CHAPTER 1

General Introduction
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Lung cancer
Lung cancer is the most common cause of cancer-related deaths worldwide [1]. In the USA, lung cancer screening by low-dose computed tomography (CT) is recommended for people at high risk, and the European Society of Radiology and the European Respiratory Society are recommending lung cancer screening within clinical trial or in routine clinical practice at certified medical centers [2, 3]. With the expected introduction of lung cancer screening, an increase of CT detected lung nodules is anticipated. Nodules larger than 10 mm in diameter and most likely even smaller nodules with significant growth will be eligible for medical work-up [3].

Bronchoscopy is often used to diagnose these lung nodules and to get a tissue diagnosis, but it is limited to centrally located lesions [4]. CT-guided transthoracic lung biopsy is a minimally invasive diagnostic procedure for tissue diagnosis of peripheral lung nodules. These can alternatively be reached with surgery, but the percutaneous approach is less invasive and associated with lower costs. Other imaging modalities used for percutaneous needle guidance include fluoroscopy, CT-fluoroscopy, ultrasound and magnetic resonance imaging (MRI). Fluoroscopy lacks three-dimensional imaging possibilities, so the operator has to be capable of translating the two-dimensional projections to a volumetric environment. Additionally, it requires the operator to be in the room during image acquisition, causing exposure to harmful radiation. Whilst CT-fluoroscopy does provide volumetric images, it too exposes the operator to radiation. Ultrasound does not induce radiation to the patient or the operator and with this technique, the nodule and biopsy needle can be followed in real-time. The downside is that only pleural lesions can be visualized as the air-filled lungs are poorly suited for ultrasound. Lastly, MRI is sometimes used but it is more cumbersome as the metallic biopsy needles are generally not MRI compatible. Additionally, patient access is limited within the bore and lung lesions are relatively poorly visualized, compared to CT. So, even though CT-guidance exposes the patient to radiation and lacks real-time feedback for the operator, it is still the method of choice for many percutaneous interventions [5].

Liver cancer
Primary liver cancer combined with liver metastases is the second most common cause of cancer death [1]. Over the last 20 years, thermal ablation has emerged as a successful treatment method for hepatic malignancies [6–8]. Radiofrequency ablation (RFA) and microwave ablation (MWA) are currently recommended for treatment of hepatocellular carcinoma (HCC) and colorectal liver metastasis (CRLM) in patients unfit for surgery or in combination with surgery [9, 10]. Currently, antenna placement is frequently performed with CT as imaging modality for planning and positional feedback of the ablation antenna.

Other imaging modalities offer similar drawbacks as those mentioned for transthoracic lung biopsy, with the exception of ultrasound. In theory, ultrasound is more suitable for percutaneous needle placement procedures in the liver compared to the lung. However, liver tumors are often not easily delineable from the underlying liver parenchyma on ultrasound. With contrast-enhanced CT, delineation of liver tumors is achieved more accurately. Because CT is a three-dimensional imaging technique, planning of multiple overlapping ablation zones to cover the entire tumor is less prone to errors.
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The main drawback of percutaneous liver tumor ablation is local recurrence of disease, with reported ablation site recurrence rates ranging from 5.0% to 32.1% [7, 11–13]. Risk factors for ablation site recurrences include larger tumor size, peritumoral vascularity, and insufficient ablation safety margin surrounding the tumor [14–16]. The latter can be caused by inaccurate placement of the ablation antenna, so for CT-guided liver tumor ablation accurate needle placement is critical. Another cause of incomplete ablation is the creation of unreliable ablation zones: when the actual ablation zone is inconsistent with the claimed protocol, there is a chance of incomplete ablation treatment, despite correct positionings of the ablation antenna. Heat-sink caused by blood vessels adjacent to the tumor is a well-known cause of ablation zone volume reduction [17]. Differences in tumor type and pathology of the underlying parenchyma have been demonstrated to affect the microwave ablation zone, too, in a two-compartment computer model [18]. Because ablation device manufacturers currently supply ablation protocols that are mainly based on ex-vivo non-perfused animal livers, these do not correlate very well with clinical practice.

Freehand approach

While CT is an excellent imaging modality for feedback of target and needle position, the actual guidance of the needle is still performed by hand (freehand method). Thus, based on the images provided by the CT, the operator has to determine how to angle and insert the needle towards the target. This is often an iterative process, where every needle repositioning increases the chance of complications.

With percutaneous needle placement, a differentiation can be made between in-plane and out-of-plane procedures. With in-plane approaches, the target is in the same axial position as the entry point on the skin, so the entire needle path can be imaged on a single axial CT slice. Here, the operator has to angle the needle towards the target on one axis. With out-of-plane approaches, the target is either cranial or caudal to the entry point. In order to image the needle path on a single slice, an oblique view must be used. Moreover, the operator has to angle the needle towards the target on two axes. Where the in-plane procedures are not too difficult to perform freehand, the out-of-plane procedures often require multiple needle repositionings in order to achieve adequate placement accuracy.

Robotic approach

Needle placement can be aided by the use of robotic systems. These generally provide some sort of needle guide, for the operator to push the needle through in order to increase needle placement accuracy. Over the years, numerous systems have been developed [19]. Despite the relatively large number of (experimental) robotic systems, there are few randomized patient studies that assess their functionality in real clinical environments. Only two RCTs could be identified that compared robotic needle placement with freehand needle placement. The study of Patriciu et al. from 2005 was the only one performed in patients with liver tumors, testing a robotic device (AcuBot) in a randomized study with only 14 patients [20]. The AcuBot reduced the number of needle repositionings and targeting time, but needle placement accuracy was not reported. To this date, the Acubot is still not on the market. In another, non-randomized clinical study Engstrand et al. analyzed the accuracy and procedural safety of the CAS-One for CT-guided percutaneous MWA of liver tumors [21]. They reported a lateral
accuracy of 4.0 mm in 28 tumors, although no comparison with freehand positioning was made. No differentiation between in- and out-of-plane procedures was mentioned in either study.

Recently, the Needle Placement System (NPS) has been developed as a system to facilitate accurate percutaneous needle placement for CT-guided interventions [22]. The NPS mounts on a rail parallel to the CT table and can be manually maneuvered towards the entry point on the skin. After locking the system, it automatically orients a needle guide towards the target. Subsequently, the needle can be inserted by the operator to the specified depth. It has the potential to offer simplicity in terms of device maneuverability, while still providing a stable platform from which automatic needle orientation is performed.

Respiratory motion
An often-overlooked issue with percutaneous needle placement is the effect of respiration. For CT-guided liver ablation, where procedures are mostly performed under general anesthesia, the respiration can be paused during acquisition of the CT scans and manipulation the ablation antenna. The chest (and thus the organs) can be expected to have returned to an approximately similar position when the CO₂ output is monitored to have reduced to zero after stopping respiration; especially when patients are positioned on a vacuum mattress. So, for procedures performed under general anesthesia, respiratory motion is less of an issue. However, less invasive procedures such as lung biopsies are performed under local sedation, because of the risk, time and cost associated with general anesthesia. The downside to local sedation is that patients are required to repeatedly hold their breath at a consistent level during the procedure. Since lung nodules move on average 25 mm up and down with inspiratory capacity, the level of breath-hold during acquisition of the planning CT scan and during needle manipulation is not the same and accurate targeting is impossible [23].

Currently available respiratory tracking systems suitable for image-guided intervention consist of respiratory belts that are cumbersome to install, only have a weak correlation with nodule position, and do not adjust for a change in breathing pattern [24]. Several groups have investigated the use of a depth camera (Kinect) to monitor patient respiratory motion for four-dimensional radiotherapy planning and the Kinect has potential to be used in image-guided interventions, too [25–27].

Outline of this thesis
The aims of the research described in this thesis are to investigate methods to improve the accuracy of CT-guided needle placement and to find factors affecting the ablation zone with liver tumor ablation.

Increased needle manipulations result in more tissue damage and can be expected to increase the chance of complications. In Chapter 2, the complication rate and factors affecting the complication rate of CT-guided lung biopsies are determined in meta-analysis, as a baseline.

In the first part of this thesis, the NPS was put to the test. Chapter 3 shows the results of a phantom study performed to validate this system. An anthropomorphic phantom
was designed to simulate CT-guided liver ablation, mimicking clinical practice. With this phantom, MWA antenna placement with the NPS was compared to freehand antenna placement by experts and novices. Subsequently, the NPS was analyzed in clinical practice. In Chapter 4, a randomized controlled trial is performed to compare the NPS with freehand MWA antenna placement, in patients undergoing CT-guided liver ablation. The primary outcome of this study was the number of antenna repositionings required to achieve adequate placement.

In order to use the NPS in interventions performed under local sedation, a solution for the respiratory motion was sought for. A system was developed in which the Kinect camera was used to provide respiratory biofeedback to patients to help them return to a consistent level of breath-hold. In Chapter 5, this system is tested with eight volunteers, using spirometry. Alternatively, increased needle positioning accuracy can be achieved by using a flexible, steerable needle. The advantage of such a needle compared to a rigid needle is that it can avoid critical structures by steering around and it can potentially compensate for respiratory movement. In Chapter 6, a CT-compatible needle steering robot that utilizes an electromagnetic tracking system is presented and tested in a phantom study.

In the last part of this thesis, the challenge of creating a predictable ablation zone is addressed. Chapter 7 presents a systematic review of all FDA approved MWA systems, in particular with regards to the variability of the ablation zone volume that is created in animal and in- and ex-vivo studies. In Chapter 8, differences in the relation between applied energy and ablation zone volume in hepatocellular carcinoma and colorectal liver metastasis are investigated. The goal of this retrospective study was to find if ablation protocols should be optimized for different tumor types for RFA and two MWA devices.

In Chapter 9, the main results of the chapters in this thesis are discussed together with future perspectives. Chapter 10 provides a Dutch summary.
References

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