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Summary and general conclusions

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Summary

The aims of this thesis, concerning patients with malignant liver tumours, were twofold. First to evaluate feasibility, analyze clinical applications and to technically improve dynamic contrast-enhanced computed tomography (DCE-CT) and dynamic contrast-enhanced ultrasonography (DCE-US) for patients with liver cancer. Secondly to assess the long term results after radiofrequency ablation (RFA) and to evaluate safety and local effectiveness of a novel bipolar RFA system for patients with liver cancer.

Chapter 1 provides a general introduction to the thesis, with a short description of prevalence, staging and treatment options for patients with primary and secondary liver cancer.

In Chapter 2 dynamic contrast-enhanced CT (DCE-CT) proved feasible to monitor changes of perfusion induced by a combination of two powerful angiogenesis inhibitors (AZD2171 and gefitinib). Patients were examined, just before and every 4-6 weeks after starting therapy. Following intravenous injection of a contrast-agent, dynamic image acquisition was obtained at the level of a selected tumour location. To calculate perfusion, the maximum-slope-method was used. Pre-treatment average perfusion for extra-hepatic masses was 84ml/min/100g, for liver masses an arterial perfusion of 25ml/min/100g and a portal perfusion of 30ml/min/100g was found. After administration of AZD2171 and gefitinib, in extra-hepatic masses an initial decrease in perfusion of 18% was followed by a plateau and in liver masses an initial decrease of 39% within the lesions and of 36% within a rim region surrounding the lesions was followed by a tendency to recovery of hepatic artery flow.

Chapter 3 shows that adding linearly co-registered subtraction-CT images to a conventional 4-phase-CT protocol does not improve detection of colorectal liver metastases (CRLM). In 50 patients suspected of CRLM a routine pre-operative 4-phase-CT-scan of the upper abdomen was obtained. All 12 possible image subtractions between two different phases were constructed applying 3D-image-registration to decrease distortion artifacts induced by differences in inspiration volume. Two experienced radiologists initially reviewed the conventional 4-phase-CT for malignant and/or benign appearing lesions and at least one-month hereafter the same 4-phase-CT now including the subtracted images. The results were compared to a combination of surgical exploration and intraoperative ultrasound. Although an additional number of 31 malignant appearing lesions were detected on the subtraction images, none proved to represent a true CRLM. Interobserver agreement (κ) decreased from 0.627 (good) to 0.418 (fair).
In Chapter 4 the feasibility for detection of CRLM using a novel in-house developed total-liver-volume perfusion-CT (CTP) technique, with 3D-image-fusion, was evaluated. Twenty patients with liver metastases underwent helical-CT of the total-liver-volume before and 11-times after intravenous contrast-material injection. To decrease distortion artefacts all phases were co-registered using 3D-image-fusion before creating blood-flow-maps. Lesion based sensitivity and specificity for liver metastases of first the conventional 4-phases (unenhanced, arterial, portal-venous and equilibrium) and later all 12-phases including blood-flow-maps was determined as compared to intraoperative ultrasound and surgical exploration. Arterial and portal-venous perfusion was calculated for normal appearing and metastatic liver tissue. Total-liver-volume perfusion values were comparable to studies using single-level CTP. Compared to 4-phase-CT, total-liver-volume CTP increased sensitivity from 78.4% to 89.2% (p=0.046) and specificity from 78.3% to 82.6% (p=0.074). Total-liver-volume CTP is a non-invasive, quantitative and feasible technique. Preliminary results suggest an improved detection of liver metastases for CTP compared to 4-phase-CT.

Chapter 5 shows the possibility of this total-liver-volume DCE-CT technique in demonstrating treatment site recurrence of liver metastases after RFA. Eleven patients considered to be at an increased risk for local RFA-site tumour recurrence received both a positron emission tomography (PET) and a CTP scan. In all cases the CTP derived blood flow maps fully paralleled the PET images in showing either the absence (9/13 lesions) or presence (4/13 lesions) of local RFA-site recurrence. Marginal lesions with a high hepatic arterial perfusion (>50ml/min/100g) and a low portal venous perfusion (<10ml/min/100g) represented recurring vital tumour tissue (p<0.05). Total liver volume CTP seems feasible for early detection and localization of treatment site recurrence after RFA.

Chapter 6 describes a correlative study to evaluate the correlation between dynamic-contrast-enhanced computed tomography (DCE-CT) and first-pass dynamic-contrast-enhanced ultrasound (DCE-US) of normal appearing liver parenchyma and of CRLM. Thirty patients with CRLM underwent DCE-CT and US. To obtain DCE-US reproducibility measurements double contrast-passages (2x2.4ml Sonovue i.v.) were acquired. From several DCE-US-derived perfusion indices, the slope (CV(a)) scored best with a reproducibility concordance correlation coefficient (CCC) ranging from 0.75–0.93 and overall highest correlation to DCE-CT-derived variables (r=0.52–0.73). The DCE-US-based tumour-to-liver perfusion gradient (G) also showed a low test-retest variability and moderately correlated to DCE-CT-based G (CCC=0.87–0.92; r=0.57–0.59). DCE-US-based CV(a) and tumour-to-liver perfusion gradient G correlated best with DCE-CT perfusion values. However, both techniques cannot be used interchangeably. DCE-
US should be restricted for studies in which a considerable change in perfusion is expected and for patients with a relatively high tumour blood-flow at baseline.

In chapter 7 the results of intraoperative ultrasound (IOUS) were compared with preoperative multiphase helical CT scanning and the impact of IOUS on surgical decision-making was evaluated. One-hundred consecutive patients underwent open surgery for colorectal liver metastases within 4 weeks after preoperative imaging. The findings on pre- and intraoperative imaging and surgical exploration were carefully noted regarding number, site and size of the hepatic lesions. The preoperative surgical plan was compared to the final surgical treatment. In 32% IOUS differed from preoperative data. In 20 cases IOUS identified more metastatic lesions. In 4 patients intraoperative findings identified less hepatic lesions. IOUS alone altered the surgical strategy 35 times during 117 treatments (30%). In nearly all (92%) cases, discrepancy between the preoperative CT-scan and IOUS resulted in a change of surgical treatment. Therefore it was concluded that the intraoperative use of ultrasonography remains of crucial importance with high consequence on surgical therapy.

In Chapter 8 the long-term results and prognostic factors of RfA for irresectable CRLM in a single center with >10-years of experience were retrospectively analyzed. One-hundred patients with irresectable histologically proven CRLM (sizes 0.2–8.3cm; mean 2.4cm) underwent a total of 126 RfA sessions (237 lesions). Mean follow-up time was 29.0 months (range 6-93 months). No direct procedure-related deaths were observed; two patients died in the first two weeks after RfA due to a massive myocardial infarction and pulmonary embolism respectively. Major complications were present in 11 patients (hemorrhage 1, abscess 4, cholangitis 1, gastric perforation 1, skin burns 2, lung embolus 1, pleural effusion 1). Local RfA-site recurrence was 12.7% (n=30/237) (for tumour-diameters <3cm, 3-5cm and >5cm this was respectively 5.6%(n=8/143), 19.5%(n=15/77) and 41.2%(n=7/17)). Centrally located lesions recurred more often than peripheral ones (21.4%(n=21/98)) versus 6.5%(n=9/139); p=0.009). Including additional treatments for recurring lesions when feasible, patient and lesion based local control reached 54% versus 93%. Mean survival-time from RfA was 56 (95%CI 45-67) months. Overall 1, 3, 5 and 8 year-survival from RfA was 93%, 77%, 36% and 24%. RfA for irresectable CRLM was concluded to represent a safe and effective treatment option, which can provide long-term survival-benefit comparable to surgical resection. Factors determining success were lesion-size, number and location of lesions.

Chapter 9 describes the first clinical experiences with a novel bipolar plan-parallel expandable system for large-size liver tumours. Although RfA is a promising method for local treatment of liver malignancies, with conventional monopolar systems
recurrence rates for large size tumours \( \geq 3.5\text{cm} \) remain high. Eight consecutive patients with either irresectable CRLM (6 patients), carcinoid liver metastases (1 patient) and hepatocellular carcinoma (HCC) of \( \geq 3.5\text{cm} \) were treated with bipolar RFA during laparotomy with ultrasound guidance. Early and late, major and minor complications were recorded. Local success was determined on 3-8 months follow-up CT scans of the upper abdomen. Nine CRLM, one carcinoid liver metastases and one HCC (3.5–6.6cm) were ablated with bipolar RFA. Average ablation time was 16 minutes (range 6-29 min.). Two patients developed a liver abscess which required re-laparotomy. In both cases bowel surgery during the same session probably caused bacterial spill. There were no mortalities. The patients were released from hospital between 5 and 29 days after the procedure (median 12 days). The 6-12 months follow-up PET-CT scans showed signs for marginal RFA-site tumour recurrence in two patients with CRLM (2/11 lesions). Preliminary results suggest bipolar RFA to be a relatively safe, fast and feasible technique which seems to improve local control for large size hepatic tumour ablation.

**General conclusions**

Although in patients with CRLM, image subtraction derived from conventional 4-phase upper abdominal CT did not reveal any additional metastases and lead to an overestimation of the number of metastases, adding blood flow maps derived from a 12-phase dynamic contrast-enhanced CT scan (DCE-CT) to the native CT images did improve sensitivity and proved feasible for early detection and exact localization of local RFA-site recurrence. Despite these and other technical developments in pre-operative imaging the intraoperative use of ultrasonography remains of crucial importance for local therapy.

Furthermore, DCE-CT was able to demonstrate and quantify significant decreases in tumour perfusion after anti-angionesis therapy. Since DCE-US derived perfusion values correlated only moderately to DCE-CT perfusion parameters, both techniques cannot be used interchangeably. DCE-US should be restricted for studies in which a considerable change in perfusion is expected and for patients with a relatively high tumour blood-flow at baseline.

Image guided RFA for irresectable CRLM represents a safe and effective treatment option, which improves long-term survival and can provide full curation in a considerable percentage of patients, comparable to surgical resection. Preliminary results show that bipolar RFA for large-size liver tumours is a relatively safe and feasible technique which seems to improve local control.