volume. For this reason, the positioning of the ablation needle tip is critical to the success of the intervention. Ultrasound (US) imaging is commonly used to monitor and to guide the insertion of the ablation needle until it reaches the target (i.e. tumour) to deliver the appropriate treatment. While this ultrasound-guided technique is commonly used clinically it nonetheless has challenges.

One of these challenges is the needle insertion technique used under US imaging, which relies on an “in-plane” approach. This “in-plane” technique is performed by inserting the needle into, and parallel to the US image plane, to visualize the entirety of the needle including needle tip and shaft . This in-plane approach is difficult to perform because it requires skillful hand-eye coordination to align the needle with the US beam plane, which is hard to maintain during needle insertion. If not performed correctly, this technique can lead to needle repositioning, which can cause harm to the patient (e.g., bleeding and tumour seeding). Thus, competency is often correlated with the experience of the practitioner.

Another challenge is that tumours may be invisible under US imaging, making the procedure under US guidance infeasible. A solution to this problem is to perform needle insertion under the guidance of other imaging modalities, such as CT and MRI, but this can increase the cost or require radiation. Alternatively, a solution to this challenge is to fuse ultrasound imaging with other imaging modalities, where the tumour is visible in the other imaging modality, to improve the visibility of internal structures (such as the tumour) under ultrasound imaging. Numerous algorithms can be used to obtain an image fusion, or image registration, but they could require specific steps and alter existing surgical workflow.

To address these challenges, we propose the development of a US-based surgical navigation system that uses a needle guider as a “laser pointer”, which allows both the “in-plane” and “out-of-plane” approaches to be performed, and an effective image fusion technique to improve tumour visualization under real-time ultrasound imaging. We hypothesize that the combination of real-time ultrasound, mechanical stabilization provided by the needle guider, and
image registration will improve the targeting accuracy for the focal treatment and reduce needle repositioning.

This thesis introduces our US-guided surgical navigation system solution. To fully understand the specifics of these challenges, the introduction chapter includes all the necessary background for the research presented in this thesis. First, the basic anatomy and physiology of the human liver are described, followed by an overview of the liver disease hepatocellular carcinoma, with the principal methods of diagnosis and the most common treatments. Emphasis on the percutaneous tumour thermal ablation, its challenges, advantages and disadvantages are discussed. The imaging modalities used to help in percutaneous ablation are explored, as well as a brief explanation of image-guided surgical navigation systems components: 1) tracking systems, 2) software and 3) aiming devices. The last part of the chapter introduces work on liver phantoms for training and validation of stereotactic image-guided surgical navigation systems. The chapter closes with the specific research goals for this thesis.

1.1 Liver

The liver is the largest gland in the human body and the only organ with regeneration capacity. This organ is located in the upper right quadrant of the abdominal cavity, below the diaphragm. The liver’s primary goal is to maintain hemostasis in the body, achieving this through the different cells that are broadly classified into parenchymal and nonparenchymal types. These cells are responsible for different functions that occur in the liver such as the production and excretion of bile; excretion of bilirubin, cholesterol, hormones, and drugs; metabolism of fats, proteins, and carbohydrates; enzyme activation, storage of glycogen, vitamins, and minerals; synthesis of plasma proteins, and blood detoxification and purification [6].

Even though the liver has many functions, it has a homogeneous appearance, making its study challenging. The external anatomy can be divided into gross landmarks: the gallbladder, the Inferior Vena Cava (IVC), and the Portal and the Hepatic Veins. The liver body is divided into two principal lobes, left and right, with the division being marked by the falciform ligament. Figure 1.1 shows the principal structures of the external anatomy of the liver.

The Portal and Hepatic vein structures function as the basis for Couinaud’s classification. This classification divides the liver into eight segments, each of which has its own afferent (portal vein, artery, and bile duct) and efferent (hepatic vein) structures. Figure 1.2 shows the eight segments of the liver and the previously mentioned vessel structures. Knowing the position of the segments and important structures in each one is useful when performing procedures such as liver resection of tumours.

1.2 Pathology: Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is a form of cancer that affects the liver cells. HCC is the seventh (9.5 per 100 000) most common cancer and has the fourth position (8.7 per 100 000) as the
1.2. Pathology: Hepatocellular Carcinoma (HCC)

The liver is divided by the falciform ligament into two major parts: The right and left lobes. The Inferior Vena Cava (IVC) separates into the hepatic veins.

Figure 1.1: Liver external anatomy.

cause of cancer-related deaths worldwide, in age-standardized rate (ASR), \(^1\) Figure 1.3 shows the graph of the statistics for the most common cancers worldwide (2020). HCC’s common risk factors include hepatitis B and C, cirrhosis, diabetes type 2, smoking, obesity, hereditary hemochromatosis and metabolic liver disease (i.e., non-alcoholic fatty liver disease) \([7]\).

Diagnosis of HCC is quite complicated, especially in the early stages and for this reason, a multidisciplinary approach is needed to diagnose HCC \([1]\). Biopsies, cytology, and medical imaging are some of the methods used to help in the diagnosis of HCC \([7]\). Diagnosis in a cirrhotic liver by imaging using modalities such as Computer Tomography (CT), Ultrasound (US) and Magnetic Resonance Imaging (MRI) is well accepted when there is an arterial hyper-enhancement and venous washout present in tumours of > 1 cm \([7, 8]\).

Surveillance of HCC had helped in the selection of the correct treatment for the disease. By studying the different stages of the disease, a more accurate treatment, with better outcomes, can be achieved in the early stages \([7]\). The European Association for the Study of the Liver mentioned, regarding the diagnosis of HCC, “Therefore, clinical decision-making and treatment recommendations should not merely be based on a simplified figure but on a complex process that requires personal insights and expertise” \([1]\).

The Barcelona-Clinic Liver Cancer (BCLC) staging system, along with treatments, is based on years of performing surveillance of HCC. In the next section, a summary of the systems is presented.

\(^1\)Data from Globocan (Global Cancer Observatory): https://gco.iarc.fr/
Couinaud’s classification divides the liver into eight segments, each one has its own afferent and efferent structures.

Figure 1.2: Couinaud’s classification.

1.3 HCC treatments

1.3.1 The Barcelona-Clinic Liver Cancer (BCLC) staging system

The BCLC staging system is one of the most widely accepted, it has been validated externally, and has a clinically oriented design that links each stage with a treatment [7, 8]. The BCLC has been performing updates to its staging system from 1999 to 2022. The last update (2022) uses the available data as of November 15, 2021.

The BCLC is based on the expertise of a professional association of liver research: the European Association for the Study of the Liver (EASL). The HCC staging and treatment schedule proposed by the BCLC is a well-structured classification that explains in detail the necessary characteristics that the patient needs to meet in each one of the possible treatments. This staging and treatment schedule system is based on the analysis of several cohorts and randomized controlled studies, allowing the continuous refinement of treatment indication and application. The system (2022) stratifies HCC patients into five stages BCLC 0: very early, BCLC A: early, BCLC B: intermediate, BCLC C: advanced and BCLC D: terminal stage.

Each stage describes different aspects that the patient needs to meet to enter that category. The related aspects of HCC used for the system are the tumour stage, the degree of liver function impairment, the patient’s general condition, and treatment efficacy to construct the system [7]. For each stage, the BCLC system established the treatments to obtain the best outcome possible. To help in the decision-making, the BCLC incorporated a specific section in the 2022 update. This section incorporates concepts and parameters that are needed to perform a personalized HCC treatment approach. Figure 1.4 shows the complete staging and treatment schedule,
1.3. HCC TREATMENTS

Graph of the most common cancers worldwide, in blue, is the incidence, and in red is the mortality. Numbers are age-standardized rate (ASR), per 100 000 (Image courtesy of the International Agency for Research on Cancer (IARC) from webpage https://gco.iarc.fr/).

Figure 1.3: Most common cancer worldwide statistics.

2022 update.

The BCLC staging system establishes the criteria for a patient to be considered part of each stage. Patients in the “Very early stage (BCLC 0)” and “Early-stage (BCLC A)” should be considered for liver transplantation, liver ablation or surgical resection. The treatment selection will depend on a multidisciplinary analysis, as previously mentioned. A liver transplant (LT) is to be considered the first solution in all cases, but it will be changed if the patient does not meet the necessary criteria [1].

1.3.2 Surgical resection and liver transplantation

Surgical resections consist of removing the tumour tissue via open surgery. During the procedure, a margin should also be extracted from the liver to reduce the possibility of HCC recurrence by leaving cancer cells in the surrounding areas of the tumour. The size of the margin is not established completely but it has been demonstrated that, if possible, a major margin should be removed to reduce HCC recurrence [9]. This type of treatment, tumour resection, was the first treatment option for non-cirrhotic patients with liver tumours [8]. Accordingly, in the new BCLC system, resection is the option if the patient does not qualify for LT directly, because of the high HCC recurrence risk of resection [1], (≥ 10% and reaches 70-80% after 5 years) [10]. Ablation is the other option to consider before surgical resection since the survival outcome of this approach is similar to that following resection [1].
The BCLC system describes the HCC stages, and patient-specific characteristics and then recommend the best treatment option accordingly to the stage and patient specifications.

Figure 1.4: BCLC staging system, 2022 update [1] (Image courtesy of Elsevier).

LT is a treatment that consists in removing the organ completely and replacing it with a healthy one. This treatment is the choice when the patient has poor liver functionality (due to cirrhosis or other specific diseases) [1]. Some limitations of liver transplantation are the waiting times before receiving the donor’s liver. For these cases, a “bridge therapy” such as ablation, chemoablation or Transarterial radioembolization (TARE) is recommended [1].

In a summary, the BCLC system proposes the treatment of tumour ablation as the first possible option for patients in BCLC 0 or BCLC A, who are not candidates for surgical resection or LT. As well, ablation can be used as bridge therapy while the patient is waiting for the LT. In the next section, we explore ablation techniques, which is the methodology addressed in this thesis.

1.3.3 Tumour ablation and percutaneous treatments

A tumour ablation attempts to eliminate all the malignant cells in the tumour, without having to extract a part of the organ [2]. An ablation procedure can be performed percutaneously (via a small incision on the skin, a minimally invasive procedure) or via open procedures. Possible advantages of minimally invasive therapies include the anticipated reduction in morbidity and mortality, low complication rate, lower cost, the potential application in a wider spectrum of patients, including nonsurgical candidates, and repeatability [11]. The BCLC staging system suggests using ablation when specific characteristics are met by the patient, such as the number of lesions, size of the lesions and liver functionality [1].

Percutaneous treatment for tumour ablation is commonly separated into two major categories:
1.3. HCC treatments

treatments chemical (ablative substances) or thermal (heating or freezing). However since the chemical approach is no longer used as a treatment [12], we are not going to explore this type of ablation in this thesis. Cryoablation employs cold temperatures to eliminate the malignant cells of the tumour. Liquid nitrogen and argon are the primary elements used in this type of ablation [12].

Thermal ablation by heat is the major type of ablation used to produce cellular damage [13]. In the thermal heat ablation field, there are several different types of technologies that are used to produce heat, such as LASER, Irreversible electroporation (IRE), Radiofrequency (RF), and microwave (MWA). RF and MWA ablation are the most widely adopted for this type of procedure [7].

For this thesis, we cover RF and MWA, as percutaneous energy-based ablation modalities, describing each one in greater detail to understand the basic principles and specific needs.

1.3.4 Thermal heat ablation techniques: Radiofrequency (RF) and Microwave ablation (MWA)

This section presents a brief description of the physics principles of thermal ablation as well as of both principal ablation techniques (RFA and MWA). To understand the difference between both ablation techniques, the advantages, disadvantages, treatment zone, and general characteristics of thermal ablation are discussed.

Independent of the type of ablation, focal heating is achieved through the placement of the applicator at the center of the target, around which heating occurs [14]. The “applicator” is a large needle that has an electrode on the tip and delivers energy using either RF or MW to heat the tissue. As mentioned in the last section, thermal ablation induces irreversible cellular damage by increasing temperature until necessary. Heat ablation operates in a range of 50 – 100 °C, with a cytotoxic temperature of ≈60°C being required to kill the malignant cells of the tumour without tissue carbonization due to excessive heating. If the temperature is higher than 110 °C, tissue vaporization and carbonization can occur [15]. Both RF and MWA have the same objective and work similarly but the way each type of ablation reaches these temperatures (50 – 100 °C) is what makes them different. A brief description of the two most common heat ablation techniques is presented next.

RF ablation produces tissue heating using an alternating electric current with a high-frequency setting of approximately 0.5 MHz (460 – 480 kHz) and a wavelength of >100 meters [15]. In contrast to the MWA, which affects the water molecules, RF excites the ions of the tissue. These ions try to follow the alternating current, which produces friction that develops heat (Figure 1.5). Pacheco et al. (2018) [15] describe RF heat production in the following manner “Produces excitement of cellular ions with consequent friction at molecular level that finally increases intracellular temperature and produces thermal cytotoxicity, coagulation and tissue necrosis.”

Microwave ablation uses non-ionizing electromagnetic (EM) radiation with a frequency of 900 – 254 MHz with a wavelength of about <10 centimetres. This electromagnetic radiation is used to heat the intracellular water molecules of the surrounding tissue [15, 12]. The water is a polar molecule with an asymmetrical electric charge, that oscillates when irradiated by
the EM wave. The oscillation is produced because the water molecule orientation is changed according to the positive or negative field of the EM wave. This oscillation produces kinetic energy resulting in tissue heat and therefore cellular necrosis [15]. Figure 1.5b shows the EM field produced by the MWA applicator and the water molecules changing orientations.

Figure 1.5: Physic principles of RF and MWA.

Both techniques use an ablation needle or applicator to reach the tumour, which functions as an electrode in both cases. RF uses two different types of electrodes: interstitial electrodes (needle) and dispersive electrodes (ground pad).

Ahmed et al. (2011) [2] describe this technique as an electrical circuit: “In this way, the RF ablation setup can be thought of as a simple electrical circuit wherein the current loop comprises a generator, cabling, electrodes, and tissue as the resistive element”. While MWA does not need the use of the “ground pad” electrode to function correctly. Figure 1.6 shows examples of both ablation setups.

Even though both techniques employ heat to achieve cellular necrosis, each system has its own protocol to reach that goal. Each system uses the manufacturer’s recommendations in terms of electrode/antenna type, potency and time duration [15].

Independent of the physical principle or the number of electrodes used, for a heat ablation treatment (RF or MWA) to be successful, heat needs to be delivered through all the tumour volume plus a margin (between 5 – 10 mm) of “health” tissue that can contain malignant cells [11, 2]. The treatment zone is called the “ablation zone” and usually is in the form of an ellipsoid with its center at the tip of the applicator.

Another difference between these ablation techniques (RF and MWA) relies on the specific designs of the applicators depending on the ablation type. RF has multiple types of electrodes designed to improve the heat delivered, increasing the ablation zone, without reaching tissue carbonization. Some examples of different electrodes for RF ablations are shown in Figure 1.7.
1.4. Imaging modalities for percutaneous ablation

Imaging is a critical tool in a percutaneous ablation because it is used in five different parts of the procedure: preprocedural planning, intraprocedural targeting, intraprocedural monitoring (real-time imaging tissue changes), controlling or modification (real-time tool adjustments), and postprocedural assessing treatment response (effectiveness) [16]. The most common imaging modalities to guide ablation procedures are Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Ultrasound (US) [17, 18]. Each imaging modality is used differently and has its own advantages and disadvantages over the others. First, it is important to understand the difference between preprocedural and intraprocedural imaging and why different imaging modalities are commonly used in each step.

1.4.1 Preprocedural VS Intraprocedural imaging

Preprocedural imaging is performed before the start of the procedure. This step usually provides the necessary data to preplan or rehearse the treatment [3]. The preplanning step helps the physicians to define where exactly the tumour is in the liver, its size, shape, vessels surrounding it and any critical structure that could be a risk during the ablation procedure. For these
a) Single internally cooled electrode.  
b) Cluster internally cooled.  
c) Umbrella or expandable electrode.  
d) Umbrella or expandable electrode (different design).

Figure 1.7: RF applicators examples [2] (Image courtesy of The Radiological Society of North America).

reasons, intraprocedural imaging needs to be of sufficiently high quality, to provide excellent differentiation between normal and abnormal tissue as well as an accurate representation of the patient, and serve as a basic guidance tool during the procedure [3]. CT and MRI are the most common image modalities chosen for this step because they enable the acquisition of a 3-dimensional image of the tumour in relation to the surrounding structures, the probes and the ablation zone [11].

Intraprocedural imaging helps in the steps of targeting, monitoring and controlling percutaneous ablation procedures. Targeting refers to the placement of the electrode (applicator or needle), monitoring to the visualization of tissue changes during the procedure and controlling to the possibility of the real-time adjustments of tools during the procedure. For the reasons mentioned earlier, intraprocedural imaging should be real-time [3].

The selection of imaging modality for preprocedural and intraprocedural steps is critical for a successful ablation [17]. Basic physic principles, advantages, and disadvantages of intraprocedural/intraprocedural of different modalities are discussed in this section.

**Real-time imaging modalities: fluoroscopy and ultrasound**

X-ray fluoroscopy and US, both being real-time imaging, are the most common options to be used for intraprocedural imaging [19]. Figure 1.8 shows an example of both fluoroscopy and US imaging. However since fluoroscopy is not one of the first options for percutaneous liver ablation, it will not be discussed further in this thesis. Mansur et al. (2022) [17], mentioned, regarding this imaging modality: “Fluoroscopy is restricted by its limited ability to navigate
out of its plane and the exposure to radiation to both the patient and operator”

US imaging provides true 2D images at real-time rates and does not use radiation. US is the most common option to guide percutaneous ablation because it does not require radiation, scanners are compact, and are relatively inexpensive in comparison to CT and MRI [19, 16]. As the most common option, US imaging will be explored in more detail in the Section 1.4.2.

Examples of Real-time imaging modalities.
- a) X-ray fluoroscopy.
- b) Ultrasound (Cardiac imaging).

Figure 1.8: Intraprocedural imaging modalities examples [3] (Image courtesy of Springer Nature).

**Computer Tomography (CT)**

CT is an imaging modality that creates 3D images volume of patient tissue densities, commonly used to visualize the skeletal anatomy and vascular structures (when using opaque contrast material) [3]. Since CT scans image structures in three dimensions, it is often used for planning, and preprocedural imaging [20]. The principal disadvantage of CT is the high radiation exposure [11]. Another disadvantage is that CT does not provide real-time imaging, but it can generate the image quickly. For this last reason, it can be used as an intraprocedural imaging modality for percutaneous ablation, using an “advance and check” approach. In this approach, the tool is moved small distances, and then the position is checked by acquiring an image [20].

**Magnetic Resonance Imaging (MRI)**

MRI has excellent soft-tissue contrast and good spatial resolution, making it ideal for identifying structures and boundaries [20], as well as visualizing normal and pathological tissue [3]. MRI is based on the phenomenon of nuclear magnetic resonance (NMR). RF waves, emitted by the magnetic field of the MRI, excite the atomic nuclei, which absorb the energy and transition to a higher energy state. This is due to the principle that certain atomic nuclei have inherent magnetic moments and their effective precession frequency scales linearly with the magnetic
field strength. After the nuclei transition to the higher energy state, they relax to their ground state and emit radiofrequency waves at their precession frequency [20].

The contrast in the MRI image is based on both the density of nuclei and their chemical environment, allowing a much better soft tissue contrast than X-ray-based techniques [20]. MRI is very useful in pre-procedural planning due to its superior signal-to-noise, faster scans, and higher resolution [3]. As an intraprocedural modality, MRI presents challenges similar to CT. Even though MRI does not use ionizing radiation, it does have higher costs, and restricted availability has limited the use of real-time MRI in clinical practice [11]. Other disadvantages are limited workspace, lack of MR-compatible tools, no real-time imaging, a relatively complicated operation, and susceptibility to artifacts [18].

CT and MRI can be also used for intraprocedural imaging, but are not ideal options for intraprocedural imaging. Both image modalities have specific high-cost equipment and a lack of real-time imaging besides their specific limitations [19]. It is true that CT, due to its high-quality imaging and 3D capability, allows more accurate placement of surgical instruments than fluoroscopy, which is a 2D projection of the scene [3]. Disadvantages of CT are high radiation exposure to patients and physicians, limited angle of needle insertion, and suboptimal visualization of intrahepatic vessels [17, 11]. Regarding MRI as an intraprocedural imaging modality, the high quality and tissue differentiation are excellent tools, but the specifications of MRI make it hard to utilize as intraprocedural imaging: the room and surgical instruments must be designed and manufactured to be MRI compatible [19].

Holmes et al. (2008) [3] established: “Minimally invasive procedures rely heavily on intraprocedural imaging modalities because the anatomical/pathological target cannot be observed directly by the interventionalist”. In the next section, the US imaging modality as an intraprocedural imaging tool is described.

### 1.4.2 Ultrasound: physical principles

As mentioned in the last section, US imaging is one of the most common methods of intraprocedural imaging used in percutaneous ablation procedures. It is commonly employed because of its specific characteristics, such as real-time imaging, low cost compared with other imaging modalities, its ease of use, repeatability, and its lack of need for ionizing radiation [16].

US depends on the propagation and reflection of sound waves. A sound wave is a mechanical disturbance that propagates through a medium (e.g., human tissue), with a specific frequency \( f \) (number of oscillations per second), wavelength \( \lambda \) (the distance between successive wave crests) and amplitude (size of the wave from the peak/trough to the middle part of the wave). With these parameters, the velocity (or speed) of sound can be calculated using Equation 1.1 [21].

\[
 v = f \lambda
\]  

Where \( v \) is the velocity of propagation, \( f \) is the frequency of the waves and \( \lambda \) is the wavelength in meters.
The velocity of sound is dependent on the nature of the medium through which it is travelling (e.g., sound travels faster in solids and slower in gases) [22]. The speed of sound in human tissue averages 1540 m/s but can vary depending on the density of the tissue. Table 1.1 shows the most common speed of sounds in different human tissues.

<table>
<thead>
<tr>
<th>Tissue/Material</th>
<th>Velocity (ms⁻¹)</th>
<th>Attenuation (dBcm⁻¹MHz⁻¹)</th>
<th>Density (kgm⁻³)</th>
<th>Acoustic Backscatter (MRayl)</th>
<th>Backscatter (10⁻¹cm⁻¹sr⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>330</td>
<td>1.2</td>
<td>1000</td>
<td>1.48</td>
<td>0.0004</td>
</tr>
<tr>
<td>Water</td>
<td>1480</td>
<td>0.0022</td>
<td>1000</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td>Soft tissue (average)</td>
<td>1540</td>
<td>0.3-0.8</td>
<td>1043</td>
<td>1.63</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>1547-1600</td>
<td>0.2-0.6</td>
<td>1050</td>
<td>1.62</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>1560-1584</td>
<td>0.2</td>
<td>1060</td>
<td>1.68</td>
<td>0.1-1</td>
</tr>
<tr>
<td>Breast</td>
<td>1510</td>
<td>0.75</td>
<td>1020</td>
<td>1.54</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>1555-1595</td>
<td>0.4-0.7</td>
<td>1060</td>
<td>1.69</td>
<td>1-25</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1576</td>
<td>0.52</td>
<td>1060</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>1450-1480</td>
<td>0.5-1.8</td>
<td>950</td>
<td>1.40</td>
<td></td>
</tr>
</tbody>
</table>

US transducers that generate sound waves in a frequency range of 1 – 20 MHz [22]. US probes use piezoelectric (pressure electricity) transducers, that convert electrical into ultrasonic energy and vice versa. Figure 1.9 shows the components of the piezoelectric transducers used in ultrasound machines.

**Figure 1.9: Components of a single element pulsed mode ultrasound transducer.**

A pulse generator produces high-frequency voltage oscillation, which causes a crystal (i.e., piezoelectric element) to change shape, which leads to a change of pressure in front of the transducer producing the US waves. This crystal is coated with a thin layer of silver, to act as an electrode and allow the conduction of electricity [22]. Usually, transducers for US are
made of a synthetic ceramic, such as lead-zirconate-titanate (PZT), or plastic polyvinylidene difluoride (PVDF) and if heated above its curie temperature the piezoelectric effect will be destroyed.

The US transducers can generate waves in a continuous or pulsed mode, and the design of the transducer also determines the properties of the sound waves that can be generated. The resonant frequency of the transducer is determined by the thickness and acoustic velocity of the piezoelectric crystal such that changing the thickness of the crystal will change the frequency of the wave but not the US amplitude or velocity. Accordingly, thin crystals produce high-frequency waves, while thicker crystals produce low-frequency waves, which allows a better tissue penetration [22].

The waves generated by the piezoelectric transducer can be reflected, refracted, scattered or absorbed when reaching tissue boundaries. The reflection of the waves occurs because of the mismatch between the speed of sound in the different tissues [3]. As mentioned earlier, each tissue has a different velocity, and acoustic impedance ($Z$), which depends on the tissue’s density ($p$) and velocity ($v$) [$Z = pv$]. Table 1.1 shows the velocity, density, and acoustic impedance of some human tissues. The acoustic impedance of a tissue interface determines the amount of energy (intensity) reflected at the interface. Figure 1.10 shows the reflection, transmission and refraction principles between mediums.

![Diagram](image)

Reflection, refraction and changes of velocity of sound of waves when entering in contact with new tissue. The angles of incidence ($\theta_i$), reflection ($\theta_r$) and transmission ($\theta_t$) are presented.

**Figure 1.10:** Principles of sound waves reflection, transmission and refraction between different tissues.

The reflected waves are called echoes and are used to generate the US image. The percentage of ultrasound intensity (energy the wave is carrying) reflected/transmitted depends on part of the angle of incidence/reflection ($\theta_i/\theta_r$) of the ultrasound beam (waves). The major the $\theta_r$ is the less probability of the transducer to detect the reflected waves. Equation 1.2 (Snell’s law) describes
the relationship between the angles of incidence ($\theta_i$) and transmission ($\theta_t$), when waves pass through a boundary between two different mediums, as shown in Figure 1.10. The intensity, (percentage of reflection/transmission waves) of a plane wave at a smooth specular boundary can be calculated using equations 1.3 (Fraction reflected) and 1.4 (Fraction transmitted) [22].

$$\frac{\sin \theta_i}{\sin \theta_t} = \frac{V_1}{V_2}$$  \hspace{1cm} (1.2)

$$R = \left( \frac{Z_2 \cos \theta_t - Z_1 \cos \theta_i}{Z_2 \cos \theta_t + Z_1 \cos \theta_i} \right)^2$$  \hspace{1cm} (1.3)

$$T = \frac{4 \times \frac{Z_1}{\cos \theta_i} \times \frac{Z_2}{\cos \theta_t}}{\left( \frac{Z_1}{\cos \theta_i} + \frac{Z_2}{\cos \theta_t} \right)^2}$$  \hspace{1cm} (1.4)

Where $\theta_i$ is the angle of incidence, $\theta_t$ is the angle of transmission, $V_1$ is the velocity in the propagation tissue, $V_2$ is the velocity on the boundary tissue, $Z_1$ is the acoustic impedance of propagation tissue, $Z_2$ is the acoustic impedance of boundary tissue.

The reflected waves are then reabsorbed by the transducer, which vibrates and transforms the energy into AC oscillations of the same frequency (piezoelectric effect) [21]. As the angle of incidence increases, the reflected waves are less likely to reach the transducer and the lack of transmission beyond an interface (Figure 1.10) generates an area of echo void called shadowing. Because of the high impedance differences between tissues and air or bone, such interfaces reflect the entire US beam. To minimize the potential large reflection caused by air trapped by the transducer and the patient skin, and the impedance difference between the transducer and soft tissue, an impedance-matching gel is employed to ensure maximum energy transfer from the transducer to the patient.

Refraction is defined as a change in the direction of the US beam when it passes from one medium to another, as shown in Figure 1.10. When refraction occurs, the frequency of the waves is maintained, but the wavelength changes to accommodate the new velocity of sound on the new tissue. If the waves are not reflected nor refracted, then they are absorbed by the tissue or scattered (dispersed). Attenuation is an effect where the intensity of the US beam decreases as the penetration depth increases, caused by scattering and absorption of the sound waves, and it increases with frequency. In soft tissue, the US attenuation is nearly linear, while in tissues such as bone the attenuation increases approximately as frequency squared [22].

US beams are generally emitted in pulses of $\approx 1 \mu$s [22], allowing the returning echoes to be received and interpreted. The returning echoes supply information regarding the depth of an interface (the time the reflection needs to reach back to the transducer) and the intensity of the echo received. These characteristics provide information about differences between two tissues which allows image generation. US images are normally displayed on a video monitor and can be presented using different US modes. A brief description of the characteristics of B-mode is presented next.
The field of view (FOV) of the US image (in B-mode) is limited and cannot provide full cross-sectional slices of the body, because of the nature of the probes [11]. Figure 1.11 shows the parts of a US FOV. Depending on the way the transducer is composed, the FOV can change. US FOV is composed of three regions: the near and far fields, and the focal zone (i.e., the region over which the beam is focused). Having a focused transducer reduces the beam width but increases its intensity improving the image quality [22].

Another important aspect is that the US transducer may consist of either a single crystal or multiple small transducers (phased array) that are sequentially activated to image a plane. The phased array transducers can be linear or curvilinear and, independent of the shape, both use all their elements (transducers) to form the US beam, and the image is created by adding together all the individual lines. Figure 1.12 shows both options and their respective FOVs.

Besides the reduced FOV, another limitation of the US images is their low contrast resolution. In general US images incorporate “speckle” whose grainy appearance can make the visualization of some structures or tumours challenging [17]. Ultrasound nevertheless has some advantages over other image modalities, such as low cost, real-time imaging and no ionization radiation being needed to obtain the images [19]. Another advantage is that even if the FOV is small, the probe can be easily repositioned to obtain information from another part [20]. Ultrasound imaging can also be used for other functions such as visualizing other properties of tissue, such as stiffness (through elastography) and flow (through Doppler imaging) [3].

An alternative modality that enhances ultrasound imaging is called contrast-enhanced ultrasound (CEUS), which uses microbubble contrast as an acoustic enhancer [17]. This modality can improve the visibility of small tumours at a relatively low cost, but some lesions are still difficult to visualize (e.g., deeply seated lesions in the hepatic dome). Other disadvantages of CEUS are operator experience, the limited number of contrast injections during each session, and its limited availability [17].
1.4. Imaging modalities for percutaneous ablation

In phased array transducers, each individual transducer element activates at different times. The information of all together generates the US image.

a) Linear phased array. b) Curvilinear phased array.

Figure 1.12: Phased array US transducers.

1.4.3 Hybrid modalities: Image fusion (IF)

Section 1.4.1 describes the characteristics of preprocedural and intraprocedural imaging. It is hard to obtain a perfect imaging technique that complies with all the necessities of percutaneous procedures. The necessity of high-quality imaging for planning and avoiding important structures (given by CT/MRI) but having real-time imaging, low cost and that does not take a lot of space in the surgical room (e.g., US) is not available in a single modality [20]. To address this challenge, the combination of preprocedural and intraprocedural patient image data is often used. Image fusion (IF) is a technique that combines two medical images, offering the best characteristics of each modality.

IF is the action of merging the information acquired from different imaging modalities [19]. In the words of Puijk et al. (2018) [11] “Image fusion refers to the partially transparent overlay of one dataset over another.” It could be positron emission tomography (PET) over CT, US over CT, US over MRI, CT over MRI, etc. Using IF in percutaneous ablation procedures helps to improve the targeting of the lesion, needle guidance and visualization of important structures, such as vessels [19, 11].

Carriero et al. (2021) [19] compiled the outcome of using IF (between different modalities) versus not using it during percutaneous liver tumour ablation, obtaining better results when using the IF technique: “IF reduces the major complications during liver ablations giving an optimal view of the lesion and the surrounding structures.”

Hybrid techniques (i.e., IF) help to achieve a better outcome of the procedure, by improving the visualization and are commonly used in Image-Guided Surgical Navigation Systems (IGSNS) to improve the quality of imaging guidance and the outcomes of percutaneous thermal thera-
pies, especially when encountering complex anatomy and difficult access [23].

The next section discusses the main components of the IGSNS.

1.5 Image-Guided Surgical Navigation Systems (IGSNS)

The purpose of Image-Guided Surgical Navigation Systems (IGSNSs) is to accurately represent the patient and surgical environment to help the physician deliver the applicator into the correct position [3]. In other words, the IGSNSs help the physician, even with little experience, to reduce the number of needle repositions during percutaneous ablation procedures. But image fusion is not the only component of an IGSNS. Stereotactic technology can be used in conjunction with IGSNSs to improve the navigation of small structures in the human body.

Stereotactic IGSNSs support surgical procedures using medical imaging, tracking information and mechanical support to allow the physicians to plan preprocedural as well as monitor and control the procedure in real-time. Navigation systems allow the tracking of surgical tools in real-time [24]. IGSNS can be seen as information that provides surgeons with the correct information at the appropriate time during the procedure [25].

According to Paolucci et al. (2019) [4], the components of a stereotactic image-guidance system are (Figure 1.13):

1. a tracking system that measures the position and orientation of the patient and the instruments in 3D space.
2. software packages for trajectory and procedure planning, validation, and visualization aids.
3. an alignment device that allows accurate placement of surgical tools (e.g., needles)

![Image of IGSNS components](Image courtesy of Licensee IntechOpen and Creative Commons)
To have a better understanding of the probable challenges that this tool presents, the next section describes each component of the stereotactic IGSNS.

### 1.5.1 Tracking systems

There are different systems to track a tool, with the most commonly used in the medical field being optical and electromagnetic tracking systems [4, 23]. Both tracking systems use different physical principles to obtain the position and orientation of the instruments in a virtual space. Each system has its advantages and disadvantages, and the choice of a system is highly dependent on the application as well as the desired working volume (space in the operating room) and accuracy requirements [26]. In this section we are going to discuss the basic principles of OTSs and EMTSs, advantages and disadvantages, focusing on EMTSs as the choice for the work on this thesis.

**Optical Tracking System (OTS)**

Optical tracking systems (OTSs) use light to track the desired instrument [27]. Overall, their functionality consists of a source that generates a signal (optical references or markers), a sensor that detects the signal and a centralized control unit to process the acquired signal to ultimately derive the position and pose of the tracked object [27]. Figure 1.14 shows the usual setup for an OTS.

![OTS diagram](image)

OTSs need a direct line-of-sight (LOS) to be able to track the instruments. This figure shows an example of the LOS as red lines and an optical sensor. If the LOS is interrupted then the OTS cannot track the instruments.

Figure 1.14: OTSs direct line-of-sight example.

There are three main categories of OTSs 1) Videometric (or visible light-based systems), 2) infrared (IR) tracking systems and 3) laser tracking systems [27].

Videometric OTS identifies marker patterns captured by a calibrated camera [26]. Figure 1.15a shows an example of the marker patterns used in videometric systems. The main characteristics of the videometric systems are that they are simple and low-cost [27].
Infrared OTS works with infrared LEDs, which produce a signal that is invisible to human eyes (IR spectrum) and a sensor that captures this IR light. Infrared sensors use a band-pass filter that eliminates all the ambient light (other wavelengths), which makes possible the identification of the infrared markers [26]. There are two types of IR trackers:

- **Active optical trackers:** light-emitting diodes (LEDs) operating in the near-IR range (approximately 900 nm) are fired sequentially and detected by the camera, with Charge-Coupled Device (CCD) sensors. Each tracker needs to have a specific geometric configuration, which in conjunction with the firing sequence will tell the system where and what tracker it is. A minimum of three non-collinear LEDs is necessary for determining six degrees-of-freedom (DOF) pose information [27].

- **Passive optical tracker:** These systems consist of spheres with retro-reflective materials. The markers are usually spherically shaped, which allows them to reflect light beamed by the cameras almost exclusively into the direction of the incoming source light [27]. Figure 1.15b shows an example of a common commercial passive optical markers. The pattern of the arrangement of the markers must be unique for each tracking probe to be able to identify them correctly. An advantage of passive over active markers is their wireless property [26].

![a) Videometric markers b) Passive optical markers](image)

Figure 1.15: OTSs markers examples.

Finally, laser tracking systems identify an object’s movement using laser beams and an array of photo sensors placed on rigid support or carrier [27].

Regardless of the type, the major limitation of the OTSs is the necessity of a direct line of sight between the source of light or marker and the sensor [23]. Operating rooms are usually crowded, which makes the line of sight complicated. This specific complication pushed the development of an alternative way of tracking systems that do not suffer the line-of-sight limitation.

**Electromagnetic Tracking System (EMTS)**

Electromagnetic Tracking Systems (EMTSs) consist of three principal components 1) a field generator (FG), 2) EM sensors and 3) a control unit [27]. Figure 1.16 shows the EMTSs common setup. EMTSs function thanks to disruptions (measuring magnetic flux or magnetic fields) made by EM sensors in an EM field of known geometry [28]. A coordinate space is
produced due to the magnetic field generated by the field generator. There are different shapes for the field generator, which will produce different shapes of magnetic fields. To obtain the information, EM sensors need to be placed and moved within the generated magnetic field.

The components of a EMTS are:
A system control unit, a field generator and the sensors that are to be tracked.

Figure 1.16: EMTSs components.

It is important to note that some systems use quasi-static direct current (DC) magnetic fields, while others use alternating current (AC) magnetic fields [28]. The principal difference between the two types of EM trackers (DC or AC) is the type of sensor that needs to be used in each case. The sensors could be “search coils” (used in AC EMTSs) or “fluxgate sensors” (used in DC EMTSs) [28]. The first type of sensor consists of small coils (inductors) where voltage is applied. The “fluxgate sensors” consist of two inversely arranged inductors.

The main disadvantage of EMTSs is their behaviour when metallic objects are near either the field emitter or the sensor, which can significantly affect the measurement accuracy [27]. Different metals can cause different scales of disruption. Franz et al. (2014) [28] comment that there are four major sources of magnetic field distortions:

- Ferromagnetic materials: iron, nickel, cobalt, and some steels become strongly magnetic in the presence of an electromagnetic field.
- Eddy currents in other conductive materials, induced by the magnetic field itself.
- External currents inside the magnetic field, e.g., caused by other electronic devices.
- Inhomogeneous wave transportation medium, such as air or the human body, because all theoretical EM equations refer to a vacuum.

The design of the EMTSs is key to reducing magnetic field disruption errors. Calibration of the FG and sensors by the developer/manufacturer is also a fundamental part to reduce this type of error [28]. For example, in the AC-based system, eddy currents (i.e., loops of electrical current) are induced in conductive materials. This could lead to the distortion of the sensor readings and interference with the non-stop magnetic field. On the other hand, DC-based tracking systems
use static magnetic field measurements (the magnetic field is turned on and off at a certain frequency) which allows the eddy currents to decay sufficiently to mitigate distortions (caused by conductive metals such as stainless steel (300 series), titanium, and aluminum) [26].

An advantage of EMTSs over OTSs, besides not needing the line-of-sight, is the small sensors used in EMTSs. The sensors are small enough to be embedded in surgical tools [26]. Figure 1.17 shows examples of the sensor sizes.

![EMTS sensors examples.](image)

EMTSs sensors come in different sizes as shown in the picture.

*Degree of freedom (DOF)*

a) 6 DOF* Cable tool (⌀ 2.5 mm)

b) 5 DOF* Flextube (⌀ 1 mm)

c) 6 DOF* Microsensor (⌀ 0.92 mm)

Figure 1.17: EMTSs sensors examples.

Both OTSs and EMTSs have their advantages and disadvantages. In general, it is more common to find the use of OTSs in the literature, but EMTSs have been scaling and improving their accuracy.

The most important relevance for our work is that EMTSs can use small sensors that can be attached to different instruments/equipment without the necessity of direct line-of-sight. While the OTSs are not affected by the metals around them, the markers or sensors need to be attached to the instruments and/or patient making a possible reduce working space for the physicians because of the necessity of direct line-of-sight. Commercial EMTSs are designed to operate in environments containing medical-grade metals by incorporating a shield in the FG for minimizing disruptions [27, 28, 26].

### 1.5.2 Software packages

The IGSNS software integrates all the information gathered by hardware devices, such as 1) imaging (to perform image fusion) and 2) tracking information (to monitor and control the instruments) and displays it to the physician in an informative way [29]. The need for software is not only for visualization of the tumour and important structures but also for the surgical
tools tracked. In the words of Paolucci et al. (2019) [4] “The navigation software consists of planning tools, validation tools, and visualization aids for the radiologist to accurately align the needle guide and place the ablation needle.”

As mentioned in Section 1.4.3, one way to improve the navigation and be able to show the structures and target during the procedure is preprocedural and intraprocedural image registration or image fusion. IGSNS software should be able to perform this registration (or mapping) between the images and display a representation of the surgical tools in virtual or even augmented reality. One important aspect of the software is that it must present all the information by following the workflow of the surgical procedure [29].

1.5.3 Needle alignment devices

Targeting the tumour can be achieved by a hand trace route technique, using ultrasound images in real-time or by implementing an aiming device. A needle guider or aiming device is commonly used to provide mechanical support to the needle insertion. Usually, these devices have stereotactic positioning characteristics, and if positioned correctly, they allow a more accurate insertion of a needle [30, 31, 32]. This section describes the “Freehand technique” followed by a general description of the existing aiming devices.

Freehand technique

The hand traceroute is the locus the ablation needle must follow to approach the tumour: the previously planned trajectory. With freehand navigation, a sensor can be attached to the ablation needle to measure the pose of the surgical tool [33]. With this approach, the radiologist can freely move the applicator and the IGSNS to demonstrate the positioning of the needle according to the defined plan [4]. Two approaches can be used when inserting a needle while using US imaging: 1) In-Plane technique and 2) Out-of-Plane technique.

The “in-plan” technique consists of maintaining a precise alignment of the needle in the active US plane [34]. If successful, a bright line will be seen in the US image. The physician needs to move the US probe and needle at the same time, always ensuring that the needle is in-plane with the US beam [31]. Figure 1.18 shows the in-plane technique. With this approach, the needle can be seen at all times and the tip can be found. The principal problem with this approach is that experience is needed to be able to maintain the needle in-plane with the US beam during all the procedures.

As the name implies the “out-of-plane” approach consists of inserting the needle without taking into consideration the active plane of the US. The reflection of the needle will be minimal (i.e., a small bright dot in the US Image), which makes the needle tip impossible to find.

The freehand technique, even with the in-plane approach, could lead to many needle adjustments during the procedure before approaching the correct target. Needle repositioning might be a significant risk to the patient (bleeding and tumour seeding), and when possible, should be avoided [35]. Wallach et al. (2014) [31] performed an experiment using an aiming device versus a freehand technique, obtaining an improvement in lateral positioning when using an aiming device: 2.3 ± 1.3 mm with an aiming device with active depth control; 2.8 ± 1.6 mm
with an aiming device with passive depth control versus $4.2 \pm 2.0$ mm with freehand technique. The aiming devices can help provide mechanical support and alignment while inserting the needle.

### Ultrasound probe attached aiming devices

Some aiming devices are attached to an ultrasound probe, in which case the US probe is positioned at the entry point and then the needle can be inserted. Figure 1.19 shows two examples of US probe-mounted aiming devices. This type of aiming device helps the physician to maintain the needle in sight [34].

This type of needle guider improves the needle placement [30, 37] The major disadvantage of these aiming devices is that they fix the angle of insertion of the needle, which limits the adjustment of its path [34].
1.5. **Image-Guided Surgical Navigation Systems (IGSNS)**

### Stereotactic arms

Other guiders are attached to the surgical table, using an adjustable mechanical/robotic arm with multiple handles, which allow adjusting and locking of each degree of freedom separately [4, 31]. Figure 1.20 shows two examples of stereotactic aiming devices. Usually, the aiming device is attached to the surgical table and then aligns to the point of entry [4]. Once positioned in the correct place, the needle is manually inserted [11].

![Image](image1.png)  
**a) ATLAS aiming device [31]**

![Image](image2.png)  
**b) Stereotactic arm [4]**

(Images courtesy of John Wiley and Sons and Licensee IntechOpen and Creative Commons)

**Figure 1.20:** Examples of stereotactic aiming devices.

Toporek et al. (2013) [32] performed a comparison of needle punctures between the freehand technique and inserting using the ATLAS stereotactic arm, concluding “Using an aiming device may increase the lateral accuracy of navigated needle insertion”. The possible disadvantage of these types of aiming devices is that they could restrict the range of movement of the physician due to their, usually, large size.

### Robotic arms

Robotic aiming devices are an ongoing field of research. These needle guiders are related to the stereotactic aiming devices with the improvement of having some sort of motorization [4]. With some devices, the needle still must be inserted by hand (sometimes with passive guidance from the robot), but others are completely motorized [38]. An important note regarding robotics arms is that they do not significantly increase available accuracy compared to stereotactic arms, and can be more expensive [4].

### Patient-attach aiming devices

One challenge for stereotactic and robotic arms is if the patient moves, it could result in a needle readjustment because of the need to reposition the aiming device into the point of entry to follow the route previously traced. Some robotic aiming devices are patient mounted (firmly, restricting patient movement) [39, 40, 41], but, as mentioned earlier, are expensive and limit the physician’s movement inside of the operating room.

The problem of patient movement could be solved using an aiming device that is attached to the patient, during the entire procedure, but that does not restrain the patient’s movement. If the
A needle guider is attached to the patient, then even if the patient moves, the entire system would move with them so the needle route would not change. Using a guider for the needle would still give the physician mechanical support achieving more accuracy and less needle repositioning to follow the route given by the image-guided surgical navigation system. To our knowledge, there are no aiming devices in the literature that comply with these specific characteristics.

IGSNSs have many components that must function simultaneously, which require training and has a learning curve [42]. The existence of simulated organs, known as phantoms, can help in the training of image-guided procedures such as percutaneous ablation, as well as the usage of IGSNS. In the next section of this introduction, we discussed the characteristics and available phantoms that exist for training and validating IGSNS and percutaneous ablation procedures.

1.6 Liver phantoms

Phantoms are devices that mimic the human body or a part of it. The design of a phantom, including its size, shape, composition, imaging, and mechanical proprieties, is determined by the purpose of the phantom [43]. In this section we will briefly discuss the most common material used for the development of phantoms for image-guided procedures, then a short literature review of the existing liver commercial phantoms will be presented. The section concludes with a description of some anthropomorph liver phantoms in the research field.

1.6.1 Common materials for development

Tissue-mimicking materials are those that simulate characteristics of human tissue with respect to a range of desired properties (i.e., imaging, elastic modules, etc) [44].

The selection of the appropriate materials is a critical step in the design of a phantom [43]. There are currently multiple publications dealing with liver phantoms, each using a variety of materials and methods.

Li et al, (2018) [44] have published a complete review of different tissue-mimicking materials used to develop phantoms for image-guided procedures, the imaging and mechanical properties are explained in detail. The materials in Li’s study include polyvinyl alcohol cryogel (PVA-c), polyvinyl chloride (PVC), gelatin, silicone, agar and agarose.

Agar and gelatin-based gels (hydrogels) are widely used as tissue-mimicking materials for phantoms; however, their short lifespan and lack of mechanical durability are major limitations to their use [45, 42, 46]. Another popular tissue-mimicking substance is the polyacrylamide gel formula, which is made by the polymerization of a highly toxic acrylamide monomer, thus requiring special precautions to be taken during its manufacture [42].

PVA-c is a widely used, non-toxic, hydrophilic and synthetic polymer [44, 47]. It has a relatively long shelf life, and its mechanical and acoustic properties can be manipulated by subjecting it to freeze-thaw (FT) cycles [45, 47]. PVA-c is a tissue-mimicking material, suitable for application in MRI and US, that also exhibits temperature memory [47].

An important aspect of phantoms is their capability to present more realistic organ shapes and
1.7. Motivation

can often contain highly detailed internal anatomy [43], making them more or less anthropomorphic. Some commercial phantoms contain anthropomorphic features and are discussed in the next section.

1.6.2 Commercial liver phantoms

Commercially, a variety of liver (or abdomen) phantoms are available for training purposes that are compatible with various imaging modalities (i.e., CIRS, Blue phantom, IOUSFANF). However, most of these phantoms contain simplified anatomy and are expensive [48].

While many also have blood vessel structures present, they lack a closed-loop vasculature through which a blood-mimicking fluid can flow [42]. Additionally, the most prominent problem associated with commercial phantoms is their cost-effectiveness, because most of these phantoms do not survive repetitive needle insertions [48].

1.6.3 Research phantoms

Multiple liver phantoms have been developed over the years, but none complies with all the anthropomorphic features (vessels, liver tissue, and ability of blood flow). Notle et al. (2021) [49] developed a simple polyacrylamide gel phantom to evaluate the ablation zone and heat sink effect but lacks the anthropomorphic characteristics and functional vasculature.

Rethy et al. (2017) [42] is the only group in our knowledge that constructed an anthropomorphic phantom with all the characteristics described before. The group constructed a polyurethane phantom with closed-loop vasculature, using a cadaver liver. For the anthropomorphically accurate vasculature and tumour models, a two-step casting procedure was performed, which required a great amount of time, effort, and proper technique, making the process hard to reproduce. The construction process of Rehty could be quite complicated to replicate, so the need for an anthropomorphic liver phantom, easily reproducible and with long life span remains an unmet need.

1.7 Motivation

Common stereotactic approaches employ US probe-attached needle guider limiting the needle insertion to be performed with an “in-plane” approach. Other systems use mechanical or robotic arms, which because of their size and setup can restrict patient movement, and are often of high cost. Another limitation is that tumours are sometimes invisible under US imaging. Image fusion is a common solution to overcome this, but currently works focus on open liver procedures (i.e. surgical resection, liver transplantation) or are specifically for laparoscopic surgery, representing different challenges than those for percutaneous approaches.

Our motivation relies on developing a tool that improves the targeting accuracy for the focal treatment and reduces needle repositioning during a percutaneous liver tumour ablation. To achieve this, we propose the development of a US-based surgical navigation system that uses a simple disposable aiming device as a virtual pointer, allowing “in-plane” and “out-of-plane” needle insertions. As part of the proposed system, a simple image fusion technique is explored.
1.7.1 Objectives

The main objective of this thesis is to develop a simple stereotactic image-guided surgical navigation system for liver tumour heat-based ablation using a tracked patient-attached puncture needle guider. The aiming device should show the needle planned trajectory to the target in real time and help position the needle tip accurately enough to perform a successful ablation procedure. In this thesis, three objectives regarding the development of our solution were established:

- Calibration of a patient-attached needle guider to generate a real-time virtual path in 3D and superimposed in the US image, to visualize the applicator trajectory before needle insertion.
- Develop a simple image fusion technique to improve tumour targeting when performing percutaneous liver tumour ablation procedures.
- Develop an anthropomorphic multimodal liver phantom that can function as a sandbox for the validation and training of our system.

1.7.2 Thesis Outline

The work related to the specific objectives is described in three chapters presented in this thesis:

- **Chapter 2** reports the preliminary steps of the development of a stereotactic IGSNS, US-based, that uses a patient-attached needle guider to generate a virtual path to visualize the applicator trajectory before needle insertion. The virtual path moves accordingly to the guider position and pose, giving the physician a real-time virtual path superimposed to the ultrasound beam, and in 3D, that corresponds to the position of the guider. In the system, the ablation zone is also shown at the tip of the virtual path and can be used to aid in the correct needle position and ensure complete tumour coverage. An accuracy analysis, including the angular and tip positional error of the virtual path after calibration, is presented.

- **Chapter 3** introduces a preliminary analysis of an image-to-image rigid-registration using liver’s vessel bifurcations. The registration process was tested using a commercial liver phantom as ground truth and in real patient US volumes.

- **Chapter 4** presents a tool for validation of the final solution (i.e., the IGSNS): an anthropomorphic multimodal liver phantom. The chapter describes the development of the phantom and its final characteristics.

- **Chapter 5** includes the thesis contributions, conclusions, limitations and future directions of the work presented.
Chapter 2

Accuracy analysis of an aiming device for a surgical navigation system

This chapter is largely based on the conference proceedings:


2.1 Introduction

For a percutaneous ablation to be successful, the tumour volume must be completely covered (plus a safety margin) by the treatment zone [50]. This zone is known as the “ablation zone” and is typically described as an ellipsoid, or sphere, whose centers are around the ablation needle tip [51].

The ablation zone is usually estimated based on the size of the applicator (i.e., ablation needle), as well as the treatment parameters (e.g., thermal energy and ablation time). Targeting the tumour can be achieved by a manual insertion (freehand) technique that could lead to needle repositioning, which can increase the risk of bleeding and tumour seeding [31, 35]. Imaging modalities, including US, CT or MRI, are used to assist with placing the needle in the correct position with respect to the tumour. Under the US-guided technique, the needle is typically inserted using an “in-plane” approach, to provide real-time monitoring of the needle advancement into the tissue. This two-handed technique can be challenging, especially for inexperienced physicians, as the clinician must maintain the visibility of the needle under 2D ultrasound while advancing the ablation needle towards the target tumor [34].

Stereotactic Image-Guided Surgical Navigation Systems (IGSNSs) support surgical procedures using medical imaging and tracking information in assisting the physicians in the preprocedural planning and intraprocedural monitoring and manipulation of the surgical instruments. Besides the software packages, and tracking system, a main component of the stereotactic IGSNSs is
an aiming device, which assists the surgeon in terms of targeting and handling, by providing mechanical support to the needle insertion [31, 34].

Common designs of the alignment device include those that are rigidly attached to the US transducer [34], those attached to the surgical table, and those with electronic characteristics, denominated “robotic” [4, 11]. The alignment devices attached to the US transducer enforce the “in-plane” alignment of the ablation needle with the US beam, and while this approach has the potential to improve targeting accuracy, it limits the needle entry angle. Another limitation of the US probe attached guiders is that once the needle is inserted, the US probe needs to be maintained in the same position making scanning the patient not possible. Respecting the mechanical/robotic guiders due to its size, the alignment device is attached to the surgical table, which could potentially restrict the range of movement of the healthcare providers (i.e., physicians and nurses) [52, 40]. Another limitation that these type of devices, mechanical and robotic arms, is the possibility of harming the patient by restricting their bodies, because of the attachment to the table.

In this chapter, we present the development of a stereotactic IGSNS to assist in the accurate placement of the ablation needle. The novel aspect of our approach is the incorporation of a disposable mini-stereotactic device, which allows the surgeon to visualize the potential needle trajectory, in 3D and 2D, before the ablation needle insertion. By tracking the pose of this mini-stereotactic aiming device, or guider, the 3D pose of the ablation needle can be determined in real-time without modification to the ablation needle itself. The use of this magnetically-tracked guider allows the needle deployment to be performed in the “needle-in-needle” fashion (i.e., using the aiming device as a hollow needle), which provides additional mechanical support to stabilize needle advancement. The use of this tracked aiming device also allows the surgeon to use an “out-of-plane” approach, which increases the flexibility to choose the optimal needle entry point. We hypothesize that the combination of spatial tracking, real-time ultrasound, and mechanical stabilization provided by the mini-stereotactic device will improve the targeting accuracy for the focal treatment of HCC and reduce needle repositioning.

2.2 Methods

This chapter details the development of a stereotactic IGSNS using a mini-stereotactic aiming device and presents the design of two clamps to attach EM sensors to the main components (US probe and aiming device) followed by an explanation of the calibrations for the US probe and the aiming device. An IGSNS module is introduced and explained. The chapter ends with an accuracy analysis of the main component of the system (i.e., needle guider).

An electromagnetic tracking system (Aurora, Northern Digital Inc., CA) was used to track all the components; all the data, image and tracking, are processed by Plus toolkit 1, an open-source toolkit for data acquisition, pre-processing, and calibration for navigated image-guided interventions. The data acquired were then broadcasted, for visualization, to 3D Slicer via the SlicerIGT module 2.

1https://plustoolkit.github.io/
2http://www.slicerigt.org/wp/
2.2. Methods

2.2.1 Ultrasound calibration

US calibration is necessary to perform 3D volume reconstructions and to place the ultrasound image in the same coordinate systems as the tools and patient. The calibration of an ultrasound probe consists of finding a transformation between the image plane origin and the position of the probe. To know the position of the probe, it must be tracked (EM sensor).

The US machine used was the Aplio i-700 series (Canon Medical Systems, Japan). The US transducer (Ultra-wideband Multi-Frequency iDMS Convex i8cx1, Aplio i-series, Canon Medical Systems, Japan) was tracked using an EM sensor (Aurora 6 DOF reference, NDI, Canada). To prevent sensor displacement, which could lead to an error necessitating re-calibration, the sensor needs to be firmly attached to the probe. To ensure the position of the sensor at all times, a sensor clamp for the US probe was designed.

**Probe sensor clamp**

The sensor clamp design was made in a solid modelling computer-aided design and computer-aided engineering computer program (SOLIDWORKS). A scan of the probe (i8cx1) was made to generate a 3D model, which was used as a base for designing the clamp while considering the following:

- **Easy of attachment/de-attachment**: maintaining the sensor in the same position if the clamp is removed, allowing the usage of the probe without the sensor, and if reattach, preventing the need for a new calibration each time the sensor is detached.

- **User comfort**: from weight and size to usage. The clamp should not interfere with the grasp and mobility of the probe while being used.

The design was updated five times, making small adjustments to the grasp of the probe and the position of the sensor and its wire. Some major adjustments consisted in adding a support “bridge” into the sides of the clamp handle to give additional strength and avoid ruptures during attach/detachment of the probe. Figure 2.1 show different design updates. The first four designs were 3D printed in Polylactic Acid (PLA) but ended up breaking after one or two attachments. The final clamp was 3D printed in resin for flexibility and durability. Figure 2.2 shows the final design of the probe clamp.

The US probe with the clamp and sensor was presented to two physicians and they were asked to scan a small phantom and provide feedback respecting the user’s comfort while scanning.

**Ultrasound probe calibration process**

The calibration was performed using a point-to-line method as described in Chen et al, (2016) [53]. This method uses reflections in the ultrasound beam, of an object with a know position and pose. To achieve this calibration a pre-calibrated needle (Aurora 5 DOF Needle, 18G, NDI, CA) was used, a basin filled with water (coupling medium), the US probe with the clamp and sensor and two mechanical arms were used. A 3D slicer module ³ was used for data acquisition and to compute the calibration transform matrix.

³https://github.com/lgroves6/UltrasoundCalibrations
The calibration process is as follows:

1. The tracked probe is placed parallel to the water inside the bin and secured with one of the mechanical arms, ensuring that an image is visible.

2. The pre-calibrated tracked needle is placed in front of the US beam (Figure 2.3a) to obtain a reflection (Figure 2.3b). The needle is secured with the other mechanical arm each time is positioned to prevent handshaking issues, which could lead to errors in the data acquisition.

3. A reflection point in the image is selected, as shown in Figure 2.3b. The tracking information (position and pose) from the needle and the sensor in the probe is obtained.

4. The needle is maintained around the same part of the US beam, but the orientation is changed.

5. The needle is then repositioned in a different part of the US beam and two new points are selected (with different orientations). A total of 16 points were obtained to compute the calibration matrix.

This method was repeated in multiple depths from 6 to 20 cm. The needle should be positioned in different parts of the US beam, at least two points in each corner should be acquired (each one with a different orientation) with random points around the US beam next (e.g., between corners, middle superior part, middle inferior part).
2.2. Methods

a) Final design printed in resin.  
b) Probe and clamp with a sensor attached.

Figure 2.2: Sensor clamp for US probe, final design printed in resin.

a) Probe calibration setup.  
b) Ultrasound image with needle reflection (red circle).

Figure 2.3: US probe calibration process.

2.2.2 Aiming device calibration

Mini stereotactic aiming device

The puncture needle guider (CuraWay Medical Technology, China), shown in Figure 2.4a, is a patient-attached “mini” aiming device with stereotactic characteristics, which is the main component of our stereotactic US-guided surgical navigation system. The needle guider comprises a metallic hollow tube at the turntable, through which the ablation needle passes, on a gimble mechanism, (Figure 2.4b), which allows a range of angular movement of approximately 180°. The turntable also has an easy locking mechanism that rigidly secures the angular positioning of the metallic tube relative to its base.

The needle guider operates in the following manner: first, the guider is attached at the needle point of entry (sticking it to the patient skin), then the turntable is moved until the correct angle of insertion is achieved and then locked to restrain future movement of the angle by turning the turntable head to the right. Once the guider is positioned, the needle is inserted into the corresponding hollow tube on the turntable. The needle is never locked and can be moved freely along the tube on the turntable.
Chapter 2. Accuracy analysis of an aiming device for a surgical navigation system

Figure 2.4: Patient-attach aiming device.

The pose of the needle guider was obtained using an EM sensor attached to the turntable of the aiming device without affecting its range of movement. To attach an EM sensor to the head of the needle guider a clamp was designed (Figure 2.5a).

Sensor clamp design for the guider

A “clamp”, designed to attach an EM pose sensor to the needle guider (Figure 2.5a) was 3D printed (Ultimaker S5, Netherlands) using PLA and then attached to the needle guider turntable base. An EM pose sensor (Aurora 5 DOF FlexTube, NDI, Canada) was placed and secured to the guider clamp, with Plus software being employed to broadcast the tracking information into the 3D Slicer platform. Figure 2.5b shows the needle guider with the clamp and sensor.

Using 3D Slicer as a visualization platform, a model of a needle (virtual path) was projected from the guider’s sensor along the long axis of the hollow tube. This virtual line moves according to the tracked pose of the sensor in the aiming device.
2.2. Methods

Guider calibration process

The virtual needle path (3D model) is projected from the aiming device sensor, as shown in Figure 2.6a, using the 3D Slicer platform and moves accordingly to the pose of the guider sensor. To ensure the correct display of the needle path at the hole of the guider, as shown in Figure 2.7b, a pose (orientation and translation) calibration was performed.

![Virtual projection of the guider sensor as a needle. In green the projection from the guider sensor, in yellow the needle model from the pre-calibrated needle when inserted into the guider.](image1)

Figure 2.6: Guider needle path projection, before calibration.

![An aiming device with an EM sensor in the clamp: In red is the projected virtual path from the sensor, in blue correct needle path, where the projection should be.](image2)

Figure 2.7: Guider calibration goal.

Figure 2.7b shows the aiming device with the sensor clamp, the virtual path projection (red line) from the sensor, and the correct needle path (blue line). Spatial calibration is needed to align one axis of the EM sensor to the long axis of the hollow metallic tube, i.e., aligning the red and blue lines in Figure 2.7b.
We devised a calibration technique to align the long axis of the metallic tube to the EM tracking using a least-squares solution. A mechanical arm was used to suspend the guider, then a pre-calibrated needle (Aurora 5 DOF Needle, 18G, NDI, Canada) was slowly inserted into the metallic guider tube, acting as a stylet and the transform matrices relating the position and pose of the needle with respect to the guider were obtained. As shown in Figure 2.8, the needle was inserted only in the guider tube, with the intention that the needle was not subjected to any possible bending.

Sixty-nine transformation matrices were used to obtain the calibration matrix for the guider sensor. The resultant transform matrix was concatenated with the tracking transform matrix of the aiming device.

Ablation zone projection

Using the mini stereotactic aiming device, the ablation zone can be projected from the virtual path tip, to assist the surgeon in the planning and positioning of the guider to ensure complete tumour coverage before needle insertion.

A 3D Slicer module was created that enabled the user to input the ablation zone dimensions (i.e., parameterized ellipsoid), the applicator size, and the active tip size. An ellipsoid is then visualized to simulate the estimated ablation zone from the data inserted. Examples of ablation zones from the ablation machine Cool-tip™ RF Ablation System E Series (Covidien, Medtronic, USA) were tested.

For visualization purposes, a liver phantom was scanned and the ablation zone was superimposed in real-time on the images obtained. The visualization of the ellipsoid can be turned on and off, and its opacity adjusted depending on the user’s needs. A slice-intersection was added so that the ablation zone periphery can be superimposed on the US images in 2D. Figure 2.9 shows an example of the visualization of the estimated ablation zone in 3D and superimposed...
upon the 2D US image of a liver phantom. The phantom characteristics are described in detail in Chapter 4.

Three interventional radiologists, experts in ablation procedures, review the prototype of the module with the needle guider and ablation zone estimation and gave feedback regarding the visualization and the usability of the aiming device.

![Figure 2.9: Visualization of ablation zone in the stereotactic IGSNS module using a liver phantom.](image)

2.2.3 Accuracy analysis

Using the transform matrix (4 × 4 matrix) of the guider sensor (after calibration) and the pre-calibrated needle, two analyses were performed: a rotation (angular) and a positional (tip position) error. For both experiments, the pre-calibrated needle was completely inserted into the guider and placed in different orientations. As Figure 2.10 shows no other medium was used to perform the analysis.

While the tip position accuracy is of high importance, the needle trajectory is also of interest to ensure not hitting surrounding structures while the ablation needle is inserted. To ensure the virtual path is showing an accurate needle trajectory a rotation analysis (i.e., angular error) was performed using the rotation component (3 × 3 matrix) of the transform matrix of both components, guider sensor and pre-calibrated needle.

Six different poses were saved, beginning at 90° and moving around the range of mobility of the turntable of the guide (Figure 2.10). This experiment is taken in an “ideal” setup, with the pre-calibrated needle not subject to any possible bending, meaning that the needle was inserted only in the guider, as shown in figure 2.10. Once the guider and needle were positioned and secured, both transform matrices, the pre-calibrated needle, and the calibrated guider were saved. This was repeated for each of the positions. Once all the matrices were saved a linear algebra equation, 2.1 for obtaining the angle differences between the lines, was used.
\[ \text{angle} = \arccos \left( \frac{\text{trace}(AB^{-1}) - 1}{2} \right) \] (2.1)

Where \( A \) is the rotation portion (i.e, \( 3 \times 3 \) matrix) of the pre-calibrated needle transform, and \( B \) is the rotation portion (i.e, \( 3 \times 3 \) matrix) of the guider sensor (calibrated) transform. Equation (2.1) was applied to each one of the saved transforms taken in different positions. If the guider calibration is perfect, then ideally the matrix product \( AB^{-1} \) would be identity. When the resultant matrix is not identity, the angle difference can be obtained as previously explained. If the two lines are perfectly aligned, then the result of this operation is equal to 0, which is the angular difference between both lines.

Figure 2.10: Rotation analysis experiment setup and position examples.

As mentioned earlier, the tip position is of high importance, so a tip position comparison between both lines was performed. Using the translation part of the transform matrix of each component the Euclidean distance between the tips was obtained. Figure 2.11 shows the 3D models of the virtual path and tracked needle, with their respective tips in different positions.

2.3 Results

2.3.1 Ultrasound probe calibration

The calibration matrix was applied to the US image (at a specific depth), and then the US image (calibrated) was concatenated to the tracking transform matrix of the US probe sensor. This allows the US image to be displayed at the correct size and position with respect to the US probe. Figure 2.12 shows the US image, the tracked needle (yellow) and the probe (green) before and after the calibration was applied.
2.3. Results

Virtual path and tip in green, needle model in yellow with a tip in orange.

Figure 2.11: Positional error setup visualized in the stereotactic IGSNS module.

2.3.2 Aiming device calibration

The calibration readjusts the virtual path position from the sensor in the guider to the hole of the guider, as shown in Figure 2.6a. The resultant matrix is then applied to the guider sensor’s real-time information. The resultant matrix was applied to the real-time tracking information of the guider sensor.

The matrix changes the position and orientation (pose) of the virtual path projected from the guider sensor. Figure 2.13, show the guider clamp in green, the virtual path projection in green, and the pre-calibrated 3D needle model in yellow. It can be appreciated that the pre-calibrated needle model is following the same direction as the green line of the virtual needle path from the aiming device.

The “depth” information of the needle is customizable, meaning that it can be adjusted depending on the needs of the physician in each case. A slide, and a numeric output, were added to the SNS module to permit changes in this parameter.

The virtual path is also shown in the 2D US imaging whenever the needle path is “in-plane” with respect to the US probe. The depth was chosen to be customizable because it will depend on the relative position of the tumour, which is case-specific. Most of the ablation needles have depth marks (passive markers) on their metallic body as an aid to depth monitoring. The passive markers in the needle can be used to match the depth displayed in the IGSNS module. Figure 2.14 shows the virtual path, with the ablation zone display, at different depths.
2. Aiming device accuracy analysis

2.1 Aiming device accuracy analysis

2.1.1 Accuracy analysis of a surgical navigation system

2.2 US probe calibration

2.2.1 US probe calibration results

2.3 Guider calibration

2.3.1 Guider calibration results

2.3.2 Guider calibration results

2.3.3 Ablation zone projection

2.3.3.1 Ablation zone projection

Figure 2.15 shows different ablation zone examples with their respective active tip sizes (two dots in the yellow line). Each ablation zone has its centre at the middle part of the active tip of the needle, so in a 3 cm active tip, the centre of the ablation zone is 1.5 cm from the current needle tip.

Figures 2.16b and 2.16d, show two 2D representations of ablation zones, of different sizes, superimposed on the 2D US image. The display in 2D shows the periphery of the estimated ablation zone and changes depending on the position of the guider with respect to the US probe. The ablation zone can be updated in real time by changing the parameters in the module, and it is always maintained in the middle of the active tip, even if the depth from the virtual line is changed.
2.3. Results

Virtual environment: Models superimposed in US image:

a) Needle path with ablation zone, before reaching the tumour.

b) Ablation zone and virtual path before reaching the tumour.

c) Needle path with ablation zone, surrounding the tumour.

d) Ablation zone and virtual path surrounding the tumour.

Figure 2.14: Ablation zone display at custom depths.

2.3.4 Accuracy analysis

Rotation analysis

After analysis, the resultant angular errors are shown in Table 2.1. Column A demonstrates the results of the data taken, for each position, with the pre-calibrated needle not subject to any possible bending. Figure 2.11 shows the 3D needle model and the virtual path overlapping, and it can be appreciated the difference in orientations. The angular accuracy of the guider calibration is (2.19 ± 0.16°), meaning that the alignment between the virtual path and the pre-calibrated needle model is not perfectly aligned, but the angle difference between them is small.

Positional error analysis

For the positional error results (Table 2.1), column B demonstrates the results of the data taken, for each position, with the pre-calibrated needle not subject to any possible bending. Figure 2.17 shows a close-up of the tips of the 3D needle model and the virtual path overlapping while Figure 2.18 shows a graph with all the tip positions in 3D space, for a visual comparison. Following the calibration, the accuracy of the needle tip position is 2.76 ± 1.11 mm.
2.4 Discussion

Accordingly to the interventional radiologists’ comments, the visualization mixture of 3D models and the 2D visibility of the needle path and the estimated ablation zone aids in the interprocedural planning of the percutaneous ablation procedure thanks to the availability to perform a “pre-aiming” using the needle path from the guider pose. This “pre-aiming” allows the exploration of alternative entry points, even in an “out of plane” approach, which could reduce the hitting of critical structures. Further experiments should be performed to evaluate the performance (time vs accuracy) of the system.

The experiment to obtain the guider accuracy shows a small angular error between the real needle and the virtual path projected from the guider sensor (2.19 ± 0.16°). The results can be attributed to the size of the guider hole being slightly larger than the actual ablation needle to allow easy insertion and extraction of the needle. For the results of the positional error (2.76 ± 1.11 mm), we can determine that the needle tip can be placed accurately at the tumour center.
2.4. DISCUSSION

Virtual environment: Models superimposed in US image:

a) Estimated ablation zone projection for active tip of 2 cm in a 3D environment.

b) Example of 2D visualization in ultrasound window of the estimated ablation zone periphery with 2 cm active tip.

c) Estimated ablation zone projection for active tip of 3 cm in a 3D environment.

d) Example of 2D visualization in the ultrasound window of the estimated ablation zone periphery with a 3 cm active tip.

Figure 2.16: Ablation zone estimations examples (stereotactic IGSNS module).

using the guider as a virtual pointer. We note that the EM-tracked needle used for this study has the EM sensor embedded at the tip of the needle so that its pose (orientation and position) while being inserted into the needle should be considered as the ground truth. Whether such results (angular and positional) are sufficient to influence the success of the ablation procedure, using the system in a user trial is the focus of future work.

An important limitation to mention is that the use of the mini-stereotactic guider, in the form of a “needle-in-needle” technique, is inherently limited to a single applicator deployment but the possibility of using it with other types of applicators (e.g., Cluster type) can be explored. This limitation can be addressed by changing the design of the aiming device to allow the insertion of another type of applicator. We chose to sensorize the disposable aiming device, instead of tracking the applicator directly, in an effort to reduce cost. Tracking the applicator instead would require a spatial calibration step during the surgical workflow, increasing times and costs, tracking the aiming device cause minimal disruption to the existing surgical workflow.

With our system, is intended that the physician can adjust the position of the guider and ensure tumour coverage before the applicator insertion. The 2D display of the ablation zone, US beam
superimposed allows the user to freely scan the patient (in-plane and out-of-plane) and ensure tumour coverage.

2.5 Conclusion

We developed a mini stereotactic guidance system for percutaneous focal liver tumour ablation that shows the needle path before needle insertion and the estimated ablation zone. The results of the angular and positional analyses imply that the needle tip can be placed accurately following the virtual trajectory shown by the needle guider, ensuring an accurate ablation zone position to cover the entire tumour volume.

We expect that by tracking the aiming device instead of the applicator, costs can be reduced because modifying a disposable needle guider design to include the tracking sensor, instead of the ablation needle, is cheaper. While the aiming device still maintains mechanical stability, helping in the needle placement. Further experiments need to be done to evaluate if these angular and positional errors are significant to the percutaneous ablation procedure and affect the needle placement.

Chapter 5 will discuss more deeply the contributions, limitations, and future directions of the work described in this chapter.
Graph showing the tips position:

The red crosses represent the virtual path tips (after calibration) positions.
The blue circles represent the 3D needle model tip (from the pre-calibrated needle) positions.

Figure 2.18: Positional analysis results.
Chapter 3

Accuracy of bifurcation vessel-based image-to-image rigid-registration

This chapter is largely based on the workshop proceedings:


3.1 Introduction

Surgical navigation systems are conformed of three major components (Section 1.5): a) a tracking system, b) software packages and d) an aiming device. In the previous chapter, an aiming device was introduced and presented as a real-time virtual pointer to be used in an IGSNS. In this chapter, the software component of the system is explored, and a preliminary image fusion technique is introduced.

In the introduction, Section 1.4, the importance of choosing the right imaging modality for preprocedural and intraprocedural steps in a percutaneous tumour ablation was discussed [17]. Using image fusion (IF) -in percutaneous ablation procedures helps to improve the targeting of the lesion, needle guidance and visualization of important structures, such as vessels [19]. US imaging is often chosen as the principal imaging modality for intraprocedural imaging for percutaneous liver ablation. The disadvantages of US imaging result in the need to perform image-to-image registration with preprocedural imaging (CT or MRI). Some groups have developed systems to overcome these difficulties, but mostly for open liver procedures (i.e., surgical resection, liver transplantation) or specifically for laparoscopic surgery [54, 55, 56, 57], representing different challenges than those for percutaneous approaches [58].

Most of the related works reported results of a Target Registration Error (TRE), using the tumour centers, of < 10 mm [54, 55, 56, 58], which is considered to be a sufficient performance goal [54, 59]. That said, some studies have been evaluated using only controlled environments...
(i.e., phantoms and in-vivo porcine with controlled respiratory movements) [55, 56], while others used only patient imaging to assess their work [54, 57, 58]. Other studies reported the necessity of a manual alignment before the application of their final algorithm [54, 58]. Manual selection of vessel bifurcations is commonly used to perform the registration [55, 56, 57, 58], which could be a disadvantage because of time-consuming steps during the procedure and human error.

In this chapter, we present an evaluation of the accuracy of a rigid registration method, based on automatically selected vessel bifurcations, for percutaneous tumour ablation. The system is evaluated using a phantom as ground truth and on a set of patient images to evaluate the generalization of the system. A description of the workflow of the registration process is presented, followed by the acquisition of Fiducial Registration Error (FRE) RMS error of the fiducial identification and TRE (Euclidean distance of tumour centers between modalities) obtained from both experiments. We hypothesize that a rigid registration is sufficient to assist in navigation when performing percutaneous ablation procedures. Our work aims to deliver a simple image fusion technique to improve tumour targeting when performing percutaneous liver tumour ablation procedures that can be included in our final IGSNS work.

### 3.2 Methods

The accuracy analysis of the image registration was evaluated using two experiments: a phantom experiment, as ground truth, and using real patient volumes acquired from a patient trial. This section describes the workflow of the data acquisition and the process to perform the registration.

#### 3.2.1 Data acquisition

**Phantom: Ground truth**

The commercial CIRS abdominal phantom (Triple Modality 3D Abdominal Phantom, Model 057, CIRS, SunNuclear, Norfolk, USA) was used as ground truth to test the registration (Figure 3.1). The phantom simulated the thorax from vertebrae (T9/T10) to the lumbar vertebrae (L2/L3) using simplified anthropomorphic geometry that includes a liver with six tumours and vasculature (portal vein). Imaging volumes, CT and US, were acquired from the phantom. Figure 3.1a shows the abdominal phantom while being scanned.

The Aquilion ONE (Prism Edition, Canon Medical Systems Corporation, Ōtawara, Tochigi, Japan) was used for the CT volumes acquisition. In the CT volume, all the branches of the vessels were visible as well as the six tumours presented in the phantom. For the US imaging, a mechanical arm system was used as a tracking system to acquire a 3D US volume [60, 61, 62]. The tracking system consists of a motor-driven 3D US scanning subsystem supported by a counterbalanced mechatronic arm and any 2D US imaging probe. The 2D US machine used in the system was the iU22 US system with a C5-1 transducer (Philips, Eindhoven, The Netherlands). Two 3D US volumes of the phantom were also acquired, each with a different probe position. For Position 1 (Ph-P1), the volume was acquired at the centre of the phantom...
(on top of the left lobe of the liver phantom), for position 2 (Ph-P2), the volumes were acquired between the ribs of the phantom, as usually performed in the OR. In both 3D volumes, the main branches of the portal vein (PV) were visible. For Ph-P1, five tumours were visible in the 3D volumes; for Ph-P2, only two were visible. Figure 3.1b, 3.1c and 3.1d shows the three 3D volumes acquired from the phantom.

**Patient trial**

A 3D US patient trial, reviewed and approved by the institutional research ethics board, was conducted between January and April 2021 (Appendix B). In the trial, eleven patients gave written consent to access their data. Preprocedural (CT or MRI) and intraprocedural (3D US) volumes acquired during their procedures were saved. The 3D US images were collected by the system previously described [60, 61, 62].

Six of the eleven patients imaged were chosen to perform the registration and accuracy analysis. The exclusion criteria relied on the ability to see sufficient vessel information in the US image to be able to perform the registration. Of those six patients, two did not present visible tumours in US, so were not included in the evaluation of TRE but included in the evaluation of the FRE. Table 3.1 shows the patient information and specifications of their volumes (e.g., tumours and vessels visibility in each imaging modality).
3.2. Methods

Table 3.1: Patients general imaging information.
Where PV stands for Portal Vein, HV stands for Hepatic Vein and Px is the patient case (patient assigned number for anonymity).

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Tumor type</th>
<th>Tumor visible in CT</th>
<th>Tumor visible in US</th>
<th>Time between imaging</th>
<th>Liver vessels visible in US</th>
<th>Enough vessels visible?</th>
<th>Liver segment during US Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>PX1</td>
<td>HCC</td>
<td>No</td>
<td>Yes</td>
<td>4 months</td>
<td>PV and HV</td>
<td>Yes</td>
<td>Right Lobe Segment VI</td>
</tr>
<tr>
<td>PX2</td>
<td>HCC</td>
<td>Yes</td>
<td>Yes</td>
<td>2 months</td>
<td>None (too small)</td>
<td>No</td>
<td>Left Lobe Segment III</td>
</tr>
<tr>
<td>PX3</td>
<td>HCC</td>
<td>Yes</td>
<td>No</td>
<td>1 month</td>
<td>PV</td>
<td>Yes</td>
<td>Right Lobe Segment VI</td>
</tr>
<tr>
<td>PX4</td>
<td>HCC</td>
<td>Yes</td>
<td>Yes</td>
<td>4 months</td>
<td>PV and HV</td>
<td>No</td>
<td>Right Lobe Segment V-VIII</td>
</tr>
<tr>
<td>PX5</td>
<td>HCC</td>
<td>Yes</td>
<td>Yes</td>
<td>2 months</td>
<td>PV</td>
<td>No</td>
<td>Left Lobe Segment III-VII</td>
</tr>
<tr>
<td>PX6</td>
<td>MET</td>
<td>Yes</td>
<td>Yes</td>
<td>2 months</td>
<td>PV and HV</td>
<td>Yes</td>
<td>Right Lobe Segment V</td>
</tr>
<tr>
<td>PX7</td>
<td>MET</td>
<td>Yes</td>
<td>Yes</td>
<td>6 months</td>
<td>PV and HV</td>
<td>Yes</td>
<td>Left Lobe Segment III</td>
</tr>
<tr>
<td>PX8</td>
<td>HCC</td>
<td>Yes</td>
<td>No</td>
<td>3 months</td>
<td>None</td>
<td>No</td>
<td>Right Lobe Segment VI-VII</td>
</tr>
<tr>
<td>PX9</td>
<td>MET</td>
<td>Yes</td>
<td>Yes</td>
<td>2 months</td>
<td>PV</td>
<td>Yes</td>
<td>Right Lobe Segment VIII</td>
</tr>
<tr>
<td>PX10</td>
<td>HCC</td>
<td>Yes</td>
<td>Yes</td>
<td>2 months</td>
<td>None</td>
<td>No</td>
<td>Right Lobe Segment VIII</td>
</tr>
<tr>
<td>PX11</td>
<td>MET</td>
<td>Yes</td>
<td>Yes</td>
<td>2 months</td>
<td>PV and HV</td>
<td>Yes</td>
<td>Right Lobe Segment V</td>
</tr>
</tbody>
</table>
3.2.2 Registration workflow

Figure 3.2 shows a simple workflow of the registration process. After the data acquisition, manual segmentations were performed in each volume, then the centrelines were extracted from the models constructed from the vessel’s segmentation. An automatic bifurcation extraction was then applied to the centrelines and these fiducials were used to perform the registration between preprocedural and intraprocedural images.

![Registration workflow diagram]

Vessel segmentation

After the volume acquisition (either phantom or patients), the vessels and tumours were manually segmented. The volumes were segmented using 3D Slicer and its “segmentation” module. For the CT, both portal and hepatic veins were segmented, trying to include as much information as possible (i.e. small vessels). For the US volumes, depending on the liver segment and specific imaging conditions sometimes the vessels were only partially segmented. For both volumes, CT and US, the tumour was segmented also. Figure 3.3 shows an example of the segmentation performed for Px6.

![Segmentation examples]

Centreline extraction

The segmentations were reviewed and approved by two expert interventional radiologists, and centerline extraction was obtained from the vessel segmentation models. The 3D Slicer mod-
3.2. Methods

The modules “Vascular Model Toolkit” and “Vascular Centerline Extraction” were used to perform the centerline extractions.

For the CT vessel’s centerlines extraction, a Region of interest (ROI) was selected depending on the US probe position when the volume was acquired (i.e., scanned liver segment). Table 3.1 shows the liver segment that was imaged during the US scan. Following the selection of the ROI, the vessels outside of the ROI were discarded. Figure 3.4 shows the process of ROI and vessel information selection. The ROI was used to reduce computational time in the centreline extraction.

The centerline consists in obtaining a point between two others on a boundary. The obtained point is at the same distance from the other two points, therefore a medial point. These points form a skeleton of the shape as shown in Figure 3.4d.

![CT segmentation and ROI selection in volume.](image1)

![ROI selection using 3D models of CT vasculature.](image2)

![Vessels discard according to ROI.](image3)

![Centerline extraction of vessels inside ROI.](image4)

Figure 3.4: Centerline extraction process in the preprocedural CT volume (PX6 example). The hepatic vein (HV) is in red and the PV is in blue.

**Automatic bifurcation extraction**

Having the points of the centerline, Figure 3.5a, an analysis can be performed to obtain the bifurcation points. A 3D slicer module was created to automatically extract the bifurcation points using the centerline information. The bifurcation module uses the information of each point of the centerline sections and compares them to obtain the bifurcation points.

---

1 GitHub: [https://github.com/vmtk/SlicerExtension-VMTK](https://github.com/vmtk/SlicerExtension-VMTK)

2 GitHub: [https://github.com/JoeCambranis/Bifurcation-Extraction-Module](https://github.com/JoeCambranis/Bifurcation-Extraction-Module)
The algorithm uses the next logic: If the final point of a section of the centerline (Figure 3.5b) is the same as the start point of another, or more sections 3.5c and d, then the code detects it as a bifurcation point. The point is then saved and a fiducial is placed, Figure 3.5e and f show an example of bifurcation extraction.

**Figure 3.5: Vessel bifurcation extraction process (PX6 example).**

**Registration process**

The registration was performed using the “Fiducial Registration” module (based on the iterative-closest-point (ICP) algorithm) in 3D Slicer. A minimum of 3 fiducials is required to perform the registration. Table 3.2 column 3 shows the bifurcation points of each case and which vessel was used to perform the registration, including the phantom information. The resultant registration transform matrix was applied to the US imaging as well as all its features (segmentations, centerlines and bifurcations). Figure 3.6 shows the US superimposed on the CT after the registration.
3.2.3 Registration accuracy analysis

Two experiments using both phantom and patient data were performed for accuracy analysis. For each experiment, the registration was applied and then the FRE and TRE of each case were obtained. The module “Fiducial registration” displays FRE (root-mean-square [RMS] error of the fiducial points) after acquiring the registration transform matrix. For the tumour (TRE) evaluation, the centers of the tumours on each modality were obtained (using the segmentation information) and then the Euclidean distance between them was calculated.

3.3 Results

3.3.1 Phantom experiment

Following registration, the FRE of the vessel’s bifurcation points was $2.21 \pm 1.03$ mm, with the results of each experiment being displayed in Table 3.2 for Ph-1 and Ph-2. Figure 3.7 shows the images (US and CT), and the models (vessels and tumours), superimposed after the registration is applied for both setups.

A TRE (between tumor centres) of $1.66 \pm 0.72$ mm was obtained for PH-P1 and $2.26 \pm 0.56$ mm for PH2-P2. Table 3.2 shows the specific results for each tumour in both setups.

3.3.2 Patient trial

Image 3.8 shows the models of vessels, centreline, tumours, the bifurcation points and tumour centre of each patient once the registrations have been applied.

An FRE of $2.35 \pm 1.40$ mm was obtained for the six patients included in the evaluation. For the patients with tumour visibility in both volumes (PX6, PX7, PX9 and PX11), the TRE between both tumour centers were acquired, yielding an accuracy of $7.23 \pm 4.45$ mm. Table 3.2 shows the specific results for each patient.
3.4 Discussion

The accuracy of our method presents results similar to other works. For the phantom experiment an FRE of 2.21 ± 1.03 mm and a TRE results of (1.66 ± 0.72 mm for PH-P1 and 2.26 ± 0.56 mm for PH2-P2), similar to the results reported in [55, 56]. For the patient trial a FRE of 2.35 ± 1.40 mm, and TRE of 7.23 ± 4.45 mm were obtained, results similar to those reported in [54, 58]. Our preliminary results suggest a robust algorithm that could be improved by an automatic segmentation method and better imaging acquisitions of the 3D US volumes.

One limitation of our work is that the resultant US volumes have a FOV. The US volumes could be improved by acquiring them using a different system, since the mechanical arm restricts the FOV, making feature acquisition more difficult. An example of this is that most of the US volumes used to calculate the TRE are scans of the right lobe of the liver (because of the selection criteria). The only left lobe volume used in the testing has also the least accurate result (TRE = 11.40 mm, PX7). Fusaglia et al. (2016) [55] performed a comparison of the TRE between the liver lobes of a phantom [55] finding better registration results in the left lobe in comparison to the right lobe, attributing this to less amount of recognizable features (i.e., vessels and vessels bifurcations) in their phantom right lobe. Another important aspect to consider is that Px7 was the only MRI volume used to test our method, all the other cases tested were CT. Future analysis should be performed to verify whether this is a one-time case (i.e PX7) or if there is a significant difference in the registration of each lobe or preprocedural modality using our method.
Table 3.2: FRE and TRE results for each case (phantom and patient trial).

*PX7 preprocedural imaging is MRI.
PV Stands for Portal Vein, and HV stands for Hepatic Vein.
Ph-p1 is the phantom volumes acquired in vertical position.
Ph-p2 is the phantom volumes acquired in a tilted position (between ribs).

<table>
<thead>
<tr>
<th>Case number</th>
<th>Vessel used</th>
<th>Bifurcation points used</th>
<th>FRE (mm) (RMS)</th>
<th>TRE (mm) Euclidean distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-p1 PV</td>
<td>4</td>
<td>1.48</td>
<td>T1 = 1.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2 = 0.59</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T3 = 2.55</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T4 = 2.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T5 = 1.47</td>
<td></td>
</tr>
<tr>
<td>Ph-p2 PV</td>
<td>3</td>
<td>2.94</td>
<td>T1 = 1.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2 = 2.62</td>
<td></td>
</tr>
<tr>
<td>PX1 PV</td>
<td>3</td>
<td>4.62</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>PX3 PV</td>
<td>3</td>
<td>0.84</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>PX6 HV</td>
<td>4</td>
<td>1.56</td>
<td>4.64</td>
<td></td>
</tr>
<tr>
<td>PX7* PV</td>
<td>3</td>
<td>1.6</td>
<td>11.40</td>
<td></td>
</tr>
<tr>
<td>PX9 PV</td>
<td>3</td>
<td>2.11</td>
<td>8.72</td>
<td></td>
</tr>
<tr>
<td>PX11 PV</td>
<td>4</td>
<td>3.42</td>
<td>4.16</td>
<td></td>
</tr>
</tbody>
</table>

Having a limited FOV for the US volumes leads us to use an ROI in the preprocedural volumes, to reduce the vessel information to those that were inside of the ROI. This could be seen as a disadvantage because of the need for the extra step (even though the ROI can be easily selected by liver segment instead of specific structures) but also can be seen as an advantage when considering the computational time when performing the registration. Another solution is performing an automatic bifurcation pairing process, such that the ROI selection step can be eliminated from the process.

In the patient trial results, displayed in Figure 3.8, is noted an increment in the size of the tumours in the US volume (blue segmentation), in contrast with the CT volumes. This could be related to the type of tumour presented in each case (HCC or Metastasis) and the time between the acquisition of each volume. Table 3.1 shows the information for each one of the patients. The case of PX7, with the higher TRE (11.40 mm), involved liver metastasis, and the time between acquisitions of the preprocedural and the intraprocedural volume was six months.

### 3.5 Conclusion

We have developed a simple image-to-image registration method that uses a small number of bifurcation points that are automatically selected from the centerline extraction of the liver vessels. The results, even though preliminary, indicate that our method is accurate enough to be evaluated in more realistic scenarios. For the patient trial experiment, we obtained TRE ≈ 10 mm, demonstrating that with better imaging acquisition (i.e., ensuring vessel visualization) the
results could be improved.

Chapter 5 will discuss more deeply the contributions, limitations, and future directions of the work described in this chapter.
3.5. **Conclusion**

a) PX6 Volumes (US-to-CT) superimposed.

b) PX6 3D models (vessels and tumour) superimposed.

c) PX7 Volumes (US-to-CT) superimposed.

d) PX7 3D models (vessels and tumour) superimposed.

e) PX9 Volumes (US-to-CT) superimposed.

f) PX9 3D models (vessels and tumour) superimposed.

g) PX11 Volumes (US-to-CT) superimposed.

h) PX11 3D models (vessels and tumour) superimposed.

Figure 3.8: Patient trial registration results.
Chapter 4

Anthropomorphic liver phantom development for training and validation

This chapter is largely based on a paper with co-authorship, published in the conference proceedings:


4.1 Introduction

Performing an animal study during a master’s work is difficult to achieve due to the limited time of the project. For this reason, the development of a phantom was contemplated as a possible solution for testing, training and validating the work performed in the master’s project. This chapter introduces a tool (i.e., liver phantom) for validation and training of the work described in the previous two chapters (2 and 3).

While a variety of phantoms are available commercially for training purposes that are compatible with various imaging modalities 1.6.2, most of them contain simplified anatomy and are expensive [48]. While many also have blood vessel structures present, they lack a closed loop vasculature through which a blood-mimicking fluid can flow [42]. Additionally, the most prominent problem associated with commercial phantoms is their short lifetime when talking of needle insertions, which can be extended with specific additives, but it is still not comparable to other more sustainable materials [48].

Current literature reveals several research efforts regarding liver phantoms concerning a variety of materials and methods. Section 1.6.1 presented an overview of the most common materials used for phantom development. To summarize, agar and gelatin-based gels (hydrogels) are widely used as tissue-mimicking- mimicking materials for phantoms; however, their short lifespan and lack of mechanical durability are major limitations to their use. Polyacrylamide
4.2 Methods

The phantom presented in this chapter consists of four major components: the liver body (divided into two lobes, left and right), the internal vasculature (blood vessels), the tumours, and the external vasculature (IVC). The main component to develop the phantom was Polyvinyl Alcohol Cryogel (PVA-c), with some parts (simulated IVC) made from silicone. To enhance US compatibility, a scattering agent (Talcum powder) was added to the PVA-c mixture. A scattering agent percentage test was made by producing multiple tumours with different percentages of talcum powder and placing them into a square made of PVA-c with the same characteristics as those chosen for the liver body. The phantom was developed using different 3D-printed moulds and then connecting all the parts.

The internal vasculature was generated by inserting positive moulds of generic vessels (made
with silicone) into the liver lobe moulds, before PVA-c filling, to create an internal network of canals. The smaller branches are connected using an interlocking mechanism, allowing them to be manufactured separately, joined during phantom manufacturing, and separated from the phantom afterwards (Figure 4.3). This creates a closed-loop system that allows a blood-mimicking fluid to flow through the phantom. A simulated IVC structure was used to connect both liver lobes by their internal vasculatures. The flow was generated using a water pump connected to the simulated IVC by two rubber tubes.

### 4.2.1 Molds

A total of five moulds were used: a mould with three generic spheres of 1.5 cm diameter for the tumours (Tumour mould – Figure 4.1a), a rectangular mould for testing different speckle concentrations (speckle testing mould -Figure 4.1b) left liver lobe body (left lobe mould Figure 4.1c), right liver lobe body (Right lobe mould - Figure 4.1d); and negative vasculature moulds (vasculature moulds: Vein Mold - Figure 4.1e; Artery mould - Figure 4.1f). All the moulds were designed using a Computer-Aided Design (CAD) software and then 3D printed (Ulti-maker S5, Netherlands) using Polylactic Acid (PLA). The manufacturing processes included sanding rough edges to prevent artifacts from appearing during imaging.

To design the liver surface moulds (both left and right lobes) a Computer Tomography (CT) scan of a real patient’s liver, from an open image data set \(^1\), was used. The liver body segmentations serve as the base to design both liver lobe moulds.

### 4.2.2 Phantom materials: Speckle agent testing

The phantoms require a tissue-mimicking material and a speckling agent to make them visible in different medical imaging modalities. Talcum powder was chosen for this purpose due to its ability to introduce speckle and backscatter under different imaging modalities [45, 65]. Initial talcum powder concentrations were chosen based on ongoing studies relating to scattering agents in PVA-c made in the laboratory. A 7.5 % w/w concentration was chosen as the starter for the liver body. To test the tumour speckle concentration, four batches of tumours were made using 10 % w/w PVA-c to water and the speckle agent. Each batch had a different percentage of talcum/PVA-c (5 %, 10 %, 15 % and 20 % w/w). The mixtures were poured into the tumour’s mould and then subjected to five freeze-thaw (FT) cycles (10 hours each) in an environment chamber (Model 1007S, TestEquity, United States) to allow the tumours to solidify. The FT cycles were split into different ranges of temperature changes as follows; ten minutes to get to -20°C, soak for two hours, then from -20°C to -3°C in two hours, from -3°C to +3°C in five hours, finally from +3°C to +13°C in one hour.

One tumour of each concentration was suspended within the speckle testing mould, using wires through the tumours (Figure 4.2a). The speckle testing mould was filled with 10 % w/w PVA-c and 7.5 % w/w talc powder and underwent an FT cycle (49 hours) in the environment chamber. The FT cycle was split into different ranges of temperature changes as follows; ten minutes to get to -20°C, soak for seventeen hours, then from -20°C to -3°C in eight hours, from -3°C to

\(^1\)https://www.ircad.fr/research/3d-ircadb-01/
4.2. Methods

- a) Negative tumour mould.
- b) Speckle testing mould.
- c) Negative liver mould: Left Lobe.
- d) Negative liver mould: Right Lobe.
- e) Vasculature Molds: Negative vein mould.
- f) Vasculature Molds: Negative liver artery mould.

Figure 4.1: Liver phantom moulds.

+3°C in sixteen hours, finally from +3°C to +13°C in eighth hours. The parameters for this FT cycle were chosen taking into consideration the size of the liver mould and properties that we wanted to acquire when building the final liver phantom. Figure 4.2b shows the speckle testing phantom after the FT cycle.

Once ready, the speckle testing phantom was imaged using two different modalities: Ultrasound (US) and Computer Tomography (CT). The Aplio i-700 series ultrasound machine (Canon Medical Systems, Japan) was used to image the speckle testing phantom with the tumours. The pre-set “abdominal settings” was used. Images of the different concentrations of tumours were saved. For the CT testing, the O-arm (Medtronic Inc.) was used following the specifications given in Petrov [66]: Cone-beam CT images were acquired in High Definition (HD) mode, where 745 projections are acquired during 26 seconds scan. Image volumes (20 cm in diameter and 15 cm in length) are reconstructed with 512 x 512 x 192 voxels (voxel dimensions are 0.415 x 0.415 x 0.830 mm³). The images were taken in the “Small Head” preset of the scanner and adjusted to 100 kVp, 20 mA and 150 mA s.
4.2.3 Phantom components

Closed-loop vasculature

To create the closed-loop vasculature, silicone-positive moulds of the vessels (arteries and veins) were made. Both negative moulds used a wire, 0.8 mm gauge for veins and 0.38 mm gauge for arteries, as a skeleton prior to silicone filling. Once the silicone was cured the resulting circumferences of the veins and arteries were 4 mm and 2 mm respectively. The positive moulds were joined by threading the artery ends through a small hole at the end of each vein branch. Figure 4.3c shows the vessels union process. This new positive mould “the vasculature positive mould” (Figure 4.3d) was used to generate a network of canals inside the liver body.

Liver phantom lobes

The vasculature-positive mould was positioned inside the left liver body mould. The skeleton wires allow different ways of accommodating the vessels. Three tumours (10 % talcum) were suspended in the inside part of the liver mould, using wires through the tumours. Figure 4.4a shows the tumours and vessels positioning inside the liver mould. Special care was taken to ensure that the tumours and vessels did not touch each other to prevent errors in the vasculature canal. The liver mould was closed and filled with a 10 % w/w PVA-c to water and 7.5 % w/w Talcum powder mixture. The filled mould underwent an FT cycle (49 hours) in the environment chamber. The FT cycle was split into different ranges of temperature changes as follows; 10 minutes to reach -20°C, soak for seventeen hours, -20°C to -3°C in eight hours; -3°C to +3°C in sixteen hours, +3°C to +13°C in eight hours. This longer FT cycle was due to the volume of the liver lobe (larger than the tumours). Increasing the times in the FT cycle ensured the phantom was entirely frozen (allowing it to properly thaw at each step) and achieved the goal of an anthropomorphic consistency similar to real liver tissue. Figure 4.4 shows the liver mould filling process, when closing the mould the tumours are suspended in the middle of the mould (touching the vessel’s structure or mould walls). After removing the liver from the environmental chamber, the positive vasculature moulds and wires holding the tumours were extracted. The vasculature created a closed-loop canal that permits free fluid flow. The same process was performed for the right lobe of the liver.
4.2 Methods

a) Veins negative mold being filled with silicone (dye blue).

b) Cured silicone veins, the wire skeleton can be appreciated at the top.

c) Vessels tip union process.

d) Vasculature positive mould (arteries and veins joined).

Figure 4.3: Vessels positive mould union process.

4.2.4 Liver phantom: Assembly and simulated blood flow

Once both the right and left lobes of the liver were made separately, they were attached using a silicone tube structure. The silicone tube was manufactured to simulate a part of the IVC. This particular structure, the IVC, was chosen because the partition of the liver lobes is close to it. The simulated IVC functions not only to join both liver lobes together but also as a connection between their independent internal vasculature structures. Figure 4.5a shows the simulated IVC and the connections to the liver lobes.

Four L-shape tube connectors were used to attach the liver lobes to the simulated IVC body. The connectors were placed inside the simulated IVC with one end attached to a rubber tube and the other to the liver lobe exit holes (Figure 4.5). After the connections between the lobes were made, a water pump (Amarine Made, Model: FLO-2202) was used to circulate water through the tubes and the internal vasculature canals on both liver lobes’ phantoms.

4.2.5 Liver phantom: Imaging testing

An Aplio i-700 series US machine (Canon Medical Systems, Japan) was used to image the completed left lobe, using the pre-set “abdominal settings”. Images of the three tumours, the
vessels filled with water and the liver body were saved. Color Doppler of the vessels with the water pump functioning was obtained to evaluate the correct flow of the simulated vasculature system. CT Scans, of the left lobe, were taken using the Acquillion PRISM Edition, TSX-306A (Canon Medical Systems, Japan). The volumes were reconstructed using the Adaptive Iterative Dose Reduction (AIDR) algorithm. After the liver was completed and assembled (both lobes) another CT scan was obtained using the O-arm (Medtronic Inc.) with the characteristics described in [66].

4.3 Results

4.3.1 Speckle testing

Figure 4.6a and b show the US imaging results from the speckle testing phantom (Figure 4.2). As expected, the tumour with 5% talc is less visible in US imaging than in the other concentrations. Comparing the other three concentrations (10%, 15% and 20%) there is no significant
4.3. Results

There is no significant difference in visibility in ultrasound for any of the tumours. Boundaries of the tumour body can be appreciated in the 10%, 15% and 20%. It is noticeable that tumours with concentrations of 15% and 20% show more shadowing than 10%. Figure 4.7 shows the CT taken of the speckle testing phantom. The 5% talcum tumour is not visible in the CT volume. All the other tumours (10%, 15% and 20%) are visible without any significant difference between them.

![Figure 4.6: Tumour speckle testing US results](image)

CT of the speckle testing phantom, from left to right: 5% (not visible), 10% (bottom), 15% (top), 20% (bottom).

Figure 4.7: Tumour speckle testing CT results

4.3.2 Phantom body

Both liver lobe phantoms exhibit a semi-firm consistency, with Figure 4.8 displaying the result of the left liver lobe phantom and its measurements. A simple test of the internal vasculature was performed by inserting a small amount of water using a syringe, without any leaks present. Figure 4.9a shows the start and ending of the internal vasculature, and the diameter of the internal canals. Figure 4.9b shows the representation of the internal vasculature.
4.3.3 Imaging results

The imaging results show compatibility with CT and US (Figures 4.10 and 4.11), with tumours being visible in both imaging modalities. Regarding the liver body, its edge can be appreciated in US imaging, while the vessels are quite visible in both image modalities (Figure 4.10b and 4.11). A bright edge can be seen in some parts of the inner vasculature, similar to the brightness that is present in the Portal Vein in real patients. The flow of the water can be observed in real-time with the ultrasound when the probe is positioned transverse to the vessel. In the CT volume, the talcum tumours are visible and are brighter than the rest of the body. The vessels are also well-perceived, showing all the branches and bifurcations.

4.3.4 Simulated blood flow

The simulated IVC gives support to the phantom and permits a connection between their internal vasculature canals. Figure 4.12a shows both liver lobes united by the simulated IVC. A complete closed-loop was achieved between the two liver lobes phantoms where no leaks were presented when the water pump was connected. Figure 4.12c shows the US images with the Doppler function enabled, showing the flow in the vasculature produced by the pump. Figure 4.12d shows the CT of the liver phantom and IVC at the centre of the image, tumours and internal vasculature of the liver lobes.
4.4 Discussion

The tumour concentration testing helped choose a starting talcum concentration for the tumours to be used in the liver phantom body. The 10% concentration showed good visibility in both US and CT imaging, without showing significant shadowing in US images. More testing regarding the tumour's concentration could be performed if needed to change the visibility of the tumours. A range between 5% - 10% talcum powder should be tested to obtain different degrees of visibility (hypoechoic or hyperechoic).

The imaging test results show a good visualization of all the phantom characteristics (i.e. tumours, vessels and liver body). The material chosen to manufacture the phantom, PVA-c, in combination with the speckle agent, talcum powder, permits imaging with US, CT and MRI [47]. Another key point to choosing PVA-c as the main component for the phantom is that the material has shown it can also be used in thermal and radiation dosimetry applications, meaning the tissue would be compatible with the use of ablation techniques [67, 47]. The material (PVA-c/Talcum powder) and multiple tumours in each lobe permit several punctures to
CT Scan of talcum tumour and vasculature.

Figure 4.11: Left lobe phantom CT imaging results

the phantom, thus it can be used many times making it an appropriate tool for training.

The key advantage of our phantom is the anthropomorphic characteristics and its possibility to be customized, such as changing the number, size and type of tumours (hyper or hypoechoic) and the wire skeleton of the positive vasculature mould (Figure 4.4) allows the positioning of the vessels in different ways before the PVA-c filling of the lobes. Physicians evaluated the visualization and feeling of the liver phantom body giving positive comments regarding the anthropomorphic characteristics of the phantom.

## 4.5 Conclusion

We created a liver phantom with sufficient characteristics to be used as a sandbox for training in different needle puncture procedures. The material allows imaging with different modalities, which means that the phantom can be used as an accessory for training surgical navigation systems or testing them. The ability of customization allows adapting the liver phantom to different activities depending on the necessities.

The next chapter will discuss more deeply the contributions, limitations, and future directions of the work described in this chapter.
4.5. Conclusion

a) Liver lobes united by the simulated IVC.

b) Complete setup of the liver phantom with the water pump to recreate the simulated blood flow.

c) US images of one of the lobes using the Doppler function.

d) CT of the complete liver phantom.

Figure 4.12: Closed-Loop vasculature results
Chapter 5

Conclusion

In this chapter, we summarize the thesis contributions, limitations and future work that can be done regarding the topics presented in this thesis.

5.1 Thesis contributions

Chapter 2 describes the development of a stereotactic IGSNS prototype for the percutaneous treatment of a liver tumour that displays, in real-time, the virtual needle path and the estimated ablation zone without needle insertion. A small clamp to attach an EM sensor was designed accordingly to the characteristics of a patient-attached stereotactic needle guider. The clamp was 3D printed and attached to the aiming device turntable to track the pose of the device using an EM tracking system. The tracking data were used to display a 3D line projection, from the guider, that shows the needle path without having to insert a needle into the guider. A spatial calibration was performed to adjust the position of the path projection from the guider to the place where the real needle will be once inserted. 3D Slicer was used to develop a surgical navigation system where all the ablation parameters (needle size, estimation ablation zone size) can be incorporated. The ablation zone estimation can be updated in real-time and displayed in 3D, with all the other 3D models, or on top of the US imaging (2D line).

The positional and angular error results, $(2.19 \pm 0.16^\circ$ and $2.76 \pm 1.11$ mm respectively) suggest that our system is sufficiently accurate for needle deployment using the guider as a pointer. One of our system advantages is that sensorizing the disposable aiming device instead of tracking the application directly could mean a reduction in costs. Another advantage of using the patient-attached aiming device to control the angle of entry, instead of using a US probe-attached aiming device(1.5.3) is the opportunity to explore the "out-of-plane" approach when choosing the point of entry. Our system offers a 3D/2D "pointer" that shows the applicator path before needle insertion, this in conjunction with the ablation zone display could mean an improvement on the targeting accuracy for the focal treatment of liver tumours. A usability study involving medical experts and novices still needs to be performed.

Chapter 3 presents a method to perform image-to-image rigid registration for percutaneous interventions that are easy to reproduce with accurate results. Our method was validated in
5.1. Thesis contributions

two scenarios: 1) a controlled environment (Phantom experiment) as ground truth; and 2) an imaging patient trial, to evaluate the feasibility in environments where breathing motion or tissue deformation could be an important factor. The experiment results, phantom (FRE of 2.21 ± 1.03 mm and a TRE results of (1.66 ± 0.72 mm for PH-P1 and 2.26 ± 0.56 mm for PH2-P2) and trial (FRE of 2.35 ± 1.40 mm, and TRE of 7.23 ± 4.45 mm), allowed us to demonstrate that the workflow is sufficiently stable and gives accurate information in spite of it being a non-deformable method.

The biggest advantage over other work in the literature is that the registration uses an automatic selection of bifurcation points and that only three/four bifurcation points are needed to obtain accurate results for liver registrations (TRE ≈ 10 mm) [54, 59]. The automation of bifurcation extraction reduces the time (and manual error) of selecting the landmarks by the physician since only a single button click is required instead of manually selecting one by one on each modality. Obtaining the bifurcation points directly from the centreline instead of computing the landmark extraction using the vessel surface could help in the accuracy of the bifurcation point placement, and therefore the registration accuracy. This type of registration could function as a pre-registration step to perform a deformable registration. The algorithm was tested in real patients’ preprocedural volumes both CT and MRI and intraprocedural US volumes, showing good results in all modalities.

Finally, chapter 4 describes the development of an anthropomorphic liver phantom based on real patient liver segmentations. The phantom consists of five major parts: the left and right lobes, the internal and external vasculature, and tumours. Talcum powder was used as a scattering agent and mixed with PVA-c to allow multimodality imaging CT, MRI and US. An experiment to determine the best talcum concentration for the tumours was performed. The concentration of the tumours was evaluated by US and CT imaging. The phantom was constructed by assembling all the parts and connecting a water pump through the external vasculature to allow water to flow in the internal vasculature of both liver lobes.

The resulting images of the phantom show anthropomorphic characteristics that can be well appreciated: the tumours, vessels, and liver body in each one of the lobes (Figure 4.8 and Figure 4.10c). The vessels are clearly distinguished from the liver body, without presenting shadowing when water is flowing through them. This phantom has several desirable characteristics: it that can be easily customized; the wire skeleton of the positive vasculature mould (Figure 4.4) allows the positioning of the vessels in different ways before the PVA-c filling of the lobes; and the number, shape, size, and type of tumours (hyper or hypoechoic), can be varied in each phantom. As a clinical achievement, the liver phantom presents good anthropomorphic characteristics, meaning that it can be used as a sandbox for validation and training of the stereotactic IGSNS and any other type of liver procedure (e.g interpretation of images, biopsies).

The stereotactic IGSNS could be used for any needle insertion procedure such as biopsies on different parts of the body, allowing the “out-of-plane” approach which could lead to more accurate needle deployment. Other possible applications include percutaneous ablations of other organs (e.g. kidney). Our system could lead to a reduction in hospitalization (because of recurrence) by performing a more accurate procedure (i.e ensuring complete tumour coverage) and also reduce the patient’s recovery times because of the reduction of needle repositioning during the procedure.
5.2 Limitations

The major limitation of this work is that the use of the aiming device is only for single ablation applicators, whereas, as mentioned in chapter 1 section 1.3.4, there are different applicator designs to perform the ablation procedure. Currently, the stereotactic IGSNS module can be modified to be used with Umbrella electrodes, by updating the ablation zone simulation only. Another limitation relies on the use of EM sensors, which are wired, and this can lead to sterile field contamination during the procedure. The cost of the EMTS could represent another possible limitation for this project to reach the clinical field, but this could be counteracted by showing an improvement in cost-benefit when using our system, such as a reduction in operating time, increase in success rates, and reduction in tumour recurrence.

Sterilization of the components could present another challenge to our system, the use of an EM tracking system requires wired-base sensors, meaning that the cables of the sensors need to be protected in order to prevent any type of contamination during the procedure. Another possible limitation, specifically for using the aiming device, is the necessity of choosing the entry point carefully before attaching the needle guider to the patient skin. The further analysis of this limitation can be addressed and explored with a dedicated user study.

Regarding the registration process, a limitation is the reduced US FOV, produced by the system used for the 3D US volume acquisition. Future work includes testing the algorithm acquiring the US volumes with different methods (e.g. freehand ultrasound scan). In spite of the reduced FOV, our process can perform accurately with 3 or 4 bifurcation points and still give us accurate results, (e.g. Px9 Figures 3.8e and 3.8f with FRE = 2.11 mm and TRE = 8.72 mm or Px11 3.8g and 3.8h with FRE = 3.42 mm and TRE = 4.16 mm). Another limitation of our algorithm is the need for manual segmentation of the vessels, requiring time and resources and the possible introduction of human error, leading to a miscalculation in the registration process. The method chosen to perform the registration, ICP, could be seen as another limitation. ICP allows a simple rigid registration method, still, a test needs to be performed to ensure that the accuracy provided by this registration method is sufficient to have it used in clinical scenarios.

A limitation of our phantom is the vessel’s diameter used for the development, which can be easily corrected. Another limitation of our liver phantom is that PVA-c needs special treatment to be stored (i.e. be in water).

To address some of the limitations and continue to develop a complete stereotactic IGSNS for percutaneous liver tumour ablations additional work needs to be done.

5.3 Future work

Future work of the stereotactic IGSNS includes testing whether the passive markers in the applicator in conjunction with the display of the depth by the system are sufficient to place the applicator correctly, eliminating the need for applicator tracking and thus reducing costs. Other future work involves designing and incorporating new aiming devices that permit the use of different applicator designs (i.e. clusters), and the testing of the same stereotactic IGSNS, using the patient-attached guider, in different ablation procedures (i.e kidney tumour ablation). Fi-
5.3. **Future work**

Finally, the development of a “sterile wire cap" or “sterile wire wrapper” that can be re-sterilized (or be disposable) that isolates the EM sensor wire during the procedure, to maintain field sterility, is necessary for future work for this project.

One of the reasons for an image-to-image registration is to achieve the visualization of tumours in cases where the tumour is not visible in the US. Future work regarding the registration process involves the full automatization of the process including the vessel segmentation, to decrease the procedure time and possible errors due to manual segmentations. Testing the method in more patient volumes acquired with different methods (e.g. freehand ultrasound scans) is also another possible future task related to the registration process. Our registration method needs to be compared to another algorithm (e.g. Coherent Point Drift) to ensure that our method could be used as initialization of the registration or as final registration. Finally, to evaluate if the system can be used for an accurate needle placement when the tumours are not visible in the US image, an analysis of the tumour coverage needs to be performed when the center of the ablation zone is at the different tumour centres: using preprocedural imaging as a target instead of the intraprocedural tumour centre. The final goal of the registration process is the possibility of adding it to the IGSNS system described in chapter 2, to improve the needle deployment.

Future work for the liver phantom should include a new design of the vessels, using actual patient segmentation and then employing the models while making the lobes. A complete liver phantom, that includes left and right lobes is another possible future work. The phantom process can be implemented for new organ phantoms. Another speckle agent testing can be performed to obtain different types of tumours that can be incorporated into the liver phantom body.

For testing the stereotactic IGSNS, the phantom could be placed in a tracked (EMTS) container that functions as an “abdomen”. Another upgrade for the phantom would be the incorporation of respiratory movements, to improve the anthropomorphic features, which could lead to more realism when used for proceeding training, but also to evaluate the needle placement using our method and the rigid registration accuracy (TRE) if respiratory movements are added. Finally, a user trial to evaluate accuracy, performance, usability and comfort should be performed as the final testing of our system.

This thesis presented the proof of the concept of a stereotactic IGSNS that uses a patient-attached aiming device and helps in the deployment of the applicator during percutaneous liver tumour ablations using US guidance. A preliminary algorithm of an image-to-image rigid registration and the construction of a liver phantom with anthropomorphic characteristics was also addressed. The stereotactic IGSNS development established the basis for a future user trial and opens the possibility of being used in different applications with the same percutaneous characteristics (e.g. kidney tumour ablation, biopsies). The complementary work (i.e. registration process and phantom development) can be incorporated into the stereotactic IGSNS, improving the accuracy of the needle deployment. A complete (including image-to-image registration) stereotactic IGSNS for focal liver tumour ablations could be developed in the coming years.
Bibliography


Appendix A

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- Stereotactic IGSNSs components [4].
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- Examples of US probe-attach needle guiders: a) Ultra-Pro II needle guide [36].
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- Examples of US probe-attach needle guiders: b) SIVA guide [30].
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- Examples of stereotactic aiming devices: a) ATLAS aiming device [31].
Examples of stereotactic aiming devices: b) Stereotactic arm [4].
Appendix B

Ethics approval for patient trial (data acquisition)

This appendix include the ethics approval documents for the patient data acquisition.
Dear Dr. Derek Cool

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

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No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Patricia Sargeant, Ethics Officer [redacted] on behalf of Dr. Joseph Gilbert, HSREB Chair
Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Protocol Title: Use of 3-Dimensional (3D) Ultrasound Imaging to Guide the Treatment of Abdominal Tumours using Focal Ablation

Principal Investigator
Dr. Derek Cool, MD Medical Imaging –Diagnostic Radiology
Victoria Hospital Campus, [redacted]

In this Consent document, “you” always refers to the study participant. If you are a substitute decision maker (SDM) (i.e. someone who makes the decision of participation on behalf of a participant), please remember that “you” refers to the study patient. If an SDM is needed for this study, you will be asked to review and sign this consent form on behalf of the participant.

Invitation to Participate
You are being asked to participate in a research study involving ultrasound imaging during an ablation procedure because you are undergoing a kidney or liver ablation treatment. Ablation is the process of placing a needle through the skin into a tumour. Energy then passes through the needles creating a small region of heat, which then destroys the cancer cells. The target group for the study are patients with hepatocellular cancer that are scheduled for treatment at the London Health Sciences Centre. The purpose of this study is to gather and transfer the ultrasound images from your procedure to The University of Western Ontario to test whether 3D ultrasound will allow better visualization of the full depth and volume of malignant tumours in the liver, resulting in more accurate ablation of the entire tumour. The new technique will be developed through comparing 3-dimensional ultrasound images to the standard 2-dimensional ultrasound, with reference to MRI and / or CT images, which is the current gold standard or currently accepted clinical diagnostic tool for viewing internal anatomy for these types of procedures. The follow up imaging may indicate that 3-dimensional ultrasound can provide a better guidance tool than traditional 2-dimensional ultrasound imaging. Your images are being transferred to research collaborators at The University of Western Ontario who have experience and skills in analyzing medical image data. The university also houses computing infrastructure that is needed to perform analysis on your data.

Study Rationale
We are adding 3-dimensional (3D) ultrasound because standard ultrasound can only show 2-dimensional (2D) “flat” images on the computer screen of what is really 3-dimensional structure within the liver or kidney. We believe that the addition of 3D ultrasound to guide the needles used during the ablation procedure will allow the doctor to better see the size and depth of the liver or kidney tumours. We hope
Protocol: Use of 3-Dimensional (3D) Ultrasound Imaging to Guide the Treatment of Abdominal Tumours using Focal Ablation

this will make removal of the liver or kidney tumour easier and more accurate. A successful result will help to create a new guidance technique for increasing the accuracy of needles used during the ablation procedure, and reduce the procedure time going forward, and could potentially improve future interventions by providing additional information about needle placement during ablation procedures.

Time Commitments Related to this Study
There are no additional time commitments by participating in this study. Your direct involvement is simply attending the procedure as you would do normally, and agreeing to include 3D ultrasound imaging during the procedure. You are not expected to perform any actions, tasks, or answer any questions by participating in this study. You will not be asked to participate in any follow-up appointments, or be limited or restricted from participating in other studies due to your participation in this study.

Up to forty (40) people will participate in this study and we anticipate that up to forty will be enrolled. This study should take a total length of one or more years to complete, depending on enrollment.

Procedure
The standard of care for these types of procedures is to undergo a CT and / or MRI scan to determine the planned placement of the ablation needle, which is then performed under intermediate ultrasound imaging as a guidance tool. Intermediate ultrasound is the periodic use of a standard ultrasound machine to record pictures of the internal anatomy while viewing needle placement. Once the clinicians are satisfied with the placement of the needles, the ablation begins, which is the actual heating of the tumor for a duration of about 8 to 12 minutes depending on the nature of the tumor. The needles act as the conduit for the ablation energy. Another MRI / CT may be taken to ensure successful treatment.

For this research study, the only difference from the standard of care will be the addition of 3-dimensional (3D) ultrasound imaging to record images of the needle. A custom designed medical device produced at The University of Western Ontario will be used to acquire 3-dimensional ultrasound images. The only other difference, is that a representative from lab that developed the device will be present in the procedural room during the procedure.

The 3D ultrasound medical device titled “3D Ultrasound Abdominal Scanning System” or simply “3D-AIS” is approved by Health Canada for investigational testing for use in this study. The device consists of a mechanical mover that guides a standard clinical curvilinear ultrasound transducer over the ultrasound gel on the surface of the skin in a fan shaped movement in order to obtain a 3D image. No other equipment will be used during this procedure relating to the study. All diagnostic images are acquired for review by the radiologist according to the standard of care and your care will not be affected in any way by your participation in this study.

Risks and Harms of Participating in this Study
The manufacturer has identified three main risks with the 3D-AIS device, which will be described in this section, along with safety measures in place. Firstly, there is a risk of electric shock with any powered device. The risk to you is minimum, as the device is very low powered, is shielded, and properly grounded, which has been approved by a certified electrical inspection agency. The second risk is the heating that comes from general use of ultrasound imaging on your skin and underlying tissue. The risk to you is very minimal, as the length of time that your skin will be exposed to ultrasound is well below the threshold for heating. The final risk is that of pinch points within the mechanical arm. There is very minimal risk to you,
as the mechanical assembly containing the pinch points is always at arm’s length, which is outside of your range of motion. Moreover, the operator of the mechanical arm would be exposed to a possible pinch point.

Images will be stored on a physical hard drive that is transported between Victoria Hospital and The University of Western Ontario. The data will be encrypted and will not contain any personal information. Although the study team does their best to protect your personal information, there is no guarantee that data won’t be breached.

Benefits of Participating in this Study
The are no direct benefits to your participation in this study. The only perceived benefit is that the physician will have the benefit of 3-dimensional visualization of the region they are targeting.

Participation
Participation in this study is completely voluntary; whereby, you have no obligation or should feel no pressure to enroll. If you do choose to participate in this study, you will not be required or expected to perform any action or involvement outside the standard of care. The ultrasound images will not be traded or sold; the results of the analysis or the images themselves may be included in a peer reviewed publication or conference presentation, but will not contain any of your personal information.

Your Rights to Withdrawal from the Study
You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your treatment. If your withdrawal is prior to any imaging, then the paper copies of the Letter of Information and consent will be stored per Lawson regulations, however you will not be involved in any imaging. Once data has been acquired, it must also be stored according to the Lawson regulations, and may be used for analysis. To withdraw from the study you should tell Dr. Derek Cool at (519) 685-8500 x54965.

Conditions Causing Withdrawal
You will be withdrawn from this study if the ablation procedure is canceled or significantly delayed by the clinical/hospital staff. A significant delay would be a date that is beyond the expiration date of this study.

Personal Costs Related to the Study
You will not incur any personal costs by participating in this study. In the event of a study related injury, you will receive medical care and treatment at no cost.

Reimbursement
There will be no reimbursement for participating in this study.

Confidentiality
The information collected will be used for research purposes only, and neither your name nor information which could identify you will be used in any publication or presentation of the study results. All information collected for the study will be kept confidential; however, representatives of The University of Western Ontario Health Sciences Research Ethics Board, Lawson Research Institute, and/or Health Canada, may contact you or require access to your study-related records to monitor the conduct of the research. While we will do our best to protect your information there is no guarantee that we will be able
Protocol: Use of 3-Dimensional (3D) Ultrasound Imaging to Guide the Treatment of Abdominal Tumours using Focal Ablation

to do so. The images used will not contain any personal identifiers or information, and will only include a sequential study number and date of exam. A master list that correlates the sequential study number to the personal information will be stored in a locked filing cabinet in the office of the PI at Victoria Hospital.

The transferred ultrasound, CT, and / or MR images taken pre-, post-, and during the procedure will be stored for twenty-five (25) years.

The Rights of the Participant
You may refuse to answer any questions related to this research study, and are under no obligation to participate. Representatives of The University of Western Ontario Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research.

Questions about Your Rights or Study Conduct
If you have any questions about your rights as a research participant or the conduct of the study you may contact: The Patient Relations Office for LHSC at (519)685-8500 x82036.

If you have any concerns regarding this study you can contact the Principal Investigator, Dr. Derek Cool, Victoria Hospital Campus, [Contact Information].

Conflict of Interest:
Dr. Aaron Fenster, who is one of the co-investigators for this study and the director of the lab that developed and build the investigational device used in this study. Although there are currently no financial benefits related to this device, Dr. Fenster could benefit in the future from commercialization or other similar business endeavors.

You will receive a copy of this letter to keep for future reference.
CONSENT FORM

Protocol Title: Use of 3-Dimensional (3D) Ultrasound Imaging to Guide the Treatment of Abdominal Tumours using Focal Ablation

Principle Investigator: Dr. Derek Cool, MD Medical Imaging – Diagnostic Radiology
Victoria Hospital Campus, [Redacted]

I have read the letter of information, have had the nature if the study explained to me and all questions have been answered to my satisfaction and I agree to participate.

For the Participant
Name (please print)___________________________
Signature_______________________
Date_____________________

For the Translator (If applicable)
Name (please print)___________________________
Signature_______________________
Date_____________________

Person Obtaining Consent
Name (please print)___________________________
Signature_______________________
Date_____________________

Participant ID: ___________
Use of 3-Dimensional (3D) Ultrasound Imaging to Guide the Treatment of Abdominal Tumours using Focal Ablation

Principal Investigators: Dr. Derek Cool, PhD, MD

PROTOCOL VERSION: 1.4
05 January 2022
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KEY ROLES AND CONTACT INFORMATION

Principal Investigators: Dr. Derek Cool, PhD, MD
Medical Imaging – Diagnostic Radiology
Victoria Hospital Campus
800 Commissioners Road East
London, Ontario N6A 5W9

Other Key Personnel

- Co-Investigators
  - Dr. Aaron Fenster, PhD
  - Dr. Amol Mujoomdar, MD
  - Dr. Leandro Cardarelli Leite, MD

- Research Staff
  - Derek Gillies, PhD
  - Dr. David Tessier, PhD
  - Katherine Junyu Li (Medical Student)
  - Shuwei Xing (PhD Student)

- Data Manager
  - Dr. David Tessier, PhD
Background and Rationale

Hepatocellular carcinoma is one of the major causes of cancer related death worldwide. The liver is also the second most common site of metastatic cancer. Cancer of the kidney accounts for 2% to 3% of all cancers, with the incident rate rising. In theory a renal mass biopsy (RMB) will determine the presence or stage of cancer; however, there are issues with accuracy targeting due to current diagnostic limitations. Currently hepatic resection has the highest success rate of all treatment techniques. However, only a small number of patients are candidates for surgery. Minimally invasive techniques such as radiofrequency (RF) and microwave (MW) ablation for the treatment of focal tumours have attracted much attention recently and the range of indications for local ablation treatments is becoming wider than surgery or intra-arterial therapies.

For the standard clinical procedure patients first undergo a Computed Tomography (CT) examination, which allows the physician to identify the location of the liver tumours and to plan the radiofrequency needle ablation. The ablation process is most commonly performed in the CT suite and guided by standard (2D) ultrasound and intraoperative CT images, allowing the physician to determine the size and location of the tumour(s) and where to insert the probes into the liver while viewing the insertion process in real-time on the ultrasound monitor during the procedure. The acquisition of the number of intraoperative CT images is also limited as due to radiation dose to the patient and the time required to generate the CT images.

Ablation works by delivering energy directly into the malignant lesions through small needle applicators, which burn and destroy the diseased tissue. Standard ultrasound is limited in only being able to show 2D “flat” images on the computer screen of what is a 3-dimensional target within the organ, making it difficult to estimate the size and depth of tumour infiltration. 3D ultrasound (3DUS) has been used with notable success to guide breasts and prostate needle biopsies and also in some neurosurgical procedures. Therefore, a medical device has been constructed to acquire 3DUS images.

Tumour and vascular structure can be immediately identified from 3D Ultrasound images without the need for multiple scans as with conventional techniques. Also, more anatomical information provided can facilitate the process of linking ultrasound with other modalities such as CT and MRI. The CT and MR images are also in 3D, so we have developed special computer programs that can transform and lay the different images on top of one another so they can be compared. This information can be used to complement the data obtained from CT/MR images for planning an appropriate treatment. The overall purpose of this study is to develop algorithms that will simplify the eventual fusion of intra-operative ultrasound data with pre-operative CT data. This fusion will be beneficial mainly because most liver tumors are more visible in CT than in ultrasound, and will provide better tumour localization information to the physician during the US-guided procedure. The augmentation process currently requires manual registration of US and CT which has to be done during the procedure. Manual registration is tedious, time consuming and error prone, so this study will be looking at developing algorithms for automatic registration that are less operator dependent and faster.

Research Device Description

The medical device used to acquire 3DUS is experimental / investigational for use by a qualified physician or sonographer in a clinical setting. The device with name 3D Ultrasound Abdominal Scanning System (3D-AIS) is licensed with Health Canada for use in this pilot study. This device has been designed and manufactured at The Robarts Research Institute at The University of Western Ontario for creating 3D US
images of soft tissue from a standard ultrasound transducer. The device consists of an active (i.e., electrically powered) mechanical mover that guides a licensed curvilinear ultrasound transducer over the surface of the patient’s abdomen in a fan shaped movement in order to obtain a 3D US image. A qualified investigator activates the mover via an original equipment manufacturer (OEM) computer workstation for acquiring, storing, and reconstructing a series of conventional two-dimensional (2D) US images from a medically licensed ultrasound machine. The 3DUS-AIS will be used to acquire, reconstruct, and record 3D US images of the abdominal region from patients.

Study Conduct
The recruiting / consenting and imaging will be performed at the Victoria Hospital (London, Ontario) by an experienced research coordinator. This study will be conducted in compliance with the protocol approved by the principal investigator and according to the standards outlined. No deviation from the protocol will be implemented without the prior review and approval of the principal investigator.

Data Acquisition
The 2D ultrasound images created by the clinical ultrasound machine, will be passively captured on the internal hard drive of the ultrasound machine. The 3D ultrasound images that are acquired with the medical device will be stored on the OEM computer hard drive. Following the procedure, the saved anonymous ultrasound images will be exported to an encrypted external hard drive for transport to The University of Western Ontario. Any CT imaging will also be de-identified and transferred onto the encrypted external hard drive. All 3-dimensional ultrasound as taken by the ITA medical device transferred onto the encrypted external hard drive.

Hypothesis
3-dimensional ultrasound imaging recording multiple planes and multiple features will make assessment of liver tumours and treatment planning easier for the radiologist.

Study Objectives
The primary objective of this study is to test whether 3D ultrasound is needed to verify the needle (electrode) position during a liver ablation procedure. The secondary objective is to use 3D ultrasound to evaluate how well the burn zone is centered over the tumour.

Consenting
The opportunity to participate in the study will be introduced to the patient by the physician at the pre-procedural appointment. The consenting process will commence at the beginning of the treatment appointment. Written consent will be used after a prospective patient expresses interest in participating in the study. A member of clinical research will interview the patient, answer their questions, and obtain consent.

Participants
Forty (40) patients with hepatocellular cancer that are scheduled for treatment at the London Health Sciences Centre will be the target mass for the study. Furthermore, patients who meet the inclusion / exclusion criteria, will be selected for the study. Current protocols followed in London Health Sciences Centre (LHSC) generally indicate non-surgical candidates for the percutaneous ablation procedures. The eligibility criteria are:
Use of 3-Dimensional (3D) Ultrasound Imaging to Guide the Treatment of Abdominal Tumours using Focal Ablation— Protocol Version - 1.4, January 05, 2022

Inclusion Criteria

- Patients who are scheduled for standard care liver or kidney ablation.

Exclusion criteria

- None

Standard of Care

As part of the treatment planning, a computed tomography (CT) imaging examination is performed before the procedure, then a separate visit for the procedure itself, during which the doctor uses conventional ultrasound to guide the electrode, and then a follow-up CT examination after 4 to 6 weeks to check that the tumour was completely removed. On rare occasions, the procedure is performed in the CT suite, where both CT and US are used to guide and verify the electrode positions prior to ablating.

Study Design

Images will be acquired on patients who are undergoing a liver ablation. Patients will be imaged during the ablation procedure according to the standard of care, and subsequent analysis will commence following the acquisition. The only deviation from standard care imaging is the addition of 3-dimensional ultrasound acquisition using the investigational device. Images of the abdomen will be the focus of the research component of the imaging. Patients will have five to ten (5 – 10) abdominal images of their liver at multiple time points during the procedure. Other than the medical device, all devices being used are all property of the LHSC health network that have been licensed for clinical use through Health Canada. In addition, 3D ultrasound only differs from conventional 2D ultrasound in that the ultrasound transducer is mounted on a special assembly that moves the transducer in precise, stepped movements while a succession of 2D images are collected by the computer. Special software written specifically for 3D ultrasound precisely aligns these 2D images into a 3-dimensional volume, allowing the area in question to be viewed in different planes. The clinical 2D and 3D ultrasound images will be checked against the pre- and post- procedure CT images to make sure the tumours were completely removed. No additional visits or follow-up appointments occur due to the patient’s participation in the study.

Procedure

The patient follows the standard of care procedure, including pre and post-procedural appointments. The use of the 3D ultrasound medical device will only take place during the intra-procedural appointment. The opportunity to participate in the study will be introduced to the patient at the pre-procedural appointment. The consenting process will commence at the beginning of the treatment appointment. The treatment will take place according to the standard of care, with the only deviation being the addition of the five to ten 3D ultrasound acquisitions throughout the procedure. At the end of the procedure the ultrasound images, as stored in the MHA format, will be exported to an encrypted external hard drive for transport to The University of Western Ontario. The CT scans taken pre, intra, or post ablation treatment related to the ablation treatment of the patient will be gathered from the PI and downloaded to the external hard drive to de-identified and transferred to the University of Western Ontario.
Patient Identification
Each patient’s study data will be given a sequential identifier number corresponding to the order of enrollment, with no connection to a personal or hospital identifier, as this data will not be used for diagnostic or clinical care.

Potential Risks
The manufacturer has identified three main risks with the 3D-AIS device, which will be described in this section, along with safety measures in place. Firstly, there is a risk of electric shock with any powered device. The risk to the patient is minimum, as the device is very low powered, shielded, and properly grounded, which has been approved by a certified electrical inspection agency. The second risk is the heating that comes from general use of ultrasound imaging on skin and underlying tissue. The risk is very minimal, as the length of time that the tissue will be exposed to ultrasound is well below the threshold for heating. The final identified risk is that of pinch points within the mechanical arm. There is very minimal risk to the patient, as the mechanical assembly containing the pinch points is always at arm’s length, which is outside of their range of motion. Moreover, the operator of the mechanical arm would be exposed to a possible pinch point during operation, but not the patient, unless they reach up to grab the device. They will be reminded by the support staff prior to the procedure that they are not to touch the device at any time.

Images will be stored on a physical hard drive that is transported between Victoria Hospital and The University of Western Ontario. The data will be encrypted and will not contain an personal information. Although the study team does their best to protect personal information, there is no guarantee that data won’t be breached.

The ultrasound images are acquired using the probe (transducer) on the surface of the skin (using sterile hypo-allergenic ultrasound coupling gel) prior to the start of the surgical procedures. The 3D ultrasound imaging will not affect the standard clinical ablation and will add no more than 5 minutes to the total time.

Potential Benefits
It is possible that the 3D ultrasound imaging will add some extra information to the physician to help with the treatment planning. In addition, the techniques developed in this study, may help improve future procedures. Future care that could be augmented by ultrasound guidance would reduce the amount of x-ray radiation a patient received during a procedure, and the total procedural time. Since the risks are very minimal to the patient, it is believed that it is worthwhile to conduct this device trial.

Image Analysis
The co-investigators will not be viewing the patient images for any specific anatomical or physiological information. This study will use 3D US imaging in addition to conventional 2D ultrasound to evaluate whether 3D US can be used to validate the needle position according to the pre-planned location. Manual registration will be done between the pre-procedural CT and intraprocedural ultrasound, and between intraprocedural ultrasound and post-procedural CT. A measurement of the needle tip location will be calculated in the 3D ultrasound images and compared with the intended treatment plan (pre-procedural), and treatment zone (post-procedural). The tumour and treatment zones will be contoured by expert observers, and the overlap regions will be compared by calculating a DICE coefficient.
Quality Control and Monitoring
The principle and/or co-investigator will be present during the procedure to assure adherence to the study protocol. A member of the study team from the manufacturer will also be present during each procedure. In addition to assisting with the set up and operation of the device, they will be monitoring the workflow and device use. A monthly communication will be made between the monitor and Dr. David Tessier. Any feedback will be documented, and disseminated to the appropriate team members to address and document. Depending on the feedback comments, complaint handling, mandatory reporting, and recall procedures will be initiated. The study monitor will also perform the following roles:

- Data Verification:
  - The data recorded during each session are 3D ultrasound images.
  - The monitor will ensure the integrity of these images by loading them into the software program 'SHIFT64_LING', and ensuring they are viewable without any error messages.
  - Each image is recorded on the data collection form, which will be checked with a checkmark once verified by the monitor.

- System validation and calibration:
  - The device was calibrated at the manufacturer's site according to the '3D-AIS Initial Calibration' SOP.
  - Prior to each patient use, the monitor will perform a routine device quality assurance test according to the '3D-AIS Device Use QA' SOP.

The investigators are not permitted to deviate from the standard of care, other than the procedure outlined in this protocol. Any adverse events that result in protocol deviation will be assessed as to its impact on the study. Impact and actions to be taken will be added into the protocol with appropriate update number, and reported to the regulatory bodies immediately as a protocol update notice.

Temperature Restraints
The 3D-AIS device must be operated within the temperature range of 10 °C to 32 °C, and stored within the temperature range of -20 °C to 85 °C. The device will be used within the hospital angiography suite, which is regulated at room temperature. Storage of the device at the hospital is in the angiography storage room, which is regulated at room temperature. Transportation of the device between the hospital and manufacturer is performed by a locally operated vendor, that are capable of maintaining the storage cabin at the requisite temperature range.

Image Storage and Transfer
Anonymous data will be copied onto a password protected external hard drive, which will be backed-up onto a UWO password protected and firewalled server cluster.

Site Selection
The study requires a hospital that performs liver ablation procedures, and diagnostic ultrasound. The site of London Health Science Centre Victoria Campus was chosen as the site for this study as it meets the above mentioned criteria. Secondly, it is in close vicinity to the manufacture, enabling a team member to be onsite during the procedures to have close monitoring perspective, which helps to gain a deeper insight for future development.
Training
All study members are required to complete and renew when applicable the following courses:

- **Tri-Council Policy Statement (TCPS2)**
  - Provided by The Government of Canada (https://tcps2core.ca/)

- **Lawson Standard Operating Procedure (SOP)**
  - Provided by Lawson Health Sciences Research (https://apps.sjhc.london.on.ca/sj_files/studentaffairs/SOPS_Clinical_Research/story.html)

- **Collaborative Institutional Training Initiative (CITI)**
  - Provided by CITI (https://www.citiprogram.org/)

At least one of the core team members must be well trained with the medical device regulations (MDR), good clinical practices (GCP), and relevant ISO standards: 14155, 14971, and IEC 60601.

Adverse Events
An occurrence that results in a negative effect to the patient’s health, whether it be minor, serious, or fatal is an adverse event. Once an adverse event takes place, it needs to be evaluated by the sponsor. A report will be filed with the Western REB using the ‘Adverse report form’. The mandatory problem reporting procedure will be initiated.
## Revision History

<table>
<thead>
<tr>
<th>Date</th>
<th>Revision</th>
<th>Summary of Revisions Made</th>
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<tbody>
<tr>
<td>January 28 – 2019</td>
<td>1.0</td>
<td>Original draft</td>
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<tr>
<td>March 08 - 2019</td>
<td>1.0</td>
<td>Modified Original Draft</td>
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<tr>
<td>May 01 - 2019</td>
<td>1.1</td>
<td>Updates were made to study design, inclusion criteria, procedure,</td>
</tr>
<tr>
<td>January 12 - 2021</td>
<td>1.3</td>
<td>Updates to Study Members</td>
</tr>
<tr>
<td>January 5, 2022</td>
<td>1.4</td>
<td>Several new sections added, including training, adverse events, site selection, temperature restraints, and consenting. Other sections updated</td>
</tr>
</tbody>
</table>
Curriculum Vitae

Name: Joeana Cambranis Romero

Post-Secondary Education and Degrees:
University of Western Ontario, London, ON, 2020 - 2022 MSc.

Universidad Modelo de Merida, Merida, Yucatan, Mexico, 2011 - 2015 Bachelor’s.

Awards and Honors:

Related Work Experience:
Robarts Research Institute, Western University, 2020 - present.
Graduate Research Assistant

Centro De Simulación Médica Montagne, Universidad Marista de Merida, Merida, Yucatan, Mexico, July 2015 - December 2019.
Biomedical Engineer
Publications:

Journals:


Conferences:


Submitted:


**Poster presentations:**


**Presentations:**

