GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
Colorectal liver metastases

Colorectal carcinoma is currently the third most common cause of cancer related death in the Western World, with around 12,000 new cases and 5000 deaths annually in The Netherlands in 2007 (1). The incidence will increase to an estimated 14,000 in 2015 (2). The main area of concern for these patients is the development of haematogenous metastases. The organ most often affected, via the portal circulation, is the liver and 40-60% of these patients develop liver metastases (3). For example, of all patients that will be diagnosed with colorectal cancer in 2015, around 7500 will develop liver metastases in the course of their disease. Fifty per cent of the patients have metastases present at time of diagnosis of the primary tumor, the other 50% will develop metastases later. Whether or not patients have liver metastases is of great importance to determine their prognosis; 5yr survival of patients without distant metastases at time of diagnosis is 60%-95%, and this drops dramatically to 8% when synchronous liver metastases are present (see table 1A and B) (4).

All patients with colorectal liver metastases (CRLM) should be evaluated for curative treatment of their metastases. Because nowadays several treatment modalities are available, this evaluation should be done by a specialized multidisciplinary (oncologic) liver team including a dedicated surgeon, an interventional and a diagnostic radiologist, a medical oncologist, a hepatologist, a radiation oncologist, a pathologist and a nuclear medicine physician.

Historically, surgical resection is considered the gold standard for potentially curative treatment. When all metastases can be resected, cure is possible resulting in a 5 year overall survival rate between 25-60% (5-9). This range can be explained by different stages of the disease; varying from a single metastasis to multiple bilobar disease and the presence of limited extrahepatic disease (10). Unfortunately, of the abovementioned 7500 patients with liver dominant metastases, a maximum of only 1500 patients (20%) will be candidates for curative resection (5;11). Site, size and number of metastases prohibit possibilities for a complete resection in 80% of the other patients. Until recently, an overwhelming 6000 patients per year would have to rely on palliative chemotherapy to slow down progression of their disease without the possibility of cure. Although modern systemic chemotherapy can provide a median survival of 20-24 months, cure is still extremely rare (8;12). Fortunately, the search for alternatives to achieve complete tumor eradication in a part of this patient population has already been started in the 1980’s and is still continuing. Local tumor ablation has emerged as a popular alternative to broaden the therapeutic possibilities for a selection of these patients.
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while compensatory hypertrophy occurs in the non-embolized lobe. This increases the future remnant liver volume and, supposedly, its function, enabling surgical resection of the tumors. Although this technique converts irresectable to resectable disease in selected patients, tumor progression has been described in the interval between embolization and resection, causing 6.4-33% of the metastases to be irresectable at time of surgery (7). Advances in the technique and possibilities of hepatic surgery have been scarce the past decade and are not expected in the near future.

In some patients, chemotherapy is able to downstage the liver lesions to convert them to locally treatable disease. This can be referred to as ‘neo-adjuvant’ chemotherapy, but since it is meant to convert locally untreatable disease to treatable disease, it is more reasonable to use the term ‘conversion chemotherapy’. Ten-twenty per cent of the patients with prior irresectable disease can become candidates for resection, with survival rates approaching patients with initially resectable tumors (8;9).

Despite the improved effect of chemotherapy and broadening of the inclusion criteria for surgical resection, still only 20-30% of the patients with CRLM are found eligible for surgery because of unfavorable tumor location, disease extent or insufficient hepatic reserve or patients’ co-morbidity (2;3;10). In the Dutch situation, this would mean 1500-2000 patients should have their CRLM resected on a yearly basis. The estimated 700 hepatectomies for CRLM per year in The Netherlands by the Dutch liver group suggests significant under-treatment.

This has led investigators to seek additional methods achieve complete tumor eradication in patients who are no candidates for a hepatectomy. In this regard, multiple liver targeted therapies have been developed in the past decades that offer local treatment options when surgical resection is precluded. Image-guided tumor ablation has emerged as one of the most widely accepted non-resection techniques for addressing CRLM, and the search for improvement is still ongoing.
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### Table 2. Survival after surgical resection of CRLM (adjusted from Wong et al [4])

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Operative Mortality (%)</th>
<th>3-Year Survival (%)</th>
<th>5-Year Survival (%)</th>
<th>Median Survival (months)</th>
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<tr>
<td>Abdalla et al [2]</td>
<td>190</td>
<td>-</td>
<td>73</td>
<td>58</td>
<td>-</td>
</tr>
<tr>
<td>Wei et al [3]</td>
<td>423</td>
<td>1.6</td>
<td>-</td>
<td>47</td>
<td>-</td>
</tr>
<tr>
<td>Hughes et al [12]</td>
<td>607</td>
<td>-</td>
<td>-</td>
<td>33</td>
<td>-</td>
</tr>
<tr>
<td>Rosen et al [15]</td>
<td>280</td>
<td>4</td>
<td>47</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Scheele et al [16]</td>
<td>434</td>
<td>4</td>
<td>45</td>
<td>33</td>
<td>40</td>
</tr>
<tr>
<td>Nordlinger et al [13]</td>
<td>1,568</td>
<td>2</td>
<td>-</td>
<td>28</td>
<td>40</td>
</tr>
<tr>
<td>Jamison et al [17]</td>
<td>280</td>
<td>4</td>
<td>-</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>Fong [11]</td>
<td>1,001</td>
<td>2.8</td>
<td>57</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Minagawa [18]</td>
<td>235</td>
<td>1</td>
<td>51</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>Choti [19]</td>
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<td>1</td>
<td>57</td>
<td>40</td>
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<td>Betti [20]</td>
<td>181</td>
<td>-</td>
<td>55</td>
<td>40</td>
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</tr>
<tr>
<td>Kato [11]</td>
<td>585</td>
<td>0</td>
<td>-</td>
<td>33</td>
<td>-</td>
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<tr>
<td>Mutsaerts [22]</td>
<td>102</td>
<td>3</td>
<td>-</td>
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</table>

### Ablative Technologies

Over 10 years were necessary to show that ablation concepts can extend to the field of (curative) treatment of CRLM. Methods of tumor ablation most commonly used in current practice are typically divided into two main categories; chemical ablation and thermal ablation. Other interventional oncologic therapeutic approaches, including the percutaneous delivery of genetic material and radioactive seeds, the transcatheter delivery of chemo- or radio-embolization agents, high-intensity focused ultrasound and stereotactic ablative radiotherapy are beyond the scope of this thesis.

#### The past: Chemical ablation, Cryoablation, Laser induced thermotherapy

Chemical ablation was described early in the evolution of local ablation. Through intratumoral administration of either ethanol or acetic acid, coagulation necrosis of the lesion occurs as a result of cellular dehydration, protein denaturation and chemical occlusion of small tumor vessels. Although the procedure is safe, cheap and easy to perform, there is a high local recurrence rate even in small lesions due to unpredictability of agent diffusion.
Therefore, this technique is abandoned in the Western world and only used in developmental countries.

Cryoablation causes tumor cell destruction by subzero temperatures. By inserting a probe into the lesion with circulating liquid nitrogen or the expansion of argon gas, temperatures of at least -40°C are reached (12). The forming of ice crystals causes the cell membrane to rupture, inducing cell death. However, cryoablation holds several limitations. The possibility for heat sink raises the risk for incomplete ablation of CRLM near large vascular structures. Complication rates after cryoablation are reported in up to 40% (13). The hemostatic effect of cryoablation is limited and haemmoraghe has been reported relatively frequent after the procedure. A potentially lethal side-effect of cryoablation is the cytokine-mediated response called ‘cryoshock’, leading to ARDS-like symptoms, myoglobinuria, coagulopathies and pleural effusion, reported in up to 1% of the patients (14). In a recent matched-pair analyses of cryoablation versus liver resection, the median overall survival of cryoablation was 20 months compared to 46 months for hepatic resection (15). A systematic review pooling 26 studies on cryoablation for CRLM showed a 5 year survival rate of 17% (16). These complications together with inferior results compared to other ablative techniques have caused this technique to be largely abandoned for ablation of CRLM.

The first technique using heat to destroy tumor cells was laser induced thermotherapy (LITT). The term LITT has been used to refer to thermal destruction of tissue by conversion of absorbed infra-red light into heat. By inserting laser fibers into tumor tissue using intra-operative ultrasound (IOUS), photons from the laser beam directly penetrate the tissue for a distance of 15mm (17). Unfortunately, the laser light is extremely vulnerable to the ‘heat sink’ effect, hereby significantly impairing the diameter of the ablative zone (18). Five year survival rates of LITT for CRLM vary between 3.8%- 37%, but studies are heterogeneous in design and tumor characteristics (19;20). Additionally, this technique has logistic drawbacks and is very time consuming especially with the need for bulky equipment and strict safety precautions. Therefore, this technique is largely abandoned.

The present: Radiofrequency ablation and Microwave ablation

Hyperthermal ablation methods rely on exposure of the tumor to supranormal temperatures to achieve cell death. Tumor cells are relatively more vulnerable to hyperthermic damage than to subzero temperatures (21). Temperatures exceeding 42°C already cause low-level thermal injuries to tumor cells, but need to be applied for a significant period of time to cause irreversible damage. Increasing temperatures and the exposure time needed to cause cellular damage are inversely proportional; with higher temperatures, the exposure time for a successful ablation lessens. The minimum temperature to achieve reliable cell death is 60°C and is based on various interactions including apoptosis, microvascular damage
ischemia-reperfusion injury, Kupfer cell activation, altered cytokine production, denaturation of proteins and an altered immune response (22;23). Thermal coagulation is described > 70°C. Recently, surgical resection is being challenged by ablative therapies relying on heat.

By far, the most well-studied and clinically relevant ablation source to date for local treatment of CRLM is radiofrequency ablation (RFA). Intended as a palliative option when first developed in the 1990’s, RFA has rapidly emerged as a serious competitor in the field of (curative) CRLM treatment. The principle of RFA is based on generation of a high-frequency alternating current which causes heat, with subsequent evaporation of intracellular water which leads to irreversible cellular changes, including intracellular protein denaturation, melting of membrane lipid bilayers, and coagulative necrosis of individual tumor cells and all other cells within the ablation zone. This effect is reached by using electromagnetic waves with frequencies less than 30 MHz (usually between 375-500 kHz). This causes agitation of ions, which creates frictional heat that extends into the tissue by conduction. A probe is inserted into the center of a tumor either percutaneously using CT-guidance or surgically using IOUS. The latter can be performed by an open or laparoscopic approach. In our institution we prefer open RFA over percutaneous for the initial treatment because due to the added benefit of uncovering unsuspected disease through the use of IOUS and a potentially lower recurrence rate (24;25). After insertion of the needle, a little ‘umbrella’ is unfolded to increase the ablation zone, so a maximal diameter of 3-3.5cm can be covered. Larger tumors need multiple ablations.

During the past decade RFA has superseded other ablative therapies. Important in this matter were the results of recent literature showing that RFA can result in complete tumor clearance and an increased life-expectancy. Median and 5-year survival rates of patients with solitary hepatic metastases are reported up to 40 months and 46.5% respectively (26). Of course, this technique is especially developed for patients with metastases that are not eligible for surgical resection, and these patients usually have more than one lesion. This makes comparing both techniques hard and unreliable. However, when treating a mean of 3 lesions per patient with RFA, a 5-year survival of 18%-43% can be achieved (26-30), which seems comparable to survival rates following resection of ≥ 3 lesions of 22-38%(31;32). Few recent studies with limited patient numbers did compare surgical resection and RFA, most retrospectively. These studies are likely subject to selection bias. Taken this into account, RFA shows promising 5-year results that did not always differ significantly from surgical resection (table 3) (33). The only prospective study comparing resection with percutaneous RFA in CRLM amenable to surgery was by Otto et al. Although patients with lesions up to 5cm were included, the results are consistent with those of other studies regarding RFA: a higher rate of local tumor recurrence and shorter progression-free survival after RFA but
An important advantage of target focused treatment like RFA over surgery includes the extended co-morbidity precluding major surgery. The percutaneous approach is a benefit over surgical resection, especially in patients with techniques; 6-9% and 0-2% respectively (4). The possibility of a minimal invasive, improved survival compared to chemotherapy alone (40;41). In this thesis we investigate the role of conversion chemotherapy was described earlier in combination with surgical resection. Patients with CRLM who are initially unsuitable for any local treatment, and thus receive palliative chemotherapy, can also become candidates for RFA after downstaging of the tumour load. Literature on this matter is surprisingly scarce, but two studies report on an improved survival compared to chemotherapy alone (40;41). In this thesis we investigate the results of RFA after conversion chemotherapy with respect to (factors associated with) survival and peri-operative imaging.

Secondly, reported morbidity and mortality of RFA are low compared to other ablative techniques; 6-9% and 0-2% respectively (4). The possibility of a minimal invasive, percutaneous, approach is a benefit over surgical resection, especially in patients with extended co-morbidity precluding major surgery.

An important advantage of target focused treatment like RFA over surgery includes the

<table>
<thead>
<tr>
<th>Article</th>
<th>Technique</th>
<th>No of patients</th>
<th>3yr survival</th>
<th>5yr survival</th>
<th>p-value</th>
<th>Median survival (months)</th>
<th>LSR (%)</th>
<th>Complications (%)</th>
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<tr>
<td>Berber et al 2008 (27)</td>
<td>Surgery</td>
<td>90</td>
<td>-</td>
<td>40</td>
<td>.35</td>
<td>57</td>
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<td>31.1</td>
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<tr>
<td></td>
<td>RFA</td>
<td>68</td>
<td>-</td>
<td>30</td>
<td></td>
<td>34</td>
<td>16</td>
<td>2.9</td>
</tr>
<tr>
<td>Lee et al 2008 (35)</td>
<td>Surgery</td>
<td>116</td>
<td>-</td>
<td>65.7</td>
<td>.227</td>
<td>44.7</td>
<td>6.9</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>RFA</td>
<td>37</td>
<td>-</td>
<td>48.5</td>
<td></td>
<td>40.0</td>
<td>29.</td>
<td>NA</td>
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<tr>
<td>Hur et al 2009 (36)</td>
<td>Surgery</td>
<td>42</td>
<td>70</td>
<td>60</td>
<td>.026</td>
<td>-</td>
<td>9.5</td>
<td>14.3</td>
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<tr>
<td></td>
<td>RFA</td>
<td>25</td>
<td>50.1</td>
<td>60</td>
<td></td>
<td>-</td>
<td>5</td>
<td>28</td>
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<td>Reuter et al 2009 (37)</td>
<td>Surgery</td>
<td>192</td>
<td>-</td>
<td>23</td>
<td>NS</td>
<td>36.4</td>
<td>2</td>
<td>29</td>
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<tr>
<td></td>
<td>RFA</td>
<td>66</td>
<td>-</td>
<td>21</td>
<td></td>
<td>27</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>McKay et al 2009 (38)</td>
<td>Surgery</td>
<td>58</td>
<td>-</td>
<td>43</td>
<td>.021</td>
<td>45.6</td>
<td>7</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>RFA</td>
<td>43</td>
<td>-</td>
<td>23</td>
<td></td>
<td>31.2</td>
<td>60</td>
<td>43</td>
</tr>
<tr>
<td>Otto et al 2010 (34)</td>
<td>Surgery</td>
<td>28</td>
<td>67</td>
<td>51</td>
<td>.721</td>
<td>-</td>
<td>4</td>
<td>36.6</td>
</tr>
<tr>
<td></td>
<td>RFA</td>
<td>82</td>
<td>60</td>
<td>48</td>
<td></td>
<td>-</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Schiffmann et al 2010 (39)</td>
<td>Surgery</td>
<td>94</td>
<td>81</td>
<td>65</td>
<td>.005</td>
<td>112.7</td>
<td>2.1</td>
<td>48.2 (death 2.1)</td>
</tr>
<tr>
<td></td>
<td>RFA</td>
<td>46</td>
<td>64</td>
<td>42</td>
<td></td>
<td>50.2</td>
<td>11</td>
<td>40</td>
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localized destruction of target tissue alone and preservation of surrounding viable liver tissue, thereby making it possible to treat multiple, bilobar, lesions (>10) in one session.

However, RFA and surgery should not be seen as two detached entities that only compete with each other and the one should not try to replace the other. On the contrary, RFA is an addition to surgical resection and combined, RFA can even extend the possibilities for surgery.

The main disadvantage of RFA is the risk of a local site recurrence, which indeed occurs more frequently than after resection. This is in fact a matter of concern, with local recurrence rates reported between 3.6-40%, compared to 2-5% and seldom 9.5% after resection, depending on the size and location of the lesion (4,33). This risk is increased for larger lesions and for tumors located near large blood vessels, since heat can be lost to the flowing blood; the so called ‘heat-sink’ effect. Lesions <2cm are hardly susceptible for this problem, but with 40% the recurrence rate after RFA of lesions >5cm is unacceptably high. To overcome this problem when treating larger tumors, a new technique has been developed: microwave ablation.

Microwave is developed based on the major principles of RFA and is the most recent development in the thermal ablation of (liver) tumors. Initially developed by Tabuse as a haemostatic technique following resection, microwave ablation is now considered a therapy in its own right (42). It also depends on electromagnetic energy but in a higher frequency than RFA (900 MHz to 2.4 GHz). This causes MWA to be more ‘aggressive’ than RFA. This presents three advantages. The generated heat is more uniformly distributed and achieves higher intra-tumoral temperatures throughout the ablation zone. This means MWA is more effective than RFA on various hepatic tumors larger than 5cm in diameter(16). Capitalizing on this principle, MWA is less sensitive to heat-sink effects than RFA (43). Additionally, a single ablation of MWA takes far less time than an equivalent RFA ablation. This also has its drawback, because a larger ablation zone considerably increases the risk of collateral damage to vessels or bile ducts. The indication for this technique is therefore highly dependent on the peripheral localization of the tumor.

Studies comparing ablation site recurrence rates report 6% and 20% for MWA and RFA respectively in a matched-cohort analysis after a median follow-up of 18 months (44). Being a relatively new technique, the first mid- to long-term survival rates of relatively small study populations are just being published. Three and 5 year survival rates vary between 36-57% and 14-32%, respectively (45-47). More long term results are eagerly awaited.
We believe a considerable part of the 6000 irresectable patients can be candidates for RFA or MWA. Lack of data unfortunately precludes substantiating the exact amount of patients who can benefit of RFA with or without chemotherapy with solid numbers.

**The future: Irreversible electroporation?**
To overcome two limitations of thermal ablation, the heat sink effect and the risk for collateral damage to surrounding structures, the search for alternatives is ongoing. Recently, a novel, non-thermal, ablation technique that addresses these limitations was introduced: irreversible electroporation (IRE).

**Some history**
Electroporation involves the permeabilization of cell membranes through the application of an electric field and was first observed in the 1970’s (48;49). Depending on the amplitude and duration of the pulses the opening of the cell membrane is reversible after which the cell survives, or irreversible after which the cell dies through loss of homeostasis. It is known in the literature that cell death can occur when the field potential across a mass of tissue reaches around 600-800 V/cm (50). Since the late 1980’s therapeutic electroporation has been studied in pre-clinical studies as a minimally invasive technique to introduce small drugs into cells in specific areas of the body (51;52). For example electrochemotherapy, where a chemotherapeutic drug is injected in the body while electrodes are placed around the targeted area and electric pulses generate reversible permeability of the cellular membrane, facilitating the drug to enter the cells (53). For this purpose, irreversible electroporation is considered an undesirable side effect and research was directed towards the determination of the upper limit of electrical parameters to obtain reversible permeability. However, in recent years IRE has proven to have several benefits in cancer treatment. Extensive in vitro studies demonstrated the ability of IRE to eradicate bacteria and amoeba in the decontamination process of water (54). In 2004, Rubinsky et al were the first to hypothesize on the benefits of IRE for cancer patients (50).

**Where we are now**
IRE is based on the pulsatile application of a strong electric field (1,000-1,500 V/cm) between electrodes inserted around the tumor. These electrical pulses alter the existing transmembrane potential. As a consequence, nanoscale defects appear in the lipid bilayer of the cell membrane. Depending on the amplitude and duration of the pulses, the permeability of the cell membrane is reversible after which the cell survives, or irreversible after which the cell dies through loss of homeostasis (55). Although IRE is believed to effectively destroy all cells within the ablation zone, the non-thermal nature of IRE results in...
relative preservation of the extracellular matrix. Pre-clinical studies show that, as a result, the structural integrity of inlaying and adjacent tissue structures like blood vessels, bile ducts, nerves and other vital structures is largely preserved (56-58). Therefore, the technique possibly provides a solution for treatment of tumors located in the hilum of the liver.

The NanoKnife (AngioDynamics, Queensbury, NY), a low-energy direct-current electroporation device, is currently the only commercially available IRE system. It consists of a generator, footswitch, and 19 standard wire gauge unipolar needle electrodes with an active working length that can be varied in length from 5mm to 40mm (59). To prevent pulse-induced arrhythmias, the Accusync electrocardiogram (ECG)-gating device (model 72; Milford, Connecticut) is connected to a five-lead ECG, which synchronizes pulse delivery within the refractory period of the heart (the R-wave on the ECG). Just before the start of IRE delivery, complete muscle relaxation must be ensured to prevent generalized muscle contractions. Electroporation can be performed during open laparotomy using IOUS or percutaneous using CT-fluoroscopy and US-guidance.

Being a novel technique, results on morbidity and survival are scarce and the technique is only available in a few specialized centers worldwide. The results of the first few human studies with IRE are promising (59-62). However, due to small patient numbers, heterogeneous inclusion criteria and a relatively short follow-up period, extrapolation to general clinical practice is preliminary. Furthermore, the effects of IRE on human cancer cells and the mechanism of cell death remain poorly understood. However, the local application of an excessive electric field is a potential hazard, since the pulses could induce cardiac arrhythmias and severe muscle contractions. Therefore the patient population that is currently treated with IRE is highly selected.

Follow-up imaging after ablation

The main area of concern regarding local ablation of CRLM is the risk of developing a local site recurrence (LSR). Follow-up imaging is the only tool we have for detection of recurrences. Intensive follow-up may be worthwhile as early detection may increase the effect of repeated (minimal invasive) local treatment. Currently, contrast enhanced computed tomography (ceCT) is most widely used to monitor post-ablative lesions for remnant and/or recurrent disease. A general shortcoming of follow-up with this imaging modality is the presence of post-ablation effect; reactive tissue around the ablated lesion which can often not be distinguished from viable tumor tissue at a single
scan without prove of lesion growth (63).

The present: PET-CT

Literature suggest a beneficial role of fluorine-18 deoxyglucose positron emission tomography (FDG-PET) for assessing treatment response after RFA (24;25). Instead of traditional anatomic imaging, it visualizes glucose metabolism of tumor cells. Since metabolism is increased in tumor sites, FDG-PET has proven a valuable tool to detect malignancies throughout the body, unaffected by distorted anatomy and with a higher sensitivity compared to conventional imaging (64;65). Unfortunately, FDG-PET lacks the anatomical reference and has a low spatial resolution (detection rate > 6mm) and therefore is less accurate in determining the exact location of the tumor. The images of the FDG-PET can be combined with CT to provide accurately fused functional and morphological data sets in a single session (66).

Several studies have looked at the utility of PET-CT in the follow-up after RFA treatment of the liver metastases. The results showed a superiority of PET-CT in identifying local recurrences compared with contrast enhanced CT with a sensitivity and specificity of PET-CT of 95% and 100% compared to 83% and 100% of contrast enhanced CT (63;64;67;68).

The benefit of multi-detector CT is the ability to provide precise 3-dimensional information about the ablation zone within a reasonably short time. In addition, the PET-CT is widely available throughout the country. However, PET-CT has intrinsic disadvantages of radiation hazards and occasionally an adverse reaction to the intravenous contrast media. Considering that routine follow-up intervals after RFA are as short as 3-4 months in the first year with the use of ceCT, this could be harmful to the patients (69).

The future: PET-MRI?

Liver MRI outperforms CT in the detection of small hepatic metastases (<1 cm) and has proven of benefit in patients which are treated with chemotherapy, without additional radiation load. Dynamic contrast-enhanced MRI (with gadolinium) techniques may improve diagnostic accuracy in detecting local recurrence after RFA (63;70). Diffusion-weighted (DW) MRI measures cellular integrity and motion of water molecules, without the use of contrast. Viable tumors are high in cellularity. These cells have an intact cell membrane that restricts the mobility of water molecules. Conversely, cellular necrosis causes increased membranous permeability, which allows water molecules to move freely and thus causes a marked increase in the diffusion coefficient (71). Several groups are studying the benefit of the use of contrast agents in MRI scanning. So far, results on sensitivity for detection of CRLM in both contrast enhanced (with gadolinium) as in un-enhanced DW-MRI (63;70;72-74) are

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comparable. A disadvantage of MRI is the length of scanning and the possibility of claustrophobic reactions.

Integrated PET-MRI is a relatively new imaging modality, combining the advantages of FDG-PET with the ability of MRI to detect small tumors without radiation exposure in one imaging session. Recent results of Donati et al show that the sensitivity of fused FDG PET and 1,5T MRI in the detection of hepatic metastases is higher than of PET-CT (75). The first studies reporting on the value of PET-MRI are starting to emerge, however reports on the comparison of different imaging modalities to PET-MRI are scarce. To the best of our knowledge, no results are yet available that compares PET-CT and PET-MRI in the follow-up after RFA or MWA.
OUTLINE OF THE THESIS

This thesis consists of two parts. In the first part, we evaluated the results of patients treated with RFA for colorectal liver metastases as the technique currently most often used and the use of PET-CT in the follow-up. In part II, we aimed to have a peek into the future, describing a new technique for tumor ablation and follow-up that can possibly overcome limitations of the techniques currently used.

PART I: THE PRESENT

In Chapter 2, the incidence of local site recurrences that can occur after RFA of CRLM is examined, along with the effect of treatment of these local site recurrences.

Systemic chemotherapy is able to convert colorectal liver metastases (CRLM), initially unsuitable for any local treatment, to locally treatable disease. Chapter 3 describes the results of patients with CRLM initially unsuitable for any local treatment that could be treated with RFA after effective downstaging by chemotherapy. We also identified factors associated with recurrences and survival.

To optimize the results of RFA, pre- and perprocedural visibility of the tumors is essential. Combining transcatheter arterial portography (CTAP) or transcatheter hepatic arteriography (CTHA) is a new use for an existing technique during percutaneous RFA and this is examined in Chapter 4.

There are several methods to evaluate treatment effect after RFA of CRLM. Currently, the PET-CT has the highest sensitivity and specificity in this regard. In Chapter 5, we studied the aspect of local site recurrences on PET-CT with special interest to the interval between treatment and recurrence. We provided suggestions for uniform timing and image interpretation.

PART II: THE FUTURE

A new technique for local ablation of CRLM is called irreversible electroporation. As an introduction to this novel technique for the ablation of CRLM, Chapter 6 is a systematic review of all literature currently available on safety, feasibility and efficacy of irreversible electroporation.

The basis of an effective technique to eradicate cancer lies in its ability to achieve cell death in a tumor. This is still largely unknown for irreversible electroporation. Therefore, we designed the COLDFIRE study; an ablate-and-resect study of CRLM treated with irreversible electroporation. This gave us the opportunity to not only evaluate safety and feasibility, but also the pathologic response. These results are presented in Chapter 7.

Irreversible electroporation relies on high voltage pulses to create cell death. To use this technique safely, an optimal informed anaesthesiologist who is aware of risks and proper precautions is required. In Chapter 8 we describe our experiences with irreversible electroporation from an anaesthesiologic point of view.

The use of PET-MRI may improve the detection rate of new small intrahepatic metastases during the follow-up after RFA of CRLM compared to PET-CT. This possibly has an influence on decision making in patients with RFA/MWA-treated CRLM and may change the way we conduct our follow-up in the future. In Chapter 9, this hypothesis is described in a prospective observational trial protocol.

Chapter 10 and 11 provide a summary of this thesis and considers future perspectives.
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