Optimal Preoperative Examination of Colorectal Liver Metastases: Assessment of the diagnostic performance of CT, PET/CT, MRI and Intraoperative Ultrasound

Doctoral thesis by
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ALL THIS IS A DREAM.

Still examine it by a few experiments.

Nothing is too wonderful to be true, if it be consistent with the laws of nature.

Michael Faraday 1849 (1791-1867)
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Anselm Schulz

Oslo University Hospital, 2016
<table>
<thead>
<tr>
<th>ABBREVIATIONS</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADC</td>
<td>Apparent diffusion coefficient</td>
</tr>
<tr>
<td>AP</td>
<td>Anterior to posterior</td>
</tr>
<tr>
<td>CCA</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>CE-IOUS</td>
<td>Contrast-enhanced intraoperative ultrasound</td>
</tr>
<tr>
<td>ce-PET/CT</td>
<td>PET with enhanced CT</td>
</tr>
<tr>
<td>CEUS</td>
<td>Contrast-enhanced ultrasound</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence intervals</td>
</tr>
<tr>
<td>CRLM</td>
<td>Colorectal liver metastasis</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DWI</td>
<td>Diffusion weighted imaging</td>
</tr>
<tr>
<td>FBP</td>
<td>Filtered backprojection</td>
</tr>
<tr>
<td>FDG</td>
<td>$^{18}$F-fluoro-2-deoxy-D-glucose</td>
</tr>
<tr>
<td>FH</td>
<td>Feet to head</td>
</tr>
<tr>
<td>FLC</td>
<td>Fibrolamellar carcinoma</td>
</tr>
<tr>
<td>FNH</td>
<td>Focal nodular hyperplasia</td>
</tr>
<tr>
<td>FOBТ</td>
<td>Fecal occult blood testing</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of view</td>
</tr>
<tr>
<td>Gd-BOPTA</td>
<td>Gadobenate dimeglumine</td>
</tr>
<tr>
<td>Gd-DTPA</td>
<td>Gadopentetic acid</td>
</tr>
<tr>
<td>Gd-EOB-DTPA</td>
<td>Gadoxetic acid / Gadoxetate disodium</td>
</tr>
<tr>
<td>GLUT</td>
<td>Glucose transport proteins</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>IOUS</td>
<td>Intraoperative ultrasound</td>
</tr>
<tr>
<td>LOR</td>
<td>Line of response</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
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<tr>
<td>MDCT</td>
<td>Multidetector-row CT</td>
</tr>
<tr>
<td>MIP</td>
<td>Maximum intensity projection</td>
</tr>
<tr>
<td>MPP</td>
<td>Mean positive pixels</td>
</tr>
<tr>
<td>MRCP</td>
<td>Magnetic resonance cholangiopancreatography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>NSA</td>
<td>Number of signal averages</td>
</tr>
<tr>
<td>OSEM</td>
<td>Ordered subset expectation maximization</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emissions tomography</td>
</tr>
<tr>
<td>PET/CT</td>
<td>Positron emissions tomography combined with CT</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>R0 resection</td>
<td>Resection of all tumor deposits; no cancerous cells are seen microscopically in the resection surface</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response evaluation criteria in solid tumors</td>
</tr>
<tr>
<td>RFA</td>
<td>Radio frequency ablation</td>
</tr>
<tr>
<td>rgPET/CT</td>
<td>PET/CT combined with respiratory gating</td>
</tr>
<tr>
<td>RL</td>
<td>Right to left</td>
</tr>
<tr>
<td>RS</td>
<td>Reference standard</td>
</tr>
<tr>
<td>SPIO</td>
<td>Superparamagnetic iron oxide</td>
</tr>
<tr>
<td>standard+rgPET/CT</td>
<td>PET/CT with and without respiratory gating</td>
</tr>
<tr>
<td>SUV</td>
<td>Standardized uptake value</td>
</tr>
<tr>
<td>SUVmax</td>
<td>Maximum standardized uptake value</td>
</tr>
<tr>
<td>TE</td>
<td>Time to echo</td>
</tr>
<tr>
<td>TOF</td>
<td>Time of flight</td>
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<td>TR</td>
<td>Time to repeat</td>
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SUMMARY

**Background:** Metastases from colorectal cancer are in many cases confined to the liver. Metastases are frequent and in many cases decisive for the prognosis. Recent developments have led to an increasing number of available treatment options. However, only surgical resection of all the CRLM has the potential of long-term survival or even cure. The choice of a suitable treatment is therefore of great importance and is usually based on imaging findings. Liver imaging in patients with CRLM must ensure the identification of all CRLM with the highest possible accuracy. However, several imaging modalities are available and the optimal diagnostic approach has yet to be determined.

**Purpose:** Our 1st study evaluated the contribution of CE-IOUS as last imaging modality prior to liver resection for the staging of CRLM and its impact on operation strategy. In the 2nd study we evaluated the preoperative diagnostic performance of CT, MRI and PET/CT in patients with CRLM scheduled to liver resection. In the 3rd study, a novel method for rgPET/CT and its impact on the preoperative diagnostic performance for the detection of CRLM was investigated.

**Materials and methods:** In the 1st study, 86 patients underwent 97 open liver resections for CRLM. The patients were retrospectively evaluated. Preoperative CT was available for all patients and MRI was available in 72%. CE-IOUS findings were compared with preoperative findings and the initial planned operation strategy with the finally performed operation. In the 2nd study, 46 patients scheduled for liver resection for suspected CRLM were prospectively included. Multiphase CT, Gd-EOB-DTPA-enhanced MRI with diffusion-weighted imaging and PET/CT were performed in all patients. Each examination was evaluated by two independent and blinded readers. The diagnostic performance for CRLM was determined for each modality and compared with each other. In the 3rd study, 43 patients with both PET/CT
and rgPET/CT available were included from the same patient cohort as patients from the 2nd study. The preoperative impact of rgPET/CT on the diagnostic performance of PET/CT for CRLM was evaluated. McNemar test was used to identify significant differences between the modalities in the 2nd and 3rd study. Mann–Whitney test was used for comparisons of SUV data in the 3rd study. The reference standard was histopathological confirmation or if not available follow-up in all studies.

Results: In the 1st study, CE-IOUS changed the initial operation strategy in 30%, resulting in a smaller resection in 11%, larger resection in 13% and 5% were found inoperable. In 17 patients additional 31 CRLM were identified. In the 2nd study, MRI had the highest sensitivity both overall and for CRLM <10 mm (P<0.001). The overall sensitivity and PPV on per-lesion basis were 68%/89% for CT, 90%/82% for MRI and 61%/97% for PET/CT. For CRLM <10 mm it were 16%/54% for CT, 74%/64% for MRI and 9%/57% for PET/CT. In the 3rd study, the combined sensitivity and PPV of standard PET/CT + rgPET/CT was 68%/94% which was significantly higher than for standard PET/CT (P=0.002) or rgPET/CT (P=0.031) alone.

Conclusion: CE-IOUS should be performed prior to liver resection for CRLM to optimize operation strategy. MRI has the highest sensitivity for CRLM, particularly for CRLM <10 mm. PET/CT with respiratory-gating has the potential to improve the diagnostic performance of standard PET/CT for CRLM.
1 BACKGROUND

1.1 LIVER MALIGNANCIES AND DIAGNOSTIC OPTIONS

In consideration of the large amount of both primary and secondary liver tumors, the most important aspects of liver imaging, beside lesion detection, is lesion characterization. Liver lesions can be divided in two main categories, benign and malign. Malignant liver lesions usually require rapid, tumor specific treatment. Benign liver lesions usually require no further treatment and only in rare cases treatment might be necessary, e.g. large hemangiomas, adenomas complicated with abdominal bleeding or in case of adenomas if malignant transformation is suspected. The increasing availability of tumor specific treatment options like different surgical approaches, ablative techniques, radiochemotherapy or molecularly targeted therapies underlines the high importance of correct lesion characterization. Since benign liver lesions only rarely require treatment, they are of lesser clinical relevance and beyond the scope of this study.

In this study different imaging modalities and their diagnostic performance for CRLM were evaluated. CRLM are the most common secondary liver tumors due to the portal venous drainage of the primary colorectal cancer. However, in clinical routine it might be difficult to differentiate between primary and secondary malignant liver tumors. Primary hepatic malignancies are less common than secondary malignancies. They are far more common in adults than in children where their appearance is very rare. Correct characterization of liver lesions with a single modality approach may be difficult but a multimodality approach can often lead towards the correct final diagnosis [1]. A short overview of primary malignant liver tumors and their imaging features is given below.
Hepatocellular carcinoma (HCC)

HCC is the most common primary malignancy of the liver and up to 80% of all HCCs develop in patients with liver cirrhosis [2]. Worldwide, it is the fifth most common type of cancer and the third most common cause of death from cancer [2, 3]. Alcohol abuse and hepatitis B and C virus infections, causing liver cirrhosis, are the most common risk factors for developing HCC. The concomitant presence of two or more risk factors for HCC can significantly increase the risk for developing HCC, especially if viral hepatitis B or C infection is involved. In Eastern countries, where most of the hepatic infections are caused by hepatitis B virus infections, up to 30% of patients with chronic disease develop HCC without cirrhosis [3]. However, for many patients the cause for the development of HCC remains unknown [4, 5] and up to 40% of patients in western countries with HCC have no history of cirrhosis. HCCs in non-cirrhotic liver tend to be solitary, encapsulated and are usually resectable with good prognosis. Alpha-fetoprotein levels are often elevated.

HCC is usually diagnosed by its characteristic appearance on contrast enhanced dynamic CT or MRI images. Increased enhancement in arterial phase and washout during portal vein/equilibrium phase are considered characteristic [6, 7]. A capsule may be seen on equilibrium phase or later imaging and can strengthen the diagnosis. CEUS has an advantage over CT and MRI by providing real-time imaging of the perfusion in suspicious lesions. This may allow a unique visualization of the typical arterial hypervascularity and late washout of HCC [1]. A recent meta-analysis by Chou et al found comparable sensitivity for CEUS, CT and MRI of about 80% [8]. GD-EOB-DTPA-enhanced MRI has probably the highest sensitivity for HCC, however its role in the diagnostic and work-up of HCC has yet to be clarified [9]. Regarding CEUS a recent discussion is ongoing and concerns have been raised about the differentiation between HCC and intrahepatic cholangiocarcinoma, where the latter may present with HCC typical enhancement patterns (early arterial enhancement followed by
The most important role of PET/CT in HCC is the detection of extrahepatic disease [13].

**Fibrolamellar hepatocellular carcinoma (FLC)**

The FLC usually develops in non-cirrhotic liver with a slow growth rate. The predominant number of all cases occurs before the age of 40 years. It is composed of neoplastic hepatocytes with extensive intratumoral fibrosis which is often arranged in parallel or lamellar cords. FLC makes up for about 1% to 8% of all HCC [14]. Differentiation between FNH and FLC is of high importance since both are seen in young adults, however only FLC requires treatment and is associated with poor prognosis if left untreated [15-17]. Reported 5-year survival rates after liver resection for FLC are about 70% [15, 17].

FLC usually has a similar enhancement pattern as HCC with intense arterial phase enhancement and may be iso- to hypoattenuating on venous or equilibrium phase images. On T1-weighted images FLC appears as heterogeneous, hypo- to isointense tumor, while it appears hyperintense on T2-weighted images. Calcifications may be seen in up to 50% of cases [18]. It has a similar appearance as FNH with a central scar and radiating fibrous threads. The main imaging features to distinguish the entities from each other are hyperintensity of the central scar on T2-weighted images and the absence of calcifications in FNH, while the contrary is seen in FLC. FLC may be isointense or slightly hypointense on postgadolinium images with a heterogeneous enhancement pattern and wash-out may be seen in delayed phases [16, 18].

**Intrahepatic cholangiocarcinoma (CCA)**

CCA is with 10-20% the second most common primary hepatic malignancy. It originates from the biliary epithelial cells. CCA can be distinguished by its growth patterns. It may present as solid intrahepatic tumor, as intra- or extrahepatic bile duct stricture with infiltration
of surrounding tissue and in some cases, as intraductal polypoid tumor or as a combination of the aforementioned appearances. For the surgical approach, the involvement or distance from the bifurcation of the hepatic duct is of main concern [19].

Dilatation of the bile ducts above the tumor is typically seen. Depending on its content of fibrosis and mucin it has a slight to pronounced hyperintense appearance compared to the normal liver on T2-weighted images [18]. On T1-weighted images CCA appears usually hypo- to isointense. On contrast-enhanced CT and MRI mass forming/exophytic CCA may appear with slight to moderate rim enhancement on arterial phase images with increasing central enhancement on later images. This is caused by gradual diffusion of the contrast media into the interstitial spaces [20]. In addition contributes the amount of fibrotic content within the tumor to the delayed contrast enhancement [20]. This feature may help to differentiate CCA from HCC, which typically presents with pronounced arterial enhancement and washout on later images [6, 7].

**Cystadenoma and cystadenocarcinoma**

Cystadenoma is a typically mucinous cystic lesion, which has malignant potential to transform into cystadenocarcinoma in about 10% of cases. However, also serous variants may occur. It is predominantly found in females where ovarian stroma may be present [21]. The tumor accounts for about 5% of all cystic liver lesions originating from the bile ducts. Cystadenomas typical features include multilocularity, internal septa, a fibrous capsule and relative large size at detection with a mean size of 12 cm as reported earlier [22]. The differentiation between cystadenoma and cystadenocarcinoma may be difficult but is of lesser clinical importance since both entities require complete surgical resection [21, 23].

Cystadenomas are T2 hyperintense and may have varying signal on T1-weighted images caused by blood or protein rich content [21]. Contrast enhancement of the solid tumor
components may occur and is better evaluated on MRI than on CT as well as its relation to the bile ducts [21]. Intramural or septal nodules/ wall thickening are indications for the present of a Cystadenocarcinoma [22].

**Hepatic angiosarcoma**

Hepatic angiosarcoma is a rare tumor, which originates from endothelial cells and accounts for <2% of primary hepatic tumors [24]. However, it is the most common tumor from mesenchymal origin in adults [24]. Hepatic angiosarcoma was first described by Block in 1974 [25]. The tumor is usually related to carcinogen exposure like Thorotrast (thorium dioxide), vinyl chloride or arsenic and has a poor prognosis [26]. Liver biopsy should be avoided due to the high risk of massive hemorrhage.

Hepatic Angiosarcoma may have hypointense signal on T1 and hyperintense signal on T2 while focal areas of high signal intensity within the tumor are associated with intratumoral hemorrhage [27]. The tumor may appear as multiple nodules, a single dominant mass or as a diffuse infiltrating lesion [28]. Fluid-fluid levels may be present. On multiphase contrast-enhanced CT and MRI, a progressive, heterogeneous peripheral enhancement pattern may be observed [26, 28]. However, multiple nodules may also appear hypoattenuating on contrast-enhanced CT. Differentiation between hepatic angiosarcoma and hemangioma may be difficult and a history of exposure to toxins or rapid tumor progression may lead to the correct diagnosis [26, 27].

**Hepatic epithelioid hemangioendothelioma**

Hepatic epithelioid hemangioendothelioma is a very rare, vascular malignant tumor, which was first described by Ishak et al. in 1984 [29]. It is a low-grade tumor, which is usually discovered incidentally. Histopathological the tumor contains epithelial and dendritic cells.
According to the growth pattern of the tumor, it is possible to distinguish a nodular type, a coalescent type and a mixed type [30].

Hepatic epithelioid hemangioendothelioma is usually hypodense on unenhanced CT. The tumor appears hypointense on T1-weighted images and heterogeneous hyperintense on T2-weighted images [30]. The center of the lesions may be hypointense due to calcification, necrosis or hemorrhage [31]. Three different contrast-enhancement patterns are described for CT and MRI [30]. The first pattern presents as homogeneous arterial enhancement with no further enhancement on later phases. On the second pattern, arterial ring-enhancement with progressive enhancement on later phases is seen. The third pattern is described as heterogeneous moderate arterial enhancement with progressive enhancement on later phases. Other imaging features that may be observed are capsular retraction, tumor invasion of the portal veins or prominent tumor vessels, which originate from the hepatic or portal vein [30, 31].
1.2 COLORECTAL CANCER

Colorectal cancer is the third most common cancer in males and the second most common cancer in females worldwide, accounting in 2012 for 1.4 million new cases and about 700,000 deaths [32]. The incidence of colorectal cancer increases with age with a median age of about 70 years at diagnosis in western countries and a predominance in males [33]. The so-called western lifestyle is associated with high-risk / high incidence rates for colorectal cancer and the highest incidence rates are found in Europe, North America and Oceania [32]. The age-standardized incidence rates per 100,000 person-years vary by up to 10 fold (44.8 vs 4.5) between high-developed counties like Australia/New Zealand and developing countries in Western Africa [32]. Similar patterns are seen for age-standardized mortality rates for central and eastern Europe with 20.1/12.2 for males/females vs. central Africa with 3.5/2.7 for males/females in 2008 [34]. In Norway the incidence rates for colon/rectum cancer were 59.2/33.4 for males and 51.4/20.7 for females [35]. The mortality rates for colon/rectum cancer were 24.8/10.4 for males and 20.3/6.2 for females.

Risk factors for colorectal cancer include smoking, excessive alcohol consumption, high consumption of red and processed meat, obesity and diabetes. The increase in relative risk induced by these factors is in the range of 1.2 to 2.0. More severe risk factors are first-degree relatives with colorectal cancer and inflammatory bowel disease with increased relative risks greater than 2.0 [34]. On the other hand, several preventive factors like physical activity, use of hormone replacement therapy and aspirin have been identified (risk reduction of 20-30%). The most significant risk reduction has been reported for large bowel endoscopy in a screening context, with removal of precancerous lesions [36, 37].

While the incidence of colorectal cancer has varied in high-income countries during the past years, it has decrease in the United States as a result of screening and removal of precancerous
adenomas [32]. Reduced prevalence of risk factors, advancements in treatment together with screening for colorectal cancer are considered the main reasons for the worldwide trend towards declining mortality rates [38]. Holme et al. showed recently both a mortality and incidence rate reduction by colorectal screening in a Norwegian population based study, including individuals from Oslo city and Telemark county [39]. The total mortality and incidence rate reduction were 11.7 and 28.4, respectively. However, screening included only flexible sigmoidoscopy and FOBT. Therefore, the screening benefit might have been even larger if full colonoscopy/CT colonography would have been used yet at the price of increased costs and resources.

1.2.1 Prognosis

The most important prognostic factor for colorectal cancer is the stage at diagnosis. The overall 5-year relative survival rate has increased during the last years to approximately 65% in industrialized countries, in contrast to 5-year relative survival rates of less than 50% in developing countries. Reported 5-year relative survival rates in the USA for colorectal cancer were 90.3% for localized stage I-IIB, 70.4% with regional spread, stage IIC-IIIC, and drops to 12.5% with distant metastases at stage IV [40, 41]. In Norway 5-year overall survival rates for colon/rectum cancer have been constantly improved from 40.3%/42.0% in the late 70s to 62.8%/66.0% during the period 2010-14 [35]. The corresponding 5-year survival rates for different disease stages during the period 2010-14 were for colon/rectal cancer 83.5%/79.9% for localized disease, 78.4%/77.2% for regional spread and 13.6%/18.7% in case of distant metastases, respectively.

However, even in the case of distant metastases, especially if the metastases are confined to the liver, prognosis can be significantly improved if radical resection of all tumor deposits is possible. For selected patients even curative treatment may still be possible [42].
1.3 COLORECTAL LIVER METASTASES

The liver is the first and most common site for distant metastases from colorectal cancer due to the portal venous pathway [43]. Therefore, the progression of colorectal cancer can be considered as a cascade where metastatic disease confined to the liver still may represent a contained situation with potentially curable disease [44, 45]. A meticulous detection of all intra and extrahepatic tumor deposits is therefore crucial to determine the optimal and individual treatment strategy for each patient [46, 47].

1.3.1 Epidemiology of Colorectal Liver Metastases

Varying incidences of CRLM have been reported, usually between 15-30%. A recent population-based study by Manfredi et al. in France found an incidence rate for synchronous CRLM of 15% [44]. The liver was the only site of metastatic disease in 77%. An inverse correlation for synchronous CRLM at detection was found with increasing patient age, 20% of the younger patients under the age of 55 years had synchronous CRLM compared with 12% in patients of 75 years or older. Patients with synchronous CRLM were more likely to have a higher number of CRLM with involvement of larger areas of the liver compared to patients with metachronous CRLM. The incidence rate of synchronous CRLM did not change significantly between 1976 and 2000. Advances in diagnostic imaging and screening programs for early detection of the primary tumor counterbalancing each other are probably the reason for the stable incidence rate of synchronous CRLM.

In case of metachronous CRLM almost 80% occur within the first 3-years after resection of the primary tumor and are confined to the liver in about 40% [48]. Furthermore, the 5-years cumulative risk for distant metastases increased with the tumor stage, from 6% at stage I to 50% at stage III. In the study of Manfredi et al. the cumulative rate for metachronous CRLM was 4% at 1-year, 12% at 3-years and 15% at 5-years [44].
1.3.2 Course of disease and treatment options in case of CRLM

If left untreated the prognosis for patients with CRLM is very poor with median survival rates of 6 to 12 month for synchronous CRLM and almost no 5-year survivors [44, 49]. However, with the introduction and broad availability of potent chemotherapeutic drugs survival rates improved dramatically. Fluorouracil and leucovorin were the only treatment option for unresectable CRLM until 1998 with median overall survival times of approximately 8 to 12 month [50]. Kopetz et al. found that survival increased to 18 months between 1998-2000 and almost 30 months between 2004-2006 [50]. The first improvement of survival was probably the result of a more aggressive surgical approach with increased rates of liver resection for CRLM in up to approximately 20% of the patients. However, mostly metachronous CRLM were addressed by resection. The introduction of oxaliplatin, bevacizumab and cetuximab and the use of multidrug treatment regimens accounted largely for the improved survival after 2004.

1.3.3 Surgical approach

Resection of all metastases is the only treatment option with a potential chance for cure. Until now, no randomized controlled trials are available comparing surgical and conservative treatment. However, long-term survival or cure were only reported after complete resection of all CRLM and a recent retrospective study by de Ridder et al. comparing systemic therapy with liver resection concluded that resection of CRLM provides superior overall survival rates and should always be considered [46, 47, 51, 52]. In selected patients 5-year survival rates of up to 60% have been reported [53]. The still high recurrence rate after liver resection underlines the importance of parenchyma-sparing surgery which has become widely accepted [54, 55]. Parenchyma-sparing surgery not only reduces the postoperative morbidity but also increases chances for a re-resection in case of recurrence. Surgical options which have to be considered when determining operation strategy include local wedge-resection,
segmentectomy, hemihepatectomy or larger resections and combination of surgical resection with ablative techniques like e.g. RFA [47, 56]. In cases of disseminated disease with involvement of both the right and left liver lobe aggressive techniques like two-stage hepatectomy or even liver transplantation may provide a survival benefit in selected patients [52, 57, 58]. For two-stage liver resection the e.g. left liver lobe is cleared of all CRLM during the first stage. This is followed by portal vein embolization of the right liver lobe which is hopefully followed by a sufficient hypertrophy of the now disease free left liver lobe. The right liver lobe can then be resected safely during the second stage operation, leaving the patient with a sufficient hypertrophic liver remnant. Excellent surgical results require an individualized treatment strategy for each patient which is mainly based on imaging findings. Therefore, optimal preoperative imaging is an important factor for high 5-year survival rates with the demand for highest possible standards regarding an accurate identification of all CRLM and affected liver segments, their relation to anatomical structures and calculation of the future liver remnant [46, 59].

1.3.4 DIAGNOSIS OF COLORECTAL LIVER METASTASIS

The choice of the right diagnostic imaging option is of high importance and has lately become increasingly difficult due to the growing number of diagnostic modalities available. A large number of varying imaging protocols for each modality complicates these choices further. The most important common options are ultrasound, CT, MRI and PET/CT. The Norwegian guidelines for pretreatment staging of colorectal cancer suggest CT of the thorax, abdomen and pelvis as the first line modality to assess the extent of the disease [60]. According to these guidelines individual indeterminate liver lesions can be further characterized by CEUS while MRI with diffusion weighted sequences and hepatocyte specific contrast should be considered in case of multiple lesions and for the detection of small lesions. The American college of Radiology appropriateness criteria assign a higher value to PET/CT in the primary staging
BACKGROUND

especially for more advanced primary tumors and consider ultrasound of the liver to be of lesser importance [61, 62]. According to the Norwegian health authorities (“Pakkeforløp”) all necessary diagnostics and the determination of the treatment strategy have to be completed within 12 calendar days after the first patient contact with the responsible institution [60]. The complete process from receiving of the initial patient referral followed by establishing of the first patient contact, diagnostic workup and finally initiation of surgical treatment or chemotherapy must not exceed 35 days, while up to 39 days are accepted in case of radiation therapy [60].

Ultrasonography

Conventional B-mode ultrasonography is a broadly available and cheap imaging modality used for the detection of CRLM. It can be useful for primary screening, follow-up after treatment of the primary tumor or surveillance of chronic liver disease. Usually it is combined with color Doppler and tissue harmonic imaging. CRLM are usually hypoechoic lesions within the liver parenchyma. A hypoechoic ring or calcifications may be present. However, in some cases the CRLM may appear hyperechoic, which makes them difficult to distinguish from hemangiomas.

Lesions that are suspicious for CRLM on abdominal ultrasonography can be further characterized by the application of ultrasound contrast agents to increase the examinations specificity. CEUS can in many cases avoid further liver imaging with more expensive modalities and avoid radiation exposure of CT or PET/CT. Ultrasound contrast agents like SonoVue® consist of microbubbles and are strictly intravascular. CEUS makes real-time evaluation of liver blood flow possible and the characteristic enhancement pattern of liver lesions can be used for lesion characterization. Usually a contrast specific imaging software and a low acoustic power output (MI < 0.1) are used. After contrast injection CRLM show contrast wash-out on portal-venous phase and they are distinctly hypoechoic or anechoic on
later phases. This washout is independent from the arterial enhancement pattern [63]. In cases where an indeterminate lesion is first detected on CT, MRI or PET/CT, CEUS often leads to a final diagnosis. On the other hand, CEUS can also improve the overall detection of CRLM.

However, there are several factors limiting sensitivity and specificity of ultrasound for CRLM like isoechoic appearance of CRLM, limited spatial resolution of transcutaneous probes, obesity, high-lying diaphragm, interposition of e.g. the colon, uncooperative patients and examiner dependent factors. In addition, liver steatosis reduces sensitivity by diminishing contrast between liver tissue and CRLM, which appear isoechoic. Optimization of imaging procedures like the use of standardized overlapping video sweeps covering the whole liver and routine application of ultrasound contrast might help to overcome some of these issues. Nevertheless, the usually used curved 3.5 MHz probes limit the spatial resolution of transcutaneous ultrasonography. Linear probes or sophisticated intraoperative probes allow higher spatial resolutions but their depth of penetration is limited [64]. Therefore, IOUS or CE-IOUS have an excellent special resolution and can overcome most limitations of transcutaneous ultrasound but are still highly examiner dependent. IOUS and CE-IOUS are often considered the gold standard when comparing the diagnostic performance for CRLM of imaging modalities prior to liver resection. Some additional intraoperative finding of IOUS and CE-IOUS are shown in Figure 1.
Figure 1 CE-IOUS of different CRLM (red arrows) compared with corresponding preoperative CT and MRI (expected locations of CRLM on CT and MRI are marked with red circles). a-d patient with two CRLM in the right liver lobe. The larger CRLM (a and b) was clearly visible on both CE-IOUS and CT. The smaller CRLM (c and d) was only identified on CE-IOUS. e-f a CRLM was clearly identified on CE-IOUS while missed on CT. g-j four CRLM were identified on IOUS (g) and CE-IOUS (h-i) while they were missed Resovist enhanced MRI (j).
Computed Tomography

CT is usually the first line diagnostic modality and the main workhorse in staging colorectal cancer and CRLM. CT can identify intra- and extrahepatic disease and allows therefore an assessment of the complete tumor load. Due to advances in CT technique, MDCT with 40-320 rows are now broadly available which makes it possible to scan the whole liver without respiratory motion artefacts and to obtain slices on submillimeter basis. These thin slices are then usually reconstructed to 2-4 mm thick slices to improve image quality and reduce image noise. Furthermore, modern MDCT with thin slices enables isotropic voxels with possible reconstruction of images in any plane and 3D applications like liver volumetry or liver segmentation.

Different contrast phases can be distinguished according to the time before or after the application of CT contrast media and its distribution within different blood vessels and tissues. Usually precontrast, late arterial (30-35 s), portal venous (55-70 s) and delayed phase (> 180 s) are of most relevance for imaging associated with the workup of CRLM. In some cases, an early arterial phase for the preoperative arterial vascular mapping can be of interest. However, each of these phases means a new acquisition and accordingly new radiation exposure for the patients.

On unenhanced images, calcifications are easily identified and cystic lesions can be distinguished from solid lesions. About 11% of patients with CRLM may show calcifications which may be obscure on contrast enhanced images [65]. On late arterial phase images, hypervascular lesions can be identified and this may increase specificity by improving lesion characterization especially for lesions < 1 cm. Portal venous images are usually optimal to identify hypovascular lesions like CRLM. Delayed images are important for the differentiation between CRLM and hemangiomas. Hemangiomas present in most cases as hypoattenuating lesions on unenhanced images with nodular peripheral enhancement on
arterial phase images, peripheral centripetal fill-in on portal venous phase images and further
fill-in on delayed phase images. If the hemangioma is already completely filled on portal
venous or delayed phase images, it usually appears as iso- or hyperattenuating lesion. CRLM
on the contrary are mostly hypovascular lesions that often show peripheral rim enhancement
and are hypoattenuating compared to the surrounding liver tissue on portal venous phase
images. In some cases, centripetal fil-in may be present. CRLM usually show wash-out on
delayed phase images which is in contrary to hemangiomas who typically remain iso- to
hyperattenuating. It was reported by Scott et al. that dual phase CT in arterial and portal
venous phase improved the detection of CRLM, however treatment strategy was not altered
by this for any of the patients included in this study [66].
Figure 2 CT examination of a patient with two adjacent CRLM in the left liver lobe with significant FDG-uptake (red arrows). Images in axial, coronal and sagittal plane in arterial phase (a-c), portal venous phase (d-f) and delayed phase after 3 min (g-i).
**Magnetic Resonance Imaging**

MRI has evolved into an essential diagnostic modality for liver imaging. MRI allows the assessment of a variety of different tissue characteristics on T1 or T2 weighted images, detection of fat and iron by chemical shift imaging, hemodynamic characteristics after contrast application, selective imaging of hepatocytes by specific contrast agents and detection and quantification of focal diffusion restriction [67]. A general characterization of liver lesions is often possible with T1-weighted, T2-weighted, in-phase and opposed-phase sequences. Liver lesions that are isointense to hyperintense on T1-weighted images or contain lipid, detected by loss of signal intensity on opposed-phase images compared to in-phase images, are usually of hepatocellular origin [67]. Liver lesions that are isointense to the spleen on T2-weighted images are often malignant. Finally, hyperintense lesions are often nonsolid or hemangiomas and liver lesions that lose signal on in-phase images compared to opposed-phase images are often iron-containing siderotic nodules [67].

Liver MRI is usually performed on 1.5- to 3.0 T systems and routine protocols include breath-hold or navigator triggered T1 and T2 sequences with or without fat-suppression. For contrast-enhanced liver MRI, different types of contrast agents can be distinguished by their characteristic distribution within the body. They are classified as extracellular agents like gadoterate meglumine, reticuloendothelial agents like superparamagnetic iron oxide, intravascular agents like Gd-DTPA labeled dextran or albumin and hepatobiliary agents like Gd-BOPTA or Gd-EOB-DTPA. The traditionally most used contrast agents were extracellular agents which allow assessment of the hemodynamic characteristics of liver lesions similar to CT. In order to improve liver imaging reticuloendothelial and hepatobiliary agents have been developed and introduced. Reticuloendothelial agents are mainly taken up into the reticuloendothelial system of the liver and spleen. The superparamagnetic iron oxide particles cause a rapid decrease of signal intensity within normal liver tissue on T2 weighted images.
while e.g. CRLM present as bright, hyperintense lesions. To allow for a sufficient contrast uptake into the reticuloendothelial system the superparamagnetic iron oxide must be administered about 10-60 min prior to liver imaging [68].

Hepatobiliary agents are mainly taken up by hepatocytes and are excreted via the biliary system. They have similar hemodynamic characteristics to CT contrast agents during arterial, portal venous and late phase. In hepatobiliary phase, hepatocytes appear bright, hyperintense on T1 weighted images in contrast to CRLM who appear hypointense. The hepatobiliary phase begins about 10-20 min after contrast injection for Gd-EOB-DTPA while it takes up to 120 min for Gd-BOPTA [69]. Gd-EOB-DTPA is increasingly used for the detection of CRLM due to its high and rapid uptake rate into hepatocytes, its high sensitivity for CRLM and cost effectiveness in the preoperative workup of CRLM [70, 71]. Gd-BOPTA might be beneficial for lesion characterization due to later onset of the hepatobiliary phase and therefore lesser interference with late dynamic phases. This might help in some cases e.g. to distinguish between CRLM and hemangiomas.

Recent advances in DWI have evolved the method into an important tool for the detection of CRLM. Due to the high cellularity and consequently high number of cell membranes and organelles within CRLM, diffusion of water molecules is impaired compared to the surrounding normal liver. DWI is based on echo-planar imaging, usually performed as a fast single-shot technique. By calculating the ADC, it is possible to quantify the diffusion restriction. Diffusion gradient strength and duration are combined in the b-value, with higher values representing more diffusion weighting. B-values of 200-1000 are usually used for liver imaging. On diffusion-weighted images, CRLM are identified as hyperintense lesions compared to the hypointense liver or other benign lesions. However, hemangiomas may appear hyperintense on diffusion weighted images due to a strong T2 shine through effect and might be difficult to distinguish from especially cystic, mucinous or necrotic CRLM [72].
ADC-map quantifies the water molecule diffusion and lesions with real diffusion restriction like CRLM can be distinguished from e.g. benign lesions with T2 shine through.

However, the variety of different assessable parameters has resulted in many different imaging protocols for MRI. These protocols may vary significantly by the included sequences, parameters of the included sequences and as a result of this the total acquisition time. Acquisition time may be as short as about 10 min for diffusion-based protocols or up to 40-60 min if a large variety of sequences is included.
Figure 3 MRI examination of a patient with two adjacent CRLM in the left liver lobe with significant FDG-uptake (red arrows). T2 weighted image with fat suppression (a), T2 SSH (b), diffusion weighted image with b800 (c), ADC-map (d), T1 weighted image precontrast (e), arterial phase (f), venous phase (g), delayed phase after 3 min (h) and hepatobiliary phase (i). Gd-EOB-DTPA was used as contrast agent.
Positron Emission Tomography

PET detects the accumulation of a radioactive tracer in different tissues within the body. The most commonly used tracer is FDG. FDG is produced within a cyclotron by bombarding $^{18}$O with high energy protons which produces $^{18}$F-flouride ions. $^{18}$F has a short half-life of 109.8 minutes and is rapidly processed by automated chemical reactions to the final tracer FDG.

The tracer is injected via a peripheral vein and distributed within the body. Upon decay, FDG emits a positron, which annihilates with a nearby electron (about 0.3 mm distance). This annihilation emits a pair of photons in opposite directions, 180° to each other, each with an energy of 511 keV. The PET-scanner registers if two photons hit the detector ring simultaneously which indicates an annihilation along the line of response (LOR) connecting the two opposing detectors within the detector ring. During an acquisition, many annihilations are registered and the number of events along a LOR directly represents the amount of radioactivity along that LOR. The final images are then reconstructed from the raw data (sinograms) by different algorithms like FBP or OSEM.

The biological functionality is that tumor tissues have a higher metabolic and glycolytic activity than other tissues. FDG is a glucose analogue which is actively transported into the cells in competition with glucose by the GLUT. Within the cells, FDG and glucose are then phosphorylated by the enzyme hexokinase, which is the first step in the glycolytic pathway. However, unlike glucose, FDG cannot be further metabolized along the glycolytic pathway and since most cells lack the enzyme glucose-6-phosphatase FDG is trapped inside the cells until radioactive decay. Therefore, FDG will accumulate especially in tissues with a high metabolism like malignant tumor tissue. However, it is not a tumor specific uptake, since also areas of inflammation have a high FDG uptake.
PET is usually combined with a CT within the same scanner (PET/CT). The CT is used for anatomical information and attenuation corrections of the PET and to a lesser degree for diagnostic purpose. By this technique, the PET and CT examinations are merged and presented as a single image set. The FDG-uptake registered by the PET-scan is displayed over the corresponding anatomical location given by the CT, please see Figure 4 for an example of a PET/CT examination. The combination of PET and CT improves anatomical correlation of PET findings and lesion characterization. The attenuation correction allows the calculation of the SUV [73]. Kuehl et al. reported sensitivity and accuracy estimates for the detection of intra and extrahepatic disease of 95% and 97% for PET/CT, which was significantly higher than for standalone PET with estimates of 54% and 75% [74].

A more recent improvement of PET imaging is the clinical application of TOF [75]. The first TOF PET systems were already build in the early 1980s, however only recently have systems with a satisfying clinical performance been developed [76]. In conventional PET systems, the temporal resolution is insufficient to measure the difference between the detection of the two photons emanating from a positron annihilation with high accuracy. PET systems with TOF capabilities can measure this time difference in the detection of the two photons which theoretically allows the precise location of the annihilation along the LOR between the two detectors. TOF reduces artifacts and image noise, increases lesion contrast, spatial resolution and lesion detectability[75]. The FDG-uptake of e.g. liver lesion can be measured more precisely by TOF.

In the work-up of colorectal cancer, PET/CT might be used for initial staging or restaging after treatment. However, Brush et al. showed that PET/CT provided little additional value for the staging of primary colorectal cancer and routine PET/CT for this purpose was not supported [77]. Treatment with chemotherapy causes a reduction of SUV within the tumor or metastases often before morphological changes become visible. This can be used for
treatment or response monitoring [78]. Furthermore, several reports indicate that SUVmax or reduction of SUV after treatment can be used as prognostic factors for tumor recurrence or overall survival [78, 79]. PET/CT has also the potential to improve radiation therapy by optimization of the planning target volumes and subsequently radiation dose [78].

In the case of metastatic colorectal cancer, PET/CT can provide additional information and change treatment strategy for some patients [77, 78]. Prior to liver resection for CRLM, PET/CT is used to rule out extrahepatic disease, which might preclude liver resection and change the therapeutic approach from a potential curative to a palliative treatment. A meta-analysis by Niekel et al. reported for the detection of CRLM by PET/CT sensitivities of 97% on a per-patient basis and 66% on a per-lesion basis [80]. The overall diagnostic performance of PET/CT was comparable to CT and MRI with sensitivities of 95% and 93% on a per-patient basis and of 74% and 80% on a per-lesion basis. However, for PET/CT only limited data were available.
Figure 4 PET/CT examination of a patient with two adjacent CRLM in the left liver lobe with significant FDG-uptake (red arrows). Physiological cerebral/myocardial FDG-uptake and FDG excretion in the kidneys and bladder are marked with a white *. Maximum intensity projection of the PET (a), fused images in coronal plane (b), fused image in sagittal plane (c) and fused image in axial plane (d)
2 STUDY AIMS

This investigation focused on the preoperative detection of CRLM in patients scheduled to liver resection. The most important diagnostic modalities in the preoperative work-up for those patients are CE-IOUS, CT, MRI and PET/CT. Rapid evolution and improvements of the diagnostic modalities and available treatment options, including both surgical and conservative approaches, have made it difficult to choose the appropriate modality. The choice of the optimal diagnostic approach is the topic of an ongoing discussion and a final consensus remains to be established [46, 47, 59, 80-82]. Therefore, an investigation of the diagnostic performance for CRLM of CE-IOUS, CT, PET/CT and MRI was performed. A special focus was set on PET/CT, which is traditionally performed without regards to respiratory motion of the liver. Respiratory-gated PET/CT has therefore the potential to improve the diagnostic performance of PET/CT for CRLM.

The specific study aims were:

Study 1:

- To evaluate the impact of CE-IOUS on the initial operation strategy, which was based on findings from CT and MRI.
- To evaluate the impact of CE-IOUS on the initial operation strategy in case of solitary CRLM.

Study 2:

- To evaluate if MRI with diffusion weighted and Gd-EOB-DTPA-enhanced sequences had a better diagnostic performance for CRLM than CT and PET/CT.

Study 3:

- To evaluate the diagnostic performance of a novel single-bin method with a modified inspiration breath-hold approach for rgPET/CT in patients with suspected CRLM.
scheduled for liver resection, and to assess its additional value when combined with standard PET/CT for the detection of CRLM.
3 METHODOLOGICAL CONSIDERATIONS

3.1 Approvals

For study 1, the necessity of written consent was waved due to its retrospective design, short life expectancy for patients with metastatic colorectal cancer and potential high value of the study for the treatment of future patients. The complete proposal to wave written informed consent for study 1 can be found in Appendices 9.1 (original in Norwegian).

Study 2 and 3 were approved by the reginal ethics committee (Appendices 9.2; original in Norwegian) and the institutional data protection officer for research. Written and oral consent were obtained for all patients. The proposal used to obtain written content from the patients can be found in Appendices 9.3 (original in Norwegian).

3.2 Patient selection and study design

Study 1 was a single-center retrospective study. Patients treated with open liver resection for CRLM between 2007 and 2009 were consecutively included. The final study population consisted of 86 patients (Figure 5).

Studies 2 and 3 were single-center prospective studies. Patients scheduled to liver resection for CRLM were prospectively included between 2011 and 2013. Exclusion criteria were prior liver resection or treatment for CRLM, Eastern Cooperative Oncology Group performance status >2 [83], incapability to carry out breath-hold instructions, other malignancy, pregnancy, contrast media intolerances, reduced renal function, severe claustrophobia, and, in case of metachronous CRLM, <6 months since the last cycle of chemotherapy for the primary tumor. The final study population consisted of 46 patients for study 2 and 43 patients for study 3 (Figure 5).
3.3 Modalities

Due to the retrospective design of study 1, modifications of the examination protocols of the included imaging modalities, CE-IOUS, CT and MRI, were made during the study period. Study 2 and 3 had a prospective study design with fixed imaging protocols for CT, MRI, PET/CT and rgPET/CT.

**Study 1**

CE-IOUS of the liver was performed by experienced radiologists with over 10 years of experience in abdominal and oncologic imaging. All examinations were performed according to a standardized examination protocol [84]. The liver was examined with overlapping sweeps first in B-mode then again after the injection of the ultrasound contrast agent (SonoVue®) in
portal-venous phase after 90 s using the inbuilt contrast program. The contrast examination was repeated if necessary e.g. if coverage of the whole liver was not possible during the provided scan time of one contrast injection. New identified lesions by IOUS / CE-IOUS were additionally examined in arterial, portal-venous and late phase for definite lesion characterization.

All CT examinations were performed on 64 slice scanners in arterial, portal-venous and late phase. The MRI examinations were performed on a 1.5T system. Three different liver specific MRI contrast agents were used (SPIO, gadobenate dimeglumine / Gd-BOPTA and Gadoxetic acid / Gd-EOB-DTPA). The MRI contrast agent was changed during the study period due to changes in the hospitals recommendations based on new available data from the literature and contracts with the providing companies. DWI was not available until August 2009. The initial operation strategy and number of identified CRLM was based on the findings from the preoperative CT and MRI examination.

**Studies 2 and 3**

The examination protocols for CT, MRI and low-dose CT for the PET/CT and rgPET/CT are shown in Table 1 and Table 2.

PET/CT examinations were performed on a scanner with time-of-flight capabilities and integrated 40 slice CT scanner. A whole-body scan from skull-base to thigh was performed after 60 min at 2 min per bed position (Table 1). A whole body low-dose CT without contrast enhancement was used for attenuation correction and image fusion.

Immediately after the PET/CT a 6 min one-bed list mode acquisition over the liver was performed. In order to obtain a respiratory gated acquisition we used an in-house made
electronic circuit that displayed a color-coded countdown from 9 to 0 for the patient, Figure 6.

Figure 6 Set-up of the rgPET/CT with the in-house made electronic circuit that displayed a color-coded countdown from 9 to 0 for the patient.

The patients were instructed to hold their breath in moderately deep inspiration the 9 s while the display showed red numbers counting down from 9 to 0, and to breathe freely for 9 s while the display counted down with green numbers from 9 to 0. Each time the display changed from red to green the circuit sent a trigger signal to the scanner, which divided the list mode into two bins. The listmode raw data from the breath-hold period was then the basis for reconstruction of the respiratory gated sequences. Only the data from the inspiration breath-hold period, which were equivalent to a 3 min static breath hold image, were used for image reconstruction. A detailed description of the method has been published by Skretting et al. [85]. An overview of other methods used for rgPET/CT is given in Figure 7. The acquisition and reconstruction parameters were identical to those used for the regular non-gated PET/CT.
Figure 7 (a) The AZ-733V pressure belt (Anzai Medical Corp.). (b) The Real-Time Position Management (RPM) system (Varian Medical Systems) (reprinted with permission from AAPM and Dr Sadek Nehmeh 15). Copyright AAPM, College Park, MD, USA. All permission requests for this image should be made to the copyright holder. (c) The BioVet CT1 System (Spin Systems) (reprinted with permission from Dr Axel Martinez-Möller 16). Copyright Technical University Munich, Germany. All permission requests for this image should be made to the copyright holder. (d) The CPX Spirometer (Medgraphics) (reprinted with permission from AAPM and Dr Bhudatt Paliwal 17). Copyright AAPM, College Park, MD, USA. All permission requests for this image should be made to the copyright holder. [86]
METHODOLOGICAL CONSIDERATIONS

Table 1: Examination protocol for CT, low-dose CT, PET/CT and rPET/CT.

<table>
<thead>
<tr>
<th>2 Iterations/2 Subjects</th>
<th>3</th>
<th>216</th>
<th>200 x 200</th>
<th>4.07</th>
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<tbody>
<tr>
<td>Maximum Full Width Half Post-Reconstruction Filter</td>
<td>mm</td>
<td>3.0 / 3.0</td>
<td>500 x 500</td>
<td>0.33</td>
</tr>
<tr>
<td>Slice Thickness</td>
<td>mm</td>
<td>1.5</td>
<td>3.0 / 3.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Iterative Image Reconstruction</td>
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<td>16 x 16</td>
<td>3.0 / 3.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Pixel Size</td>
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<td>120</td>
<td>2010 / 1900</td>
<td>160</td>
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<tr>
<td>Field of View</td>
<td>mm</td>
<td>20</td>
<td>Arterial/venous phase 5 min.</td>
<td></td>
</tr>
<tr>
<td>PET-Scans:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PET/CT</td>
<td></td>
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<td>PET/CT</td>
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</table>

Table 1: Examination protocol for CT, low-dose CT, PET/CT and rPET/CT.
Table 2 MRI examination protocol and overview of the included sequences. The used contrast agent was Gd-EOB-DTPA.

<table>
<thead>
<tr>
<th>MRI-Sequences</th>
<th>Contrast Enhanced</th>
<th>Actual TR/TE</th>
<th>Flip Angle</th>
<th>Respiration Correction</th>
<th>FOV RL/AP/FH</th>
<th>Voxel RL/AP/FH</th>
<th>Reconstructed Voxel Size</th>
<th>Bandwith</th>
<th>NSA</th>
<th>Slice Gap</th>
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<tr>
<td>T2-Weighted Single-Shot (Axial)</td>
<td>No</td>
<td>-/80</td>
<td>90</td>
<td>Navigator</td>
<td>350.0/209.0</td>
<td>1.4/5.0</td>
<td>0.8</td>
<td>337.7</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>T1-Weighted FFE In* and Opposed** Phase</td>
<td>No</td>
<td>180/2.3** and 4.6*</td>
<td>80</td>
<td>Navigator</td>
<td>350.0/278.6/209.0</td>
<td>1.8/2.3/5.0</td>
<td>1.0</td>
<td>523.3</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Diffusion-Weighted Sequence b=0/50/800 s/mm²</td>
<td>No</td>
<td>1313/65</td>
<td>90</td>
<td>No</td>
<td>376.0/303.2/227.0</td>
<td>3.0/3.0/5.0</td>
<td>2.0</td>
<td>2705.6</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>T1-Weighted 3D FFE THRIVE (Axial) Breath-Hold</td>
<td>Pre-/Postcontrast and Hepatobilar</td>
<td>3.8/1.78</td>
<td>10</td>
<td>Breath hold 16.9 s duration</td>
<td>350.0/276.3/200.0</td>
<td>2.3/2.3/2.0</td>
<td>2.0</td>
<td>440.1</td>
<td>1</td>
<td>-</td>
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<td>T2-Weighted TSE SPIR</td>
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<td>1747/100</td>
<td>90</td>
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<td>0.7</td>
<td>252.5</td>
<td>2</td>
<td>1.0</td>
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</table>

Time to Repeat (TR); Time to Echo (TE); Field of View (FOV); Right to Left (RL); Anterior to Posterior (AP); Feet to Head (FH); Number of Signal Averages (NSA)
3.4 Image and data evaluation

On CT hypovascular CRLM were defined as hypoattenuating lesions with less enhancement than normal liver in portal-venous phase and showed washout out/remained hypoattenuating on delayed phase.

On MRI CRLM were defined as moderate hyperintense lesions on T2-weighted images and hypointense lesions on precontrast T1-weighted images. During the early dynamic phases poor central enhancement and increased peripheral rim enhancement were considered characteristic. In hepatobiliary phase (with Gd-EOB-DTPA), CRLM were hypointense due to the lack of hepatocytes and subsequently intracellular contrast uptake (10). On DWI, lesions hyperintense on both b=50 s/mm² and b=800 s/mm² with ADC-values less or equal to that of the adjacent liver parenchyma were regarded as CRLM if an equivalent lesion was present on contrast-enhanced images.

On PET/CT, CRLM were based on focal FDG uptake exceeding the uptake of the surrounding liver tissue, and distinctly visible on maximal-intensity-projection. An uptake was regarded as pathological when the SUVmax within the lesion was significantly higher than the SUVmax of a large ROI within the normal liver, without any numerical cut-off.

On CE-IOUS, lesions with rim-enhancement in arterial phase who showed wash-out or were hypoenhancing on portal venous phase and late phase were considered as CRLM [63]. Wash-out or hypoenhancement on portal venous phase was used as the main criteria.

3.4.1 Study 1

Two independently, experienced readers evaluated retrospectively all CT, MRI and CE-IOUS examinations. The readers agreed on a consensus that was used for further analysis. The examinations were evaluated successive, beginning with CT and MRI, CE-IOUS was evaluated last. CT and MRI were evaluated without knowledge of the findings from CE-
IOUS. Due to the retrospective nature of the study, differentiation between IOUS and CE-IOUS was not possible. Although both IOUS and CE-IOUS were performed in all cases, it is only referred to as CE-IOUS. The standard of reference was histopathology and follow-up. All additional CRLM identified by CE-IOUS were confirmed by histopathology if resection was possible or in case of inoperability a definite diagnosis could be made on basis of lesion growth/progression on follow-up examinations.

3.4.2 Study 2

Four readers with experience in oncological, hepatobiliary and nuclear medicine imaging were involved in the imaging analysis; one reader with seven years of experience, the other three each with more than ten years of experience. To prevent recognition, the minimal time between evaluations of different modalities was six weeks. The readers knew that the patients had colorectal cancer with suspected CRLM, but were blinded for all other information. Each reader created a report for each exam including number of lesions, characterization, size (maximum axial diameter) and location according to the Couinaud classification. On PET/CT only CRLM were identified. The two readers agreed to a final consensus which was used for further data-analyses.

The reference standard consisted of findings made intraoperatively, by histopathology and follow-up. During resection, the liver was inspected, and during open procedures bimanually palpated. IOUS was used if requested by the surgeon. The specimens were formalin fixated for histopathological examinations and depending on the shape of the specimen cut into parallel slices of 3 mm in axial plane. Hematoxylin and eosin staining were provided. Clinical data, operation reports including the number of resected lesions were available to the pathologist, but a detailed radiological imaging report was usually not given. Unidentified CRLM, when found by the histopathology examination or identified on the first postoperative routine CT-control (MRI in 4 cases where the lesions were not visible on CT) after 4 months,
were defined as false negative CRLM. For size dependent subgroup analysis those CRLM were considered <10 mm. Histopathology confirmed 58% of all CRLM (81/140 CRLM). If no histopathological examination was available, the lesion was monitored with follow-up exams until definite characterization was possible. Lesions were classified as CRLM if the lesion increased in size, or decreased in size/disappeared after receiving chemotherapy.

3.4.3 Study 3

Two readers with experience in oncological, hepatobiliary and nuclear medicine imaging were involved in the imaging analyzes. One reader had seven years of experience, the other had more than ten years of experience. PET/CT and rgPET/CT were independently evaluated. To prevent recognition bias, the minimal time between evaluation of PET/CT and rgPET/CT was six weeks. The readers knew that the patients were evaluated for suspected CRLM, but they were blinded for further information. The report from each reader and the reference standard was created as described for study 2 in 3.4.2. Histopathology confirmed 55.7% of all CRLM (73/131 CRLM).

3.5 Statistical considerations

For study 1 all data were collected retrospectively at the Department of Gastroenterological Surgery and the Department of Radiology and Nuclear Medicine of the Oslo University Hospital (Ullevål). For Study 2 and 3 data were collected prospectively and patients included in consecutive manner at Oslo University Hospital. Patient inclusion and treatment took place at the Department of Hepato-Pancreato-Biliary Surgery (Rikshospitalet) while all diagnostic imaging was performed at the Department of Radiology and Nuclear Medicine (Ullevål).

Statistical analysis was performed with SPSS (SPSS Inc., Chicago, IL, USA), for study 1 version 18.0.1 was used and for study 2 and 3 version 21.0.0.1. When appropriate, mean values were given with their standard deviation. Sensitivity, specificity, positive- and
negative-predictive-value were calculated based on the number of statistical units (patients/lesions) defined by RS. For this purpose, it was differentiated only between CRLM and benign lesion or if a patient was negative or positive for CRLM. Indeterminate lesions (no definite confirmation by RS) were excluded. Kappa-statistics were used to estimate inter-observer agreement for CRLM: Less than 0.20=poor; 0.21–0.40=fair; 0.41–0.60=moderate; 0.61–0.80=substantial; and 0.81–1.00=almost perfect. 95% CI were used for statistical inference. CI for sensitivity and specificity were adjusted for clustering as proposed by Genders et al. (method 2) [87]. McNemar test was used to determine differences in sensitivity and specificity. Comparisons of SUV data were performed using the Mann–Whitney test and only CRLM identified on PET/CT and rgPET/CT were used. P <0.05 was considered to indicate a significant difference.

For study 2, CI-width for the difference between proportions (not adjusted for clustering) of ≤20% for overall-analysis on a per-lesion basis was considered to represent a sufficient sample size.

For Study 3, the statistical power was 81% to detect a sensitivity increase of 12% for rgPET/CT compared to the expected 60% sensitivity of the reference PET/CT at 5% significance level and 45 patients included with a mean of 4.4 CRLM per patient, as found in study 1 [88].
4 SUMMARY OF STUDY RESULTS

Study 1

Impact of contrast enhanced intraoperative ultrasound on operation strategy in case of colorectal liver metastasis

To evaluate the current impact of CE-IOUS with SonoVue™ on the initial surgical strategy for CRLM. Retrospectively 86 consecutive patients were included between 2007 and 2009. The patients underwent 97 operations for CRLM. The preoperative diagnostic was based on CT and additional MRI was available in 77%. Inspection and bimanual palpation of the liver by the surgeon (Figure 8) followed by standardized CE-IOUS was performed during all operations and it was evaluated if intraoperative findings changed the initial preoperative operation strategy. Preoperative imaging identified 328 CRLM. Intraoperatively 72 additional CRLM were identified. Inspection and bimanual palpation by the surgeon before CE-IOUS accounted for 41 additional CRLM. The succeeding CE-IOUS performed by an experienced radiologist accounted for the remaining 31 additional CRLM. Findings from CE-IOUS changed the initial operation strategy in 29.9% (Table 3). For Patients with initially solitary CRLM operation strategy was changed in 19% by CE-IOUS (Table 4). In conclusion, CE-IOUS is essential to ensure optimal and complete tumor resection both for patient with solitary CRLM and multiple metastases.
Figure 8 Intraoperative bimanual palpation of the liver by the surgeon. Superficial hemangioma (green arrow), CRLM (white arrow).
Table 3. Intraoperative changes of the initial operation strategy due to findings by the surgeon (Inspection and Palpation) or the radiologist (IOUS / CE-IOUS). Of the 97 (100%) operations remained 51 (53%) unchanged. Contrast-enhanced ultrasound (CEUS); contrast-enhanced intraoperative ultrasound (CE-IOUS); colorectal liver metastasis (CRLM); radio frequency ablation (RFA).

<table>
<thead>
<tr>
<th>Inspection and Palpation</th>
<th>IOUS / CE-IOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Changes of Operation Strategy</strong></td>
<td></td>
</tr>
<tr>
<td>17 (18%) Operations</td>
<td>29 (30%) Operations</td>
</tr>
</tbody>
</table>

### Smaller Resection
- 1 (1%) Operation
- 1 (1%) Too small Future Liver Remnant

### Larger Resection
- 8 (8%) Operations
- Additional CRLM 8 (8%)

### Inoperable
- 8 (8%) Operations
- 4 (4%) Additional CRLM
- 2 (2%) Extrahepatic disease
- 2 (2%) Larger Tumor Extend

Table 4. Patients with preoperative solitary CRLM. Intraoperative changes of the initial operation strategy due to findings by the surgeon (Inspection and Palpation) or the radiologist (IOUS / CE-IOUS). Of the 21 (100%) operations remained 14 (67%) unchanged. Contrast-enhanced ultrasound (CEUS); contrast-enhanced intraoperative ultrasound (CE-IOUS); colorectal liver metastasis (CRLM); radio frequency ablation (RFA).

<table>
<thead>
<tr>
<th>Inspection and Palpation</th>
<th>IOUS / CE-IOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total changes of Operation Strategy</strong></td>
<td></td>
</tr>
<tr>
<td>3 (14%)</td>
<td>4 (19%)</td>
</tr>
</tbody>
</table>

### 3 (14%) Additional CRLM
- 1 (5%) No CRLM
- 1 (5%) Changed to RFA
- 1 (5%) Smaller Resection
- 1 (5%) Additional CRLM*

* No MRI available and preoperative CT ca. 2 month preoperative
Study 2

Diagnostic performance of CT, MRI and PET/CT in patients with suspected colorectal liver metastases: the superiority of MRI

To evaluate prospectively if MRI with diffusion-weighted and Gd-EOB-DTPA-enhanced sequences had a better diagnostic performance for CRLM compared to CT and PET/CT. The included 46 patients were examined preoperatively with CT, MRI and PET/CT between 2011 and 2013. According to the reference standard 140 CRLM were present. On a per-lesion basis, MRI had the significantly highest sensitivity overall and for CRLM <10 mm (p<0.001). Overall sensitivity and PPV were 68% and 89% for CT, 90% and 82% for MRI, and 61% and 97% for PET/CT. The complete diagnostic performance for CRLM <10 mm and ≥10 mm is given in Table 5. In conclusion, MRI had the significantly highest sensitivity compared with CT and PET/CT, particularly for CRLM <10 mm. Differences in sensitivity between CT and PET/CT were not significant. Therefore, detection of CRLM should be based on MRI.
Table 5. Diagnostic performance for the detection of CRLM of <10 mm and ≥10 mm in size.

### Diagnostic performance on a per-lesion basis of CRLM <10 mm in size

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>MRI</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
<td>CI</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>16</td>
<td>7/43</td>
<td>5-27</td>
</tr>
<tr>
<td>CI Adjusted for Clustering</td>
<td>2-31</td>
<td>52-97</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>96</td>
<td>147/153</td>
<td>93-99</td>
</tr>
<tr>
<td>CI Adjusted for Clustering</td>
<td>93-99</td>
<td>79-97</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>54</td>
<td>7/13</td>
<td>25-81</td>
</tr>
<tr>
<td>NPV</td>
<td>80</td>
<td>147/183</td>
<td>74-86</td>
</tr>
</tbody>
</table>

### Diagnostic performance on a per-lesion basis of CRLM ≥10 mm in size

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>MRI</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
<td>CI</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91</td>
<td>88/97</td>
<td>85-97</td>
</tr>
<tr>
<td>CI Adjusted for Clustering</td>
<td>84-98</td>
<td>94-100</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>88</td>
<td>43/49</td>
<td>79-97</td>
</tr>
<tr>
<td>CI Adjusted for Clustering</td>
<td>78-98</td>
<td>68-96</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>94</td>
<td>88/94</td>
<td>87-98</td>
</tr>
<tr>
<td>NPV</td>
<td>83</td>
<td>43/52</td>
<td>70-92</td>
</tr>
</tbody>
</table>

Colorectal liver metastases (CRLM); positive predictive value (PPV); negative predictive value (NPV); 95% confidence interval (CI); not significant (n.s.)

* No False Positive Findings. CI for not Adjusted Specificity by Alternative Method (91 to 100)
Study 3

Respiratory gated PET/CT of the liver: A novel method and its impact on the detection of colorectal liver metastases

To evaluate the diagnostic performance of a new method for rgPET/CT for CRLM, secondly, to assess its additional value to standard PET/CT. The prospectively included 43 patients underwent preoperative PET/CT and rgPET/CT in the same session between 2011 and 2013. According to the reference standard 131 CRLM were present. The overall per-lesion sensitivity for detection of CRLM was for PET/CT 60.0%, for rgPET/CT 63.1%, and for standard+rgPET/CT 67.7%, respectively. Standard+rgPET/CT was overall significantly more sensitive for CRLM compared to PET/CT (p=0.002) and rgPET/CT (p=0.031). No significant differences were found for PPV. In conclusion, combination of PET/CT and rgPET/CT significantly improved the sensitivity for CRLM. However, high patient compliance is mandatory to achieve optimal performance and further improvements are needed to overcome these limitations. The diagnostic performance of the evaluated new method for rgPET/CT was comparable to earlier reported technically more complex and expensive methods.
5 DISCUSSION

**CT and PET/CT in the preoperative work-up of CRLM**

CT is still the main workhorse and first-line imaging modality for primary staging and follow-up of colorectal cancer. CT and PET/CT offer both the advantage of a whole-body examination while MRI or ultrasound usually only covers a specific target area like the liver. Therefore, CT and PET/CT are essential for correct assessment of the whole tumor extent and final staging. Generally, a CT of the thorax, abdomen and pelvis is performed in portal-venous phase. To increase detection of liver lesions and improve lesion characterization additional acquisitions are performed without contrast and in arterial and delayed phase. The preoperative assessment of liver blood vessels and possible anatomic variations is essential for determining the required operation strategy [89, 90]. CT based liver volumetry and liver segmentation are used to simulate the planned liver resection and verify that the future liver remnant will be of a sufficient size of at least 20-25% of the total liver volume (without the tumor volume) to preclude postoperative liver failure [91-95]. However, CT offers only a suboptimal visualization of the biliary tract, especially if biliary vessels are not dilated [59]. This might cause postoperative complications if intrahepatic biliary vessels are accidentally injured during liver resection.

PET/CT has a high sensitivity for CRLM of ≥10 mm and extrahepatic disease and might help to characterize liver lesions since benign lesions show no FDG-uptake, as confirmed by the results of this investigation [80, 96]. Besides tumor detection and lesion characterization PET/CT provides a functional assessment of CRLM, allows calculation of a patients total glycolytic tumor volume and metabolic response to chemotherapy. In some instances, the pretreatment SUVs might be used as a prognostic factor for tumor biology and patient outcome [79]. PET can change the clinical management in up to 25% [73]. Preoperative
screening with PET/CT for extrahepatic disease might optimize the selection of suitable patients for liver resection which subsequently improves postoperative 5-year survival [97]. However, the additional value of PET/CT in terms of detection of additional extrahepatic tumor deposits and the following change in management varies or might not reach significance as reported by Kuehl et al. [46, 74]. It was reported that false-negative PET results might occur in the presence of mucinous or necrotic CRLM [98]. This was not an issue in the present investigation where 10 of 11 mucinous CRLM >10 mm showed increased FDG-uptake and were correctly identified by PET/CT.

PET/CT is often performed only with an unenhanced low-dose CT for attenuation correction and anatomical correlation. The diagnostic performance of PET/CT might be improved by the combination of contrast-enhanced CT and PET into ce-PET/CT [99]. However, the results of the present investigation showed a poor sensitivity for both CT and PET/CT for CRLM ≤10 mm which indicates a limited potential to increase the detection of small CRLM.

Respiratory motion in the thorax and upper abdomen affects imaging of these regions. This is especially concerning PET since several minutes of acquisition time are usually required per bed position, in contrast to other imaging modalities. Ultrasound can provide images in real time. CT is almost unaffected by respiratory motion since only a few seconds are required per acquisition. For MRI fast sequences are available, which can be acquired within a breath hold or by navigator gating. The present investigation showed that PET/CT can be improved by respiratory gating. However, the optimal technique has yet to be determined [100].

The summarized evidence from the literature supports the preoperative application of both CT and PET/CT [46, 47]. A new preoperative CT examination might be necessary to obtain in the cases of insufficient quality of the CT from the referral institutions, a long period since the initial imaging was obtained or as a baseline before neoadjuvant chemotherapy. If preoperative CT and PET are required ce-PET/CT should be performed, optionally with...
respiratory-gating if local expertise and equipment are available. This single-session approach combining a full diagnostic CT with PET can potentially reduce patient discomfort, radiation exposure and is more cost-effective [101, 102].
The multimodality approach to CRLM or one-stop shopping?

Imaging techniques with fundamentally different physical and biological principles, are used for the detection of CRLM. Sound waves are employed in CE-IOUS. CT is based on the absorption of ionizing radiation. PET combines the emission of ionizing radiation from radioactive decay with molecular biology. While MRI uses one of the four known fundamental forces of nature, electromagnetism, to differentiate biological tissues by their electromagnetic properties. This variety of physical principles allows imaging and utilization of a large range of different tissue properties.

In clinical imaging there is often an overlap between specific characteristics of different liver lesions. Furthermore, several technical and logistical considerations have to be taken into consideration to make an imaging modality applicable in clinical routine. This results in specific pearls and pitfalls for CE-IOUS, CT, MRI and PET/CT. However, the pitfalls, besides different basic physical principles, should be seen as an expressions of the present state of the modality rather than fixed limitations. Constant research from all branches of science assists in the improvements which can help to overcome the current drawbacks.

CE-IOUS provides excellent spatial resolution, especially if dedicated high frequency probes are applied. The perfusion of liver lesions can be visualized in real time with the option of repeated examinations in indeterminate cases. This allows lesion characterization with a specificity of up to 100% [64]. CE-IOUS does not use ionizing radiation and is therefore not potentially hazardous to the patient or attending medical personnel. The contrast media used is very well tolerated with almost no adverse effects reported [63, 103]. However, CE-IOUS is highly examiner dependent (compared to CT, MRI and PET/CT), invasive and often time consuming which subsequently increases operation time and total costs.
CT has a high spatial resolution, yet attenuation differences of soft tissues are often low with overlapping thresholds even after application of contrast media. Dynamic multiphase CT imaging provides important information about the perfusion of liver lesions, which is essential for correct characterization/diagnosis. MRI is similar to CT with a high spatial resolution but offers superior soft tissue contrast. Besides evaluating morphologic and perfusion characteristics of liver lesions, MRI allows for further characterization by visualization of the different magnetic properties of liver lesions by their appearance on different weighted sequences, usually T1 or T2 weighted. Furthermore, diffusion weighted sequences and hepatocyte specific contrast agents allow further assessment of liver lesions with the potential to increases both sensitivity and specificity [104]. The current spatial resolution of PET/CT is lower than CE-IOUS, CT or MRI, even for systems with TOF capabilities. However, since PET/CT visualizes the metabolism of tumor cells, it is not dependent on morphological changes caused by growing CRLM. This should theoretically allow assessment of tumor cell deposits even before morphological changes could be identified on other imaging modalities. However, identification of CRLM by PET/CT is impaired by technical issues like e.g. limited spatial resolution. Likewise, physiological phenomena like the high metabolic activity of hepatocytes and respiratory motion impair the identification of CRLM. The high metabolic activity of hepatocytes results in a heterogeneous appearance of the liver on PET/CT which particularly hampers the identification of small CRLM. Respiratory motion of the liver causes focal FDG-uptake to be distributed over a larger area. That causes a blurred appearance of the CRLM and they might not be distinguished from the background FDG-uptake of the hepatocytes at all. In addition, respiratory motion impairs the assessment of SUV for CRLM.

The present investigation assessed the preoperative diagnostic performance for CRLM of CT, MRI and PET/CT. The overall sensitivity on a per-lesion basis was 68% for CT, 90% for MRI and 61% for PET/CT [96]. A large meta-analysis by Niekel et al. from 2010 reported
DISCUSSION

sensitivities of 74% for CT, 80% for MRI and 66% for PET/CT [80]. None of the studies in this meta-analysis included both diffusion-weighted sequences and hepatocyte specific contrast agents in the MRI protocol which probably explains the increased sensitivity in our study. The slightly reduced sensitivity for CT and PET/CT in the meta-analysis might be explained by the number of small CRLM within the included studies, the limited data about PET/CT and the quality of the reference standard. The reference standard in studies assessing the diagnostic performance for CRLM includes often CE-IOUS or IOUS which are associated with a high sensitivity, histopathological examinations of the operation specimen and postoperative follow-up. All components included in the reference standard might be subject to various bias which might heavily influence study results. However, the optimal reference standard of a meticulous histopathological examination of the whole liver is usually not possible in clinical studies. Therefore, it is mandatory that all components included in the reference standard are of the highest possible quality to minimize possible bias.

The most important reasons for the high preoperative sensitivity of MRI are high spatial resolution, high soft tissue contrast, assessment of impaired intralesional diffusion and selective enhancement of hepatocytes. Despite the superior preoperative diagnostic performance of MRI, recent literature indicates that it might still be outperformed by CE-IOUS which provides superb spatial resolution and the ability to assess lesions perfusion in real time [105]. The present investigation showed difficulties with the differentiation between hemangiomas and CRLM. Some hemangiomas did not show the typically expected centripetal rim enhancement and remained hypointensive on all Gd-EOB-DTPA enhanced images. This was especially a problem when simultaneously mucinous CRLM were present. In these cases, T2-weighted images were almost worthless to differentiate between hemangiomas and CRLM. The reason for the difficulties to distinguish between hemangiomas and CRLM was probably the suboptimal hemodynamic characteristics of Gd-EOB-DTPA for
characterization of those lesions (Figure 9). Gd-EOB-DTPA is rapidly taken up by the hepatocytes while contrast uptake into the hemangioma occurs significantly slower [106, 107]. This might give the impression of a pseudo washout or missing contrast uptake into the lesion due to the relatively low signal intensity within the lesion compared to the surrounding hepatocytes which might mimic CRLM. However, after consideration of the corresponding CT and PET/CT examination the correct diagnosis was made preoperatively in all cases.

A multimodality preoperative imaging approach has the advantage that the shortcomings of one imaging modality can be compensated by the other modalities to maximize the diagnostic accuracy. However, it is preferable to keep the number of preoperative imaging modalities and examinations that are necessary for complete tumor staging to a minimum. Ideally one examination should be sufficient, also referred to as one-stop shopping [59]. A one-stop shopping approach would simplify and accelerate preoperative logistics, increase patient comfort and reduce total costs [70, 101, 102]. The preoperative diagnostic work-up should fulfill the highest standards to avoid intraoperative changes of the operation strategy due to findings by the surgeon or CE-IOUS since additional findings might have required a completely different treatment approach in the first place [71]. Patients found to be unresectable during operation are exposed to an unnecessary operation which increases morbidity in a palliative situation. Other patients with additional intraoperative findings might have benefited from additional preoperative treatment. Furthermore, additional intraoperative findings and deviation from the initial operation strategy may prolong operation times, cause logistical problems and increasing the costs for the healthcare provider.

Beyond the detection of CRLM precise mapping of vascular and biliary structures which is essential for planning of the optimal operation strategy and liver volumetry must determine if a sufficient future liver remnant can be achieved [59]. Virtual operation planning has been the domain of CT, however with the routine application of high-resolution contrast-enhanced 3D
sequences, MRI is equally suited for the task [59]. Furthermore, with the possibility of MRCP and the application of Gd-EOB-DTPA, which is excreted into biliary system, MRI is superior to depict the biliary architecture compared to CT.

The results of this investigation and the recent literature suggest that MRI has the highest preoperative sensitivity for CRLM compared to other imaging modalities [80, 104]. MRI with an imaging protocol based on Gd-EOB-DTPA enhanced and diffusion weighted sequences is therefore currently the best preoperative stand-alone imaging modality. This is the closest to the ideal of a preoperative one-stop-shopping liver evaluation. However, some drawbacks regarding the characterization of liver lesions with Gd-EOB-DTPA enhanced sequences and suboptimal whole-body assessment with MRI remain. These remaining issues might be solved by a combination of MRI and PET into PET/MRI as described in more detail below in chapter 7 on future perspectives.
Figure 9 Difficulties of lesion characterization. MRI of a 61-year-old woman with a mucinous colorectal liver-metastasis (CRLM, indicated by red arrows) and a hemangioma (indicated by green arrows) in close proximity in liver segment 7. The hemangioma was falsely characterized as CRLM on MRI. (a) On coronal single-shot (SSH) and (b) axial T2-weighted sequences both lesions appear with a comparable high signal intensity. Axial diffusion-weighted sequences with b-values of 50 (c) and 800 (d) indicate restricted diffusion and (e) the apparent diffusion coefficient map misleadingly indicates a rather benign lesion in case of the CRLM. (f-j) During the dynamic Gd-EOB-DTPA-enhanced sequences in axial plan, both lesions show some level of contrast-enhancement but remain hypointense. (f) Pre-contrast, (g) arterial phase, (h) venous phase and (i) late phase after 3 min. (j) No contrast-enhancement of the lesions on axial hepatobiliary phase.
CE-IOUS - Where are we today? Essential tool or problem solver in selected cases?

Preoperative liver imaging is usually based on CT, PET/CT and MRI, however CEUS might be used as a second line imaging modality for indeterminate focal findings [108]. CEUS lacks the superb spatial resolution of CE-IOUS due to the use of abdominal transcutaneous transducers with lower frequencies for improved penetration depth and might be impaired further by suboptimal assessment of the whole liver by e.g. superimposed air filled bowels or in obese patients [109, 110].

After the initial operation strategy has been determined based on preoperative imaging the patients proceed to operation where CE-IOUS is the last imaging modality prior to liver resection. CE-IOUS may improve both lesion detection and characterization. Advantages like the lack of radiation exposure, comparatively low costs, real-time assessment of lesion perfusion and strictly intravascular contrast agent with almost no adverse effects verify the value of CEUS and subsequently CE-IOUS [10, 63]. However, these examinations depend on local expertise and examination protocols and CEUS/CE-IOUS remain in many cases a tool in specialized centers.

Earlier reports have indicated that CE-IOUS was significantly more sensitive for CRLM than CT/MRI or IOUS with sensitivities of 96% vs 77% and 82%, respectively (MRI without DWI and hepatocyte specific contrast agents) [111]. These reports are similar to the results of our investigation and indicate that CE-IOUS should be performed prior to liver resection. However, it is debatable if the results would be similar in a study performed in 2016 due to the recent improvements especially of MRI regarding DWI and hepatocyte specific contrast agents.

In 2015 Arita et al. reported a sensitivity of 99% for CE-IOUS while it was 81% for CT, 82% for MRI and 75% for CEUS [105]. In this study, both diffusion-weighted sequences and Gd-
EOB-DTPA enhanced sequences were included in the MRI protocol. Additional CRLM were identified by CE-IOUS in 19% of the patients and operation strategy was altered in 74% of those patients. Also, in 2015 Hoareau et al. suggested that CE-IOUS should be performed in all patients undergoing surgery for colorectal liver metastases [112]. In this study, lesion detection and characterization was improved by CE-IOUS in 20% of patients and operation strategy was altered and optimized in 54%. The preoperative MRI included diffusion weighted-sequences but no hepatocyte specific contrast agent was used. These recent results demonstrate that CE-IOUS might still be of high value as found in our study from 2012 (10.1) [88]. This applies even if routine preoperative CEUS, CT and Gd-EOB-DTPA enhanced MRI with DWI are performed.

Imaging of CRLM is especially challenging after neoadjuvant chemotherapy. For the preoperative detection of CRLM after neoadjuvant chemotherapy and consecutive diffuse fatty infiltration of the liver, Kulemann et al. found MRI to be superior to MDCT, especially for the detection of small lesions with sensitivities of 65% for CT vs 88% for MRI and for CRLM $\leq 10$ mm of 11% for CT vs 66% for MRI [113]. CE-IOUS performed in patients treated with neoadjuvant chemotherapy improves sensitivity and R0 hepatic resection rate [114]. In case of disappearing CRLM (no longer detectable by preoperative imaging = complete clinical response) CE-IOUS might detect even small tumor residuals which is crucial to ensure true R0 resection [115]. If possible disappearing CRLM or their former location should be identified intraoperatively and treated with parenchymal conservation techniques such as ablations or limited resections [46, 116]. The application of parenchymal conservation techniques increases the chances for a re-resection in case of recurrence with similar outcome and prognosis as for the primary resection [117, 118]. In some cases, a wait-and-see policy can be supported as alternative to complete resection of all lesions/lesion sites that were identified before treatment. This applies even if CE-IOUS cannot identify
disappearing central CRLM or fails to characterize small indeterminate lesions which would require a major hepatectomy or significant change of operation strategy, however close follow-up is mandatory in these cases [46, 116].

Summarized, CE-IOUS is still of high value and might be the most effective or even mandatory after preoperative chemotherapy for CRLM [47, 114, 119].
DISCUSSION

Tumor Biology

With the availability of effective chemotherapy regimens, response or even complete response of some or all CRLM has become common. However, that also means new challenges for the imaging of CRLM treated with chemotherapy, especially if a more targeted treatment such as anti-angiogenic agents are used [46, 82]. Recent studies have shown that alternative treatment response criteria like immune-related response criteria or PERCIST may be more predictive of pathologic response in metastatic colorectal cancer than conventional criteria such as RECIST 1.1 [81, 120-122]. In particular, disappearing CRLM (no longer detectable by imaging = complete clinical response) do not guarantee complete pathological response or cure. Auer et al. reported that 66% of disappearing CRLM represented a complete pathological response. However in the cases of unresected CRLM only 1-year follow-up was available [123]. On the other hand, complete pathological response does not correlate with complete clinical response as stated by Adam et al. where none of the patients with complete pathological response also had complete clinical response [124]. Another aspect of disappearing CRLM after neoadjuvant chemotherapy is that patients can be converted to resectable in 13% to 48% with survival benefits similar to initially resectable patients [116, 125].

Extending the observation time of CRLM may provide valuable information about tumor biology in case of response evaluation after neoadjuvant chemotherapy in indeterminate liver lesions or disappearing CRLM [82]. Promising results for early response evaluation have been reported for PET/CT and MRI/DWI, however none of these techniques have been applied in clinical routine and further research is needed to assess their clinical value [126-128]. A disadvantage with these techniques is the need to first start a specific treatment in order to assess its effectiveness after a defined period of time. Imaging based assessment of tumor biology prior to treatment would be a valuable tool for the optimization of a personalized
treatment approach and first results from texture analysis, based on preoperative/pretreatment images from CRLM have been promising as described in chapter 7.

Knowledge about tumor biology may improve patient selection for liver resection or may help finding alternative treatment options [46, 82]. Tumor biology is probably the most important prognostic factor determining response to chemotherapy, time to recurrence after resection and subsequently overall survival [82].
Critics and limitations of the presented studies

There were some limitations to the studies included in this investigation. Study 1 was a retrospective study including a heterogeneous patient cohort in terms of disease extent and preceding treatment which can be bias to the overall results of this study. The transducers used for CE-IOUS were not dedicated for intraoperative application which might have caused an underestimation of the value of CE-IOUS. On the other hand, this demonstrated the usefulness of CE-IOUS even in the absence of dedicated equipment. This might be of great importance if costs are a limiting factor. In study 2 and 3 the included patients represented a highly selected cohort with almost all patients having CRLM. All the readers were aware of the fact that the patients had suspected CRLM. No CE-IOUS was available in this study and some small CRLM might have been missed. These limitations might have skewed the results towards an overestimation of the diagnostic performance. Due to the low number of patients without CRLM data on a per-patient basis have to be used with caution. Finally, the reference standard regarding benign lesions was not optimal which might have biased specificity estimates and the number of false positive findings is therefore of greater clinical relevance. Regarding study 3, there was no objective registration of patient compliance during the examination. Arguments referring to patient compliance have to be understood as assumptions and subjective observations which are not directly proven by the study results.
6 CONCLUSION AND CLINICAL IMPLICATIONS

- CE-IOUS can improve the detection of CRLM and optimize operation strategy as last imaging modality prior to liver resection. CE-IOUS should always be considered intraoperatively as last imaging modality prior to liver resection. That applies also when preoperative MRI is available and might even be necessary in case of neoadjuvant chemotherapy and disappearing CRLM.

- CT and PET/CT have a comparable diagnostic performance for the detection of CRLM. If preoperative CT and PET/CT are required ce-PET/CT should be performed.

- The diagnostic performance of PET/CT might be improved by the investigated novel method for respiratory gating. Respiratory gating can easily be applied at low costs and should therefore be considered when performing PET/CT. However, further research is needed to evaluate the optimal technique and its value in the assessment of CRLM.

- MRI has a superior diagnostic performance for CRLM, especially for small CRLM ≤10 mm. MRI may provide all necessary requirements to determine the optimal surgical strategy prior to liver resection. Regarding liver resection MRI comes closest to the optimal preoperative one-stop shopping approach, however satisfying whole-body assessment is still lacking.
7 FUTURE PERSPECTIVES

The optimal preoperative diagnostic approach should ensure the best achievable diagnostic performance for CRLM, provide the necessary information required for determination of the operation strategy and include a whole-body assessment to identify extrahepatic disease. Ideally a one-stop shopping approach would address all these aspects within a single examination [59]. The increasing availability of PET/MRI and promising initial results might be a possible solution towards a true one-stop shopping approach, however further research is needed to optimize the method and cost benefit analysis has to evaluate its cost-effectiveness [129-131].

As for PET/CT respiratory motion will be an issue when performing PET/MRI. While inclusion of MRI may offer new possibilities for motion correction, the best method for a whole-body approach correcting both for respiratory and cardiac motion has yet to be established [132].

Liver segmentation has been a traditional field of CT. In a one-stop shopping approach based on liver MRI, liver segmentation would have to rely on MRI as well. Due to the high signal intensity of Gd-EOB-DTPA-enhanced MRI threshold based accurate and time-saving liver segmentation might be possible and could be implemented into clinical routine [133].

MRI kurtosis imaging, an emerging imaging technique based on the non-gaussian diffusion of water molecules with b-values $>1000 \text{ s/mm}^2$, has until now mainly been used in neuroradiology to evaluate the complexity of the microstructural environment in the imaged tissue [134]. The main limitation of these techniques are the relatively long acquisition times of about 7-10 minutes which makes imaging highly susceptible for motion artefacts [134]. While the brain is largely unaffected by motion artifacts, this limitation is of great concern in the liver, which is affected by both respiratory and cardiac motion. However, recent reports
indicate that fast imaging may be possible and promising results were made to assess the response of HCC to chemotherapy or feasibility of whole body kurtosis imaging [134-136]. MRI kurtosis imaging might have great potential within liver imaging if clinical applicable imaging sequences can be established.

Evaluation of the preoperative liver function is important to predict postoperative functional reserve. Today liver function is mainly determined by laboratory tests of blood samples, however some imaging based tests from nuclear medicine like planar scintigraphy or single-photon emission computed tomography exist. Promising results with Gd-EOB-DTPA-enhanced MRI for liver function assessment have been made, yet the optimal sequences and parameters remain to be determined [137].

Post-processing in terms of texture analysis of CT, MRI or PET images have recently been the center of a fast growing research field. Texture analysis can assess heterogeneity or complexity of a tumor, which is hallmark of cancer biology, in a standardized and objective manner [138]. Particularly texture analysis can measure and quantify heterogeneity within a tumor, potentially caused by local variation in hypoxia, necrosis, metabolic activity, proliferation and neovascularization [139]. Differences in heterogeneity may be associated with different tumor biology, genetics, response to treatment and finally prognosis. Texture analysis may provide important information for the determination of the optimal treatment approach. However, the optimal texture parameter and its clinical impact have yet to be determined [140, 141]. Initial results from our institution have shown promising results predicting early recurrence in patients with CRLM prior liver resection (CT based Figure 10) or for the discrimination of low grade and high grade gliomas (MRI based Figure 11) [142, 143]. Further research is need before texture analysis may be implemented into clinical routine.
Figure 10 Entropy a parameter derived from CT texture analysis in patients with CRLM prior to liver resection has the potential to identify patients at high risk for early recurrence as demonstrated by the Kaplan Meier graph [142].

Figure 11 MPP a parameter derived from MRI texture analysis and its threshold value (marked with a horizontal line) may differentiate between low and high grade glial tumors [143]. Values for MPP from all included patients are shown in a scatterplot graph.
8 REFERENCES


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9 APPENDICES

9.1 Study 1 - Proposal to wave written informed consent

Original proposal in Norwegian:

Søknad om frikjenning fra behov for samtykke for den planlagte studien og bruk av pasientjournalen:


Prosjektlederen har allerede vært involvert i pasientene når de ble diskutert på tverrfaglig levermøte og kjenner derfor pasienthistoriene. Det er bare opplysninger som allerede er "kjent fra før" som blir sett på i pasientjournalen.

Ut fra dette ansees det ikke som nødvendig å innhente nytt samtykke for å se på pasientjournalene.

Studien kan også oppfastes som en kvalitetssikringsstudie, men med tanke på senere publikasjoner bør dataene kunne brukes som forsknings data. Pasientene har til i dag ikke gitt deres samtykke til den aktuelle studien, siden studien ikke var planlagt ved oppstart av kontrast forsterket intraoperativ ultralyd (CE-IOUS). Men en tror at det foreligger tilstrekkelige og tungveide grunner for å kunne gjennomføre prosjektet uten aktuelt samtykke.

Studien påvirker ikke på noen måte pasientens behandling eller oppfølgning. Kvaliteten og gjennomføring av CE-IOUS er et sentralt og helt avgjørende element i behandling av

Kreftpasientene som skal inkluderes i studien er i en vanskelig livsfase, livets sluttfase eller noen er allerede døde av sin sykdom. Det kan derfor være unødvendig belastende å konfrontere disse pasientene på nytt med deres minner etter at de har opplevd et stort og komplisert operativ inngrep, påfølgende sykehusopphold samt videre kreftbehandling som i mange tilfeller er svært krevende for pasientene. Innhenting av samtykke fra disse over 2-300 pasienter oppfattes som ekstremt vanskelig. Det antas at ca. 30-50 % av pasientene allerede er døde av sin sykdom eller komorbiditet. Siden det antas at CE-IOUS overproporsjonalt ofte ikke klarte å oppdage alle CRLM hos pasientene som allerede er døde er det veldig viktig å helst kunne inkludere alle de pasientene som fremdeles er i livet. Ellers ville det være veldig vanskelig å vurdere den virkelige effekten / nytte av CE-IOUS, da det ville være stor fare for å få overvekt av undersøkelser hvor CE-IOUS har sviktet pga. evt. reservasjoner fra de gjenværende pasienter mot studien (blant pasienter som fremdeles er i livet antas metoden som overproporsjonalt ofte vellykket).
Samfunnets interesse i den aktuelle studien antas å være meget høyt. CE-IOUS betyr for noen pasienter en reell mulighet for kurativ behandling av en ellers dødelig sykdom. Deltagelsen i studien uten samtykke på andre siden representerer kun en relativ liten ulempe for pasientene. Derfor overstiger samfunnets interesse klart ulempene for den enkelte.
9.2 Study 2 and 2 - Approval of the reginal ethics committee

Original approval in Norwegian:

Dr. Med. Nils-Einar Klow
Oslo Universitetssykehus HF
Røntgenavdelingen, Ullevål sykehus
Kirkeveien 166
0407 Oslo

Dato: 12.04.11
Deres ref.: 2011/536-1

2011/536b Breathhold FDG-PET/CT i preoperativ evaluering og terapi monitorering av pasienter med colorectale levermetastaser.

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk, REK sør-øst B, i møte 16.03.2011.

Prosjektleder: Nils-Einar Klow
Forskningsansvarlig: OUS ved øverste ledelse og UiO ved øverste ledelse

PhD studenter i prosjektet er klinisk stipendiat Anselm Schultz og overlege Tore Bach Gansmo

Saksfremstilling

**Forskningsetisk vurdering**
Komiteen oppfatter prosjektet til å være i gråsonen mellom metodeutvikling/kvalitetssikring og forskning. Komiteen har kommet til at prosjektet er et forskningsprosjekt som skal ha REK godkjenning fordi «Målsetningen med denne studien er å benytte «breath hold» PET/CT i preoperativ planlegging før leverreseksjon hos pasienter med CRLM og sammenligne med andre radiologiske metoder (CT, MRI, CE-IOUS), histologi og klinisk forløp. Komiteen har ingen forskningsetiske merknader til prosjektet.

**Informasjonsskriv og samtykkeerklæring**
Komiteen har ingen kommentarer til studiens informasjonsskriv og samtykkeerklæring.

**Vedtak**
Komiteen godkjenner at prosjektet gjennomføres i samsvar med det som framgår av søknaden.

Komiteens avgjørelse var enstemmig.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Forskningsdata i studien er direkte personidentifiserbare som skal lagres i aidentifisert form på OUS sin forskningsserver. Ved prosjektsslutt skal prosjektdata slettes fra OUS sin server og koblingsnøkkel i prosjektet skal destrueres.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veiledere for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren». Personidentifiserbare data slettes straks det ikke lenger er behov for dem og senest ved prosjektets avslutning.

Godkjenningen gjelder til 01.03.2021. Prosjektet skal sende sluttmeddeling på eget skjema, senest et halvt år etter prosjektsslutt, jfr helseforskningsloven § 12.

Komiteens avgjørelse var enstemmig.
Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen,

Stein Opjordsmoen Ilner (sign.)
Professor dr. med
Komitéleder

Katrine Ore
Komitésekretær/Rådgiver

Kopi:
- OUS ved øverste ledelse, ousfdlgodkjenning@ous-hf.no
9.3 Study 2 and 3 – Proposal to obtain written consent

Original proposal used to obtain written consent in Norwegian:

_Forespørsel om deltakelse i forskningsprosjektet_

"_Breathhold PET-CT i preoperativ evaluering og terapi monitorering av pasienter med colorectale levermetastaser._"

**Bakgrunn**

Dette er et spørsømlig til deg om å delta i en forskningsstudie. Du ble valgt ut til studien siden du nylig har fått påvist kreft i tykk- eller endetarmen. Samtidig ble det oppdatert en spredning av kreftsykdommen til leveren og det er derfor planlagt kirurgisk behandling i form av fjerning av rammende leverområder. Formålet med studien er å evaluere en forbedring av undersøkelsen PET/CT, særlig hvordan en "hold-pusten"-seksjon, såkalt breathhold PET/CT (bPbPET/CT), kan bedre oppdagingen av mindre lesioner. Denne "hold-pusten"-seksjonen vil bli sammenlignet med vanlig PET/CT ved den samme undersøkelsen, med de andre undersøkelsene som gjøres forut for operasjon (CT, MR og kontrast forsterket intraoperativ ultralyd) og med vesvprøver etter at operasjonen er utført. I etterkant av operasjonen vil gjentatte undersøkelses bli gransket for å lete etter nye lesioner. Studien gir oss muligheter for å undersøke om bPbPET/CT kan forbedre muligheten for å finne små lesioner, om bedre resulterer også gir bedre prognose og om funnene kan benyttes i monitorering av behandlingen.

Studien skal gjennomføres i regi av avdeling for radiologi og nuklearmedisin i samarbeid med avdeling for gastroenterologisk kirurgi på Oslo universitetssykehus (Ullevål Sykehus).

**Hva innebærer studien?**


**Mulige fordeler og ulemper**


**Hva skjer med informasjonen om deg?**

Frivillig deltakelse
Samtykke for deltakelse i studien "Breathhold PET-CT i preoperativ evaluering og terapi monitorering av pasienter med colorectale levermetastaser."

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Bekreftelse på at informasjon er gitt deltakeren i studien

Jeg bekrer å ha gitt informasjon om studien

(Signert, rolle i studien, dato)
9.4 Study 2 and 3 – Image evaluation sheets

Evaluation sheet for CT. Corresponding evaluation sheets were used for PET/CT, rgPET/CT and MRI.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Total lesions #:</th>
<th>CRLM #:</th>
<th>Other #:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modality:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PET Study**

**Observer:**

**m: malignancy**
1. definitely benign; 2. probably benign; 3. possibly benign; 4. probably malignant; 5. definitely malignant

**type**
1. cysts; 2. haemangioma; 3. FNH; 4. adenoma; 5. other; 6. CRLM; 7. focal fatty infiltration; 8. focal fatty sparing

**rl: real lesion**
1. probably not present; 2. possibly present; 3. probably present; 4. definitely present

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Multiple lesions in a single segment are listed in craniocaudal direction and the slice no. with the largest axial diameter for each lesion shall be noted.
10 PAPERS 1-3