CT- and ultrasound-characteristics of hepatic lesions in patients with multiple endocrine neoplasia syndrome. A retrospective image review of 25 cases

Nassim Fard¹, Heinz-Peter Schlemmer¹, Friedhelm Raue², Björn Jobke¹,3 *
1 Department of Radiology, German Cancer Research Center (DKFZ), Heidelberg, Germany, 2 Endocrine Practice Heidelberg, Heidelberg, Germany, 3 Telemedicine Clinic/Unilabs, Barcelona, Spain

*bjobke@msk-radpath.net

Abstract

Introduction
Liver metastases from neuroendocrine tumors in multiple endocrine neoplasia syndrome are common (75%) and significantly impairs the prognosis. Characterisation of liver lesions in these patients is challenging, as liver metastases are difficult to differentiate from benign liver lesions such as haemangioma.

Methods
In this study we aimed to characterize the radiological findings of hepatic metastases in MEN patients. The findings of contrast-enhanced CT were considered for the main diagnosis. We retrospectively evaluated 25 patients with MEN-syndrome (10 MEN1/ 15 MEN2) including 11 men and 14 women between 28–62 years of age.

Results
Liver metastases (48%, 12/25) and hemangioma (40%, 10/25) were the most common liver lesions among our patients. The most common primary tumors in our MEN1 and MEN2 patients with liver metastases were of pancreatic neuroendocrine tumor (70%, 7/10) und medullary thyroid carcinoma (100%, 15/15) origin, respectively. CT-characteristics were grouped into three main categories, depending on contrast dynamics. The majority of hepatic metastases (75%, 14/25) are presented as multiple lesions with a slow growth in an average 5 years of follow-up-period. We were able to find a common CT pattern and categorise these for each MEN-syndrome. Hepatic metastases in MEN1 presented commonly a blurred arterial enhancement with a low portal venous enhancement and less frequently a prominent enhancement in the arterial phase, which mimics the classical haemangioma. In MEN2 the liver metastases exhibited disseminated mixed hyper- and hypo-enhanced lesions in CT-scans. Moreover, lesion calcifications are pathognomonic in MEN2. The main limitation of this study is the missing histopathological confirmation in the majority of cases.
Conclusions
In this retrospective imaging study, we were able to categorise and find a common CT pattern for hepatic lesions in patients with MEN-syndrome. In order to differentiate these lesions sufficiently, a combination of a 3-phasic CT-scan with US is required. Other liver specific imaging modalities (MRI, CEUS, SMS-PET/CT) should complement the diagnosis in individual cases.

Background
Multiple endocrine neoplasia syndromes (MEN-syndrome) are rare complex heredity cancer syndromes (incidence rate in MEN1: 2–20/100,000[1] and MEN2: 1/350,000 [2]) with variable endocrine manifestation. Distant metastases in medullary thyroid carcinoma (MTC) occur in approximately 20% of the cases [3]. Liver is a common site for distant metastases in both type of MEN-syndromes and it causes significant increases in morbidity and mortality rate [4–6]. Liver metastases (LM) are found in about 46%-93% of the patients with neuroendocrine tumors (NETs), including those with MEN1 [6]. Distance metastasis of MTC depends on tumor stage and calcitonin (Ctn) level. Liver metastases are observed in 13% of MTC with a serum Ctn level more than 400pg/ml [7]. These lesions are generally hypervascular and exhibit variable atypical imaging appearances, therefore, the differentiation between LM and other vascular hepatic lesions, especially hemangioma, is challenging [8–10]. State-of-the art 68Ga-DOTA-somatostatin analogue-PET/CT improves specificity in detecting the metastases of NET, especially in liver and lymph nodes; nevertheless this imaging technique is not yet a routine protocol for every follow-up in patients with long-term stable disease in Germany. The indications for new treatments (such as systematic therapy with tyrosine kinase inhibitors) are based on RECIST criteria, which cannot be accurately applied to PET. Moreover, its value in MTC is still disputable, for one due to missing correlations between PET positive findings (sensitivity) and calcitonin levels [11–14].

In this article we review liver lesions in 25 patients with MEN-syndrome. The assessment of focal liver lesion is highly relevant in patients with MEN-syndrome because the initiation of a systemic treatment is largely dependent on the existence of metastases[6]. The rational of this study was to acquire more knowledge about the incidence and features of common lesions in MEN patients and building confidence in imaging professionals to support an early diagnosis of disease progression vs. non-relevant incidental findings, reaching for improved survival in these patients [15].

We focus on the lesional imaging characteristics with contrast-enhanced computer tomography (CE-CT) as well as ultrasound (US) that are currently basic care in the life-long surveillance and generally available modalities in radiology departments. We evaluate the imaging characteristics of liver metastases in order to improve the radiological specificity for the clinical benefit in this rare chronic and systemic condition.

Material and methods
We retrospectively searched our databases for all cases with MEN-syndrome (type 1 or 2), who received radiological assessment from 2004–2014. The initial research yielded 43 patients. All cases were referred from a single specialised local endocrinological partner institution (FAR) and investigated at the DKFZ.
All the data were derived from central scientific data bank (Wissenschaftliche Datenbank (WdB)) of the German Cancer Research Center with an approval from the Ethics Committee of the Medical Faculty of Heidelberg (Nr: S-316/2013). The DKFZ is a primary research center and written informed consent is regularly obtained from all patients at the time of the examination for prospective or retrospective scientific research and potential publication of their anonymized images. The examinations performed in our study were not experimental and were undertaken in the context of routine clinical practice, further informed consent for this retrospective study was not required according to our ethic commission.

The reports and imaging studies were searched for cases with hepatic lesions. Finally, 25 patients were identified suitable for the further evaluation. In these 25 genetically proven cases of MEN-syndrome (type 1–2) the findings of Contrast-Enhanced Computer Tomography (CE-CT) were considered for the main diagnosis, and the group without CT examination, findings of US were used alternatively for the main diagnosis. Moreover, the findings of MRI and PET (68Ga-DOTA-somatostatin analogue-PET/CT) occasionally complemented the diagnosis in the cases without histopathological results. In summary CT, US, MRI and PET (68Ga-DOTA-somatostatin analogue-PET/CT) were available in 80% (20/25), 80% (20/25), 36% (9/25) and 24% (6/25) of the cases, respectively (details in Table 1). Additional data such as tumor-markers, time of surgery, duration of the radiological follow-up, histopathology, and presence of extrahepatic metastases were noted for each individual. In 8/12 cases of liver metastases histological confirmation were available and known at the time of image interpretation. The diagnosis in the other four cases of LM (n = 3 in MEN-2 group and n = 1 in MEN-1 group) were based on the rapid tumor-progression and significant increase in tumor-markers over a ten-year period as well as the radiological appearances of the lesions in CT/US in addition to PET-CT and MRT examinations.

Image analysis

The CE-CT-examination were performed by a second-generation 128-row dual energy CT (Siemens Somatom Definition Flash, Siemens Healthcare Sector, Forchheim, Germany) with intravenous application of nonionic iodinated contrast-medium (Imeron 300, Bracco) via an automated injector with the amount and flow rate adapted for body weight. A fixed delay of 10s was used for the early arterial phase (AP) after the cut off value of 120HU was detected (Bolus tracking technique), field of view was from neck to upper abdomen. A fixed delay of 60s was used for the portal venous phase (PVP) with a field of view from the upper abdomen to the proximal part of the upper leg. The majority of the patients were scanned with a 3-phasic scanning protocol (native phase, AP, PVP) with a section thickness of 0.7mm/0.5mm for MPR and reconstructed at 3mm intervals for diagnostic interpretation.

The abdominal US were obtained by two sonographic systems (Siemens ACUSON Sequoia 512 and z.one Ultrasound Systems) with a curved abdominal transducer.

Consensus reading was performed by two radiologists, one in training and one with over 10 years of experience in abdominal imaging who made the final call in cases of disagreements.

In this observational study the CT scans and US studies were reviewed for the presence of lesions. The number (1, 2, multiple ≥3) and location, in addition their morphologic characteristics in CT and US were noted. The maximum diameter of the lesions on axial images were also noted in every first and last imaging study of each patient in order to calculate the relative growth rate during the follow-up period (d2-d1)/(t2-t1).

In proven cases of LM, the morphologic characteristics of hepatic lesions were grouped into three main categories including: group i, group ii and group iii based on their contrast-
Table 1. General information of all patients, CT-characteristics as well as ultrasound-findings in patients with liver metastasis.

| NR. | MEN Type | Modalities | Number of hepatic lesions | Hepatic imaging Diagnosis | MEN-manifestation | Extrhepatic metastasis | CT-charactrisics of metastatic liver lesions. | Lesional calcification | Ultrasound findings of metastatic liver lesions |
|-----|---------|------------|---------------------------|--------------------------|-------------------|----------------------|---------------------------------|---------------------|------------------------------------------|
| (1) | 1       | CT, PET (CT), US | 2 | LM | Pancreatic NET, pHPT | Lung | ii | No | Hyperechogenic |
| (2) | 1       | CT, PET (CT) | multiple | LM | Pancreatic NET, pHPT, adrenal tumor | - | ii | No | - |
| (3) | 1       | CT | 1 | FNH | Pancreatic NET, pHPT, adrenal tumor | Lymph nodes | - | No | - |
| (4) | 1       | CT, PET (CT) | 1 | LM | Gastrinoma, Zollinger-Ellison syndrome | Lymph nodes | i | No | - |
| (5) | 1       | CT, US, MRT | 1 | Hemangioma | Pituitary microadenoma, pHPT | - | - | No | - |
| (6) | 1       | CT, US, MRT | 1 | Hemangioma | Pancreas tumor, pHPT | - | - | No | - |
| (7) | 1       | CT, US, MRT | multiple | Hemangioma | Gastrinoma of duodenum, multiple NET of stomach and pancreas | - | - | No | - |
| (8) | 1       | CT, PET (CT), US, MRT | multiple | LM | Insulinoma, prolactinoma | - | ii | No | Isoechnogenic/ hypoechogenic |
| (9) | 1       | US, MRT | 1 | FNH | pHPT | - | - | No | - |
| (10) | 1       | CT, PET (CT), MRT | multiple | LM | Prolactinoma, Pancreatic tumor, adrenal tumor | - | i/ii | No | - |
| (11) | 2       | CT, US | 1 | LM | MTC, adrenal tumour | Lymph nodes | iii | Yes | Hyperechogenic |
| (12) | 2       | CT, US | 2 | Hemangioma | MTC, adrenal pheochromocytoma | Lymph nodes | - | No | - |
| (13) | 2       | CT, US, MRT | multiple | LM | MTC, adrenal tumour | Lymph nodes, lung | i / ii / iii | Yes | Hyperechogenic |
| (14) | 2       | CT, US | multiple | LM | MTC | Lymph nodes, bone | i / ii / iii | Yes | Hyperechogenic |
| (15) | 2       | CT, US, MRT | multiple | LM | MTC, adrenal pheochromocytoma | Lymph nodes | ii / iii | Yes | Hyperechogenic |
| (16) | 2       | CT, PET (CT) | multiple | LM | MTC | Lymph nodes, lung | i / ii / iii | Yes | - |
| (17) | 2       | CT, US | multiple | LM | MTC, bilateral adrenal pheochromocytoma | Lymph nodes, bone | i / ii / iii | Yes | Hyperechogenic |
| (18) | 2       | CT, US, MRT | multiple | LM | MTC, adrenal pheochromocytoma | Lymph nodes, bone | i / ii | No | Isoechnogenic/ hypoechogenic |
| (19) | 2       | CT, US | 1 | AVM | MTC, adrenal pheochromocytoma | - | - | No | - |
| (20) | 2       | CT, US | 1 | Hemangioma | MTC, adrenal pheochromocytoma | - | - | Yes | - |
| (21) | 2       | CT, US | 2 | Hemangioma | MTC | Lymph nodes, lung | - | No | - |
| (22) | 2       | US | 1 | Hemangioma | MTC | - | - | No | - |
| (23) | 2       | US | 2 | Hemangioma | MTC, adrenal pheochromocytoma | - | - | No | - |
| (24) | 2       | US | 1 | Hemangioma | MTC | - | - | No | - |
| (25) | 2       | US | 1 | Hemangioma | MTC, pheochromocytoma | Lymph nodes | - | No | - |

CT: Computer Tomography, US: Ultrasound, MRT: Magnetic Resonance Imaging, PET: Positron Emission Tomography (68Ga-DOTA-somatostatin analogue PET/CT), LM: liver metastasis, FNH: Focal nodular hyperplasia, NET: neuroendocrine tumour, MTC: medullary thyroid carcinoma, pHPT: primary hyperparathyroidism

https://doi.org/10.1371/journal.pone.0212865.t001
Results

Twenty-five consecutive cases of genetically proven MEN-syndrome were evaluated in our study including 10 patients with MEN1 and 15 patients with MEN2. The mean age of all patients including 11 (44%) men and 14 (56%) women was 40 years (SD ±12). Moreover, the mean average follow-up-period of all cases was about 5±3 years (range: 6 months–12 years). In 40% of all cases multiple hepatic lesions (≥3 lesions) were observed (MEN1: 5/10 vs. MEN2: 9/15 patients), whereas only 16% had a solitary lesion (MEN1: 5/10 vs. MEN2: 6/15 patients).

LM with a prevalence rate of 48% followed by haemangioma in 40% were the top two diagnoses of liver lesions. Other aetiologies of the liver lesions were FNH and AVM in two and one patient respectively. All cases were also screened for lymphadenopathy in our routine protocol. Indeed hepatic metastases were frequently associated with nodal metastases in 8/12 (67%) cases. In general, about 75% of cases with LM were found to be associated with other non-hepatic metastases (Table 1). LM were found in 50% of patients with MEN1 and 47% of patients with MEN2. Multiple LM were also more common than single lesions in each group separately. In each group of MEN1 and MEN2, only one patient had a single LM, and all the other cases had two or more hepatic metastases (MEN1: 4/5 vs. MEN2: 6/7 patients).

The vast majority of the metastatic lesions presented a slow growth in the follow-up-period with a mean rate of increase in diameter of 0.8mm/year (range: 0.2 to 2mm/yr, SD:± 0.7). The relative growth rate in MEN1- as well as MEN2-groups were 0.9mm/yr (SD: ± 0.8) and 0.8 mm/yr (SD: ± 0.7), respectively (Fig 1).

The radiological findings of LM varied from hyper-arterialised lesions to hypodense lesions with low marginal contrast-enhancement (Fig 2). Table 3 presents the prevalence of hepatic calcifications in our cohort.

The CT-finding in LM in patients with MEN1 were most frequently central hypodense lesions with marginal contrast-enhancement (4/5 patients). Only in one patient with MEN1 the LM showed an early enhancement in the arterial phase (i).

On the other hand, the most common CT-finding for LM in MEN2 were multiple lesions with a mixed appearance including a combination of all the aforementioned groups (i+ii+iii) (4/7 patients). About 85% (6/7 patients) of these cases revealed an initial disseminated involvement of the liver (miliary pattern). Notably, calcified metastatic lesions were only found in MEN2.

With US nearly all the lesions in MEN1 and all the liver metastases in MEN2 demonstrated a hyper-echogenic appearance (Table 4), which mainly mimics the classic haemangioma. In two cases isoechogenic lesions were found additionally.

Table 2. Three main categories describing the characteristics of metastatic liver lesions of neuroendocrine tumors in 3-phasic CT-imaging.

| Native phase | Arterial phase | Portal venous phase |
|--------------|---------------|--------------------|
| i Isodense   | Hyper-enhancement with blurry margins | Mild enhancement/ isodense |
| ii Hypodense | Marginal enhancement | Hypodense +/- mild marginal enhancement |
| iii Hyperdense(calcification) | +/- Hyper-enhancement | - |

CT: Computer tomography, CEA: Carcinomembryonic antigen, Ctn: Calcitonin

https://doi.org/10.1371/journal.pone.0212865.t002
All patients in MEN2 group underwent a total thyroidectomy after the diagnosis of medullary thyroid carcinoma. The average serum level of Ctn in the patients with MEN2 and LM ranged between 775 picograms per milliliter (pg/ml) to 44276 pg/ml (normal range < 10 pg/mL). Moreover, the serum level of carcinoembryonic antigen (CEA) in the same group at the time of liver metastases ranged between 14 nanograms per milliliter (ng/ml) to 677 ng/ml (normal range < 5 ng/ml) (Table 5). Patients with a mixed CT pattern including all three types (i+ii+iii) of CT-characteristics of the LM had the highest CEA-level at the time of examination.

In our cohort, haemangiomas presented as single lesions in most of the cases. Multiple haemangiomas were also found in four cases. Only one patient had a calcified haemangioma.

The general patients’ characteristics, CT-imaging features as well as US findings are summarised in Table 1.

**Discussion**

MEN1- and MEN2-syndromes may include benign (parathyroid, pituitary) or malignant tumors, which can be secretory or non-secretory, but both syndromes are defined by the presence of NET in two or more different hormonal tissues [16].
LM are common in MEN1- as well as MEN2-syndromes and significantly impair the prognosis in these patients [4–6, 17]. The metastatic hepatic tumors in MEN patients are highly vascular and may be few in number and relatively small (<1–2 cm) at the time of the primary diagnosis. Early detection of the LM is still a challenge for radiologists as lesions have variable appearances and can be easily missed or mistaken for other benign lesions such as frequent incidental hemangioma [10, 18]. LM in both MEN syndromes may originated from various endocrine tumors, for instance from gastrinoma or thymic carcinoid in MEN1 [4] or primarily from medullary thyroid carcinoma in MEN2-syndrome [19]. In this study we reviewed the spectrum of imaging findings of the LM regarding growth pattern, contrast-behaviour in CT-scans and US characteristics. Due to the rare occurrence of this entity, the recognition and correct interpretation of liver lesions in this syndrome are most likely relatively low and it is our goal to contribute basic information for the understanding of this rare disease.

Table 3. The prevalence of liver calcification as well as calcified metastatic lesions MEN1 and MEN2 groups.

| Prevalence of calcification | Number of the patient with MEN1 (total = 10) | Number of the patient with MEN2 (total = 15) |
|----------------------------|--------------------------------------------|---------------------------------------------|
| Hepatic calcification      | 0                                          | 7/15                                        |
| LM with calcification      | 0                                          | 6/15                                        |
Nearly half of our patients in both MEN1 and MEN2 groups combined, had hepatic metastases. LM in these patients mostly appeared as two or more (multiple) lesions in the follow up. In both groups LM exhibited a slow growth in an average follow-up period of 5 years (<1mm/year), which is similar to the slow growing nature of the primary tumors in neuroendocrine heredity syndromes [20]. This feature itself contributes to the difficulty in the differentiation to hemangioma since growth changes may not be detected easily in a prospective follow-up manner. The RECIST-criteria were not applied to our study as the metastatic lesions in the liver were frequently too small to be accurately measured and had no apparent change in size over many years.

Although both MEN1- and MEN2-syndromes are categorised together as familial neuroendocrine neoplasia, they differ in many aspects. In our cohort, LM in each syndrome also depicted different imaging characteristics.

**MEN1** is a complex syndrome involving endocrine tumors of the parathyroid glands, the pancreatic islet cells, and the anterior pituitary as well as other tumors [1, 16].

In our study the LM in MEN1 patients were mostly poor vascularised lesions with a relatively lower attenuation than liver parenchyma in the PVP(ii). Hyper-vascularised lesions with prominent contrast-enhancement in AP(i) were less frequent in this group. Similar imaging findings were described in review articles previously [15, 21].

The metastases within group ii manifestation were highly demarcated in the PVP, representing a rapid washout. These lesions were larger in size compared to the lesions in group i and they demonstrated a marginal enhancement during AP. A low contrast-enhancement of a

| Radiographic features | Hemangioma | FNH | Liver metastases MEN1 | Liver metastases MEN2 |
|-----------------------|------------|-----|-----------------------|-----------------------|
| **US**                | Nodular, homogenous, well defined, internal septa | Well defined with a Central scar | Well-defined | Miliary pattern, multiple |
|                       | Hyperechogenic, homogenous, posterior enhancement (less frequent: large lesion with heterogeneous echo pattern) | Varied | homogenous Hyperechogenic, (less frequent: isoechogenic) | homogenous hyperechogenic, (less frequent: isoechogenic) |
| **CE-CT**             | Early peripheral or globular enhancement, persistent centripetal enhancement at venous phase (less frequent: nodular peripheral enhancement, rapid filling, progressive and complete centripetal filling) | Early centrifugal arterial enhancement with a hypodense centrum in venous phase | Low vascular, hypodense lesion with a blurred marginal enhancement (less frequent early enhancement in arterial phase) | Mixed appearance including hypervascular lesions with early enhancement in arterial phase as well as hypodense lesions with a blurred marginal enhancement |

**Table 4. Characteristics of the most common differential diagnoses of hepatic lesions in patients with MEN-syndrome.**

| Number | CT-characteristics | Ctn (pg/ml) | CEA (ng/ml) |
|--------|--------------------|-------------|-------------|
| 1      | iii                | 775         | 14          |
| 2      | i/ii/iii           | 7142        | 115         |
| 3      | i/ii/iii           | 1848        | 108         |
| 4      | ii/iii             | 818         | 32          |
| 5      | i/ii/iii           | 4722        | 328         |
| 6      | i/ii/iii           | 44276       | 677         |
| 7      | i/ii               | 7964        | 23          |

**Table 5. The values of calcitonin as well as CEA at the time of CT-Examination in Patients with MEN2-syndrome.**

https://doi.org/10.1371/journal.pone.0212865.t004

https://doi.org/10.1371/journal.pone.0212865.t005
tumoral lesion can result from the central cystic/necrotic changes during the tumor-growth process [22, 23]. However, in our observations there were also lesions with marginal contrast enhancement, but a strong tracer uptake in SMS-PET/CT, representing their homogenous cellular density (Fig 3).

In our MEN1 group, none of the LM were calcified, although, calcifications can be found in larger hepatic metastases in MEN1-syndrome [21].

In the gray scale US the hepatic metastatic lesions were commonly hyperechogenic. Only in one case with fatty liver, the metastatic lesion represented as isoechogenic to low echogenic in comparison to diffused hyperechogenic liver parenchyma. This appearance has been reported previously in the patients with fatty liver. Moreover, tumoral degenerative changes such as central necrosis can also cause a central hypoechogenic appearance in these lesions [21]. In previous studies, variable US-findings are described for LM mainly based on the lesion size. Smaller metastases (<1 cm) were reported as low echogenic round shaped lesions, whereas the larger ones (>1 cm) were frequently hyperechogenic with a low echogenic halo. Similar to CT-characteristics, the US findings of these lesions are basically depending on the cellular composition of each tumor.

**MEN2** is characterised by a combined occurrence of medullary thyroid carcinoma (MTC) with pheochromocytoma and parathyroid tumors [16]. MTC is a well-differentiated neoplasia originating from parafollicular cells (C-cells) of the thyroid gland, which secrete Ctn as well as other polypeptides such as CEA [24].

Similar to findings reported in previous studies, MTC occurred in 100% of our MEN2 patients [2, 25]. Among them, the ones with LM (half of our patients with MEN2) all had highly elevated serum levels of Ctn and CEA, which are known as indicators of distant metastases in MTC [2, 24], as it is reported in the literature that in the presence of increasing tumor infiltration or distant metastases the Ctn-level and CEA-levels will rise to more than 400pg/ml and 100 ng/ml, respectively [19, 26]. Among all patients with LM, the CEA-levels were higher in the patients with mixed type appearance of the LM in comparison to the patients who present one or two different types of the aforementioned CT-characteristics. However, due to the small sub-group size the level of significance could not be evaluated. Furthermore, in the case of stable Ctn-level, elevated CEA level alone can be a sign of dedifferentiation of the tumor which is associated with a worse prognosis and aggressive metastases, although elevated levels of serum Ctn and/ or CEA are not always associated with evidence of tumor-foci during imaging [8]. These cases may have a longer life expectancy with a good quality of life and do not
require systemic treatment, though they should be followed by serum tumor-marker measurements and repeated imaging at regular time-intervals, depending on the doubling-time of serum marker level [27].

CT findings of liver metastases in our cohort demonstrated a heterogenic pattern including diffuse multiple hypo-/hyper-enhanced lesion with calcifications (i+ii+iii). Until now, no larger studies have been published exhibiting the imaging features of liver metastases of the familial MTC. Few studies report them as small, hypervascular lesions similar to liver metastases of the NETs [15, 19, 25]. Besides, the literature states that LM of MTC frequently demonstrate a specific initial miliary pattern, which further complicates the radiological detection [25]. We were able to confirm this pattern in nearly 85% of our cases.

Ball et al reported low-attenuating lesions in PVP, which can be easily misdiagnosed with hepatic cysts [19]. Doppman described a doughnut appearance for the liver lesions in MEN2 patients, including a hypervascular rim and avascular centre due to central amyloid accumulation in these tumors [8]. Similar to intra-thyroidal lesions, the metastatic lesions in MEN2 are commonly calcified [28, 29]. We found calcified metastatic lesions in our MEN2 group with a prevalence of 85%. The origin of calcification is yet not clear and it can be either a product of the tumor or result of haemorrhage or necrosis (dystrophic calcifications) induced by chemotherapy [25, 28]. The calcifications are usually scattered and punctuate and can be located both centrally and peripherally in the lesion. Punctate calcification without a defined mass have also been observed previously and were likewise observed in our study.

The hepatic metastases of MTC are one of the few metastases that tend to be hyperechoic in US, but they may also be hypochoic or mixed [25]. The most common findings in US of the hepatic metastatic lesions among our MEN2 patients were multiple hyperechogenic lesions, mainly similar to what we found in MEN1 group (Fig 1). The only difference between MEN1 and MEN2 lesions were the presence of calcifications.

Differential diagnosis

LM in both MEN-syndromes can mimic the appearance of other benign hypervascular lesions especially when they are necrotic or cystic [15]. Benign liver lesions, such as focal nodular hyperplasia (FNH), small hemangiomas as well as other hypervascular metastases are the most common differential diagnosis for enhancing LM in these patients. In Table 5, the most important characteristics of these lesions are summarised.

The hypervascular nature of the hepatic metastases of neuroendocrine tumors causes overlapping radiological findings and complicates the differential diagnosis. There have been a number of cases in the literature in which LM were misdiagnosed as hemangiomas [18, 30, 31]. Hemangiomas are the most common benign non-cystic finding in the liver with features similar to small LM [10, 32, 33]. Similarly, hemangiomas were the second most common finding in our cohort. The high prevalence of these benign lesions increases the rate of radiological misdiagnoses.

Limitations

Our study was limited by its retrospective study-design and its long time-span. Due to the slow growth nature of MEN, detection and follow-up of the LM are not possible in an appropriate time-period. Another limitation was availability of histopathology results in only 8/12 cases with LM. It should be considered that in most cases, a biopsy was not indicated due to stable tumor-markers. In these cases, the pattern of tumoral progression over time, tumor-markers, CT-characteristics (group i, ii and iii) sonographic appearance as well the findings of 68Ga-DOTA-somatostatin analogue-PET/CT and MRT were decisive for the diagnosis. Also, the...
liver lesions may have originated from different primary tumors depending on manifestation of MEN. Since all tumors in each MEN1-/MEN2-groups exhibit similar imaging characteristics and all histopathologically proven LM confirmed a NET pattern, we believe that this does not taper our results. Moreover, it has been previously shown that the imaging features of NET in a contrast-enhanced CT correlate the histological findings [34, 35]. Another limitation in our study was the variable modalities in the follow-up-controls. This includes application of different imaging modalities as well as different imaging protocols within the same modality. To our knowledge, an optimum radiological monitoring for MEN patients has not been established so far and the available imaging guidelines are tailored to the individual patients and are dependent on local resources and clinical judgments [9, 36]. This diversity was inevitable due to the individual-based follow-up procedures. Moreover, the advances in imaging over the 10-year time period need to be considered. In particular the recent evolving role of PET/CT imaging using $^{68}$Ga Dota peptide (a somatostatin analog), not only for detecting NET and their metastases in the body, but also for image-guided drug delivery as well as targeted radiotracer therapies [37–39]. Most of our patients did not warrant the application of PET-CT as a first line imaging technique since they presented clinically with stable disease. Other reasons for yet limited application of receptor PET techniques may have resulted from lack of experience with $^{68}$Ga-DOTA-peptide in the last decade that covered our retrospective analysis, high expenses and lower sensitivity of this technique in detecting small LM with slow growing nature and a low metabolic rate due to higher physiological hepatic uptake of $^{68}$Ga-DOTA-peptide [40, 41].

The common imaging modalities for follow up controls in MEN-syndrome are US and CT [9] mostly because they are widely available in medical centers. Moreover, their diagnostic role is continually evolving by breakthroughs in new therapies such as Azedra, as these imaging techniques can easily be applied in assessing new sites of disease in patient’s follow-up. Azedra (iobenguane I 131)) is a new FDA-proved drug which targets iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytomas and paragangliomas, who require systemic anti-cancer therapy [11]. MRI could not be included in our study since it has only been added in the imaging protocol lately. With regards to MEN-syndrome, a triple-phasic or 4-phasic (native, AP, PVP and late venous) CT-scan is essential to identify LM and a careful inspection is needed. The average MEN patient is relatively young, thus CT radiation dosage over time needs to be considered. US may support the diagnosis, especially applying new techniques such as contrast-enhanced sonography (CEUS), increasing the sensitivity, specificity and detection rate of conventional US [21, 42]. We therefore believe that a second look by other imaging modalities such as CEUS or MRI is extremely helpful for a precise radiological characterization of these oftentimes small liver lesions.

**Conclusion**

Metastatic liver lesions in MEN patients are mostly multiple and very slow-growing thus very difficult to characterise in a prospective manner. In this cohort, we categorised our CT-findings in order to provide an index for diagnosing metastatic lesions in liver. LM in patients MEN1 commonly appear with a blurred arterial enhancement with a rapid wash-out in PVP. In MEN2 patients the LM were associated with high levels of Ctn and CEA and exhibited a disseminated mixed appearance including hyper- and hypo-enhanced lesions in CT scans. Lesional calcifications in MEN2 were pathognomonic. With US, a hyperechogenic pattern was the main feature in both syndrome types. There are less common findings in both syndromes, which mimic the classical haemangioma as well as other liver metastases. The essential key for differentiating LM in MEN syndrome from other focal hepatic lesions is a combined
radiological examination including US, observation of contrast-behaviour in 3-phasic CT-scan as well as monitoring tumor markers. Furthermore, other liver specific and disease imaging modalities (MRI, CEUS, ⁶⁷Ga-DOTA-somatostatin analogue-PET/CT) can complement the diagnosis in individual cases.

Supporting information
S1 Data. MEN raw data file.
(XLSX)

Acknowledgments
We like to thank Prof. Dr. S. Delorme for his diagnostic decision support during the supervision of ultrasounds performed on MEN patients.

Author Contributions
Conceptualization: Nassim Fard, Friedhelm Raue, Björn Jobke.

Data curation: Nassim Fard, Björn Jobke.

Formal analysis: Nassim Fard.

Investigation: Nassim Fard, Björn Jobke.

Methodology: Nassim Fard, Friedhelm Raue.

Project administration: Nassim Fard, Heinz-Peter Schlemmer.

Supervision: Heinz-Peter Schlemmer, Björn Jobke.

Validation: Nassim Fard, Friedhelm Raue.

Writing – original draft: Nassim Fard, Björn Jobke.

Writing – review & editing: Nassim Fard, Heinz-Peter Schlemmer, Friedhelm Raue, Björn Jobke.

References
1. Thakker RV. Multiple endocrine neoplasia type 1. Indian journal of endocrinology and metabolism. 2012; 16(Suppl 2):S272–4. https://doi.org/10.4103/2230-8210.104058 PMID: 23565397
2. Raue F, Frank-Raue K. Update multiple endocrine neoplasia type 2. Familial cancer. 2010; 9(3):449–57. https://doi.org/10.1007/s10689-010-9320-2 PMID: 20087666
3. Nose VG, JK.; Paner GP. Diagnostic Pathology: Familial Cancer Syndromes :: Lippincott Williams & Wilkins; 2013.
4. Ito T, Igarashi H, Uehara H, Berna MJ, Jensen RT. Causes of death and prognostic factors in multiple endocrine neoplasia type 1: a prospective study: comparison of 106 MEN1/Zollinger-Ellison syndrome patients with 1613 literature MEN1 patients with or without pancreatic endocrine tumors. Medicine. 2013; 92(3):135–81. https://doi.org/10.1097/MD.0b013e3182954af1 PMID: 23645327
5. Heshmati HM, Hofbauer LC. Multiple endocrine neoplasia type 2: recent progress in diagnosis and management. European journal of endocrinology / European Federation of Endocrine Societies. 1997; 137(6):572–8.
6. Harring TR, Nguyen NT, Goss JA, O'Mahony CA. Treatment of liver metastases in patients with neuroendocrine tumors: a comprehensive review. International journal of hepatology. 2011; 2011:154541. https://doi.org/10.4061/2011/154541 PMID: 22013537
7. Szavcsur P, Godeny M, Bajzik G, Lengyel E, Repa I, Tron L, et al. Angiography-proven liver metastases explain low efficacy of lymph node dissections in medullary thyroid cancer patients. Eur J Surg Oncol. 2005; 31(2):183–90. https://doi.org/10.1016/j.ejso.2004.06.011 PMID: 15698736
Hepatic lesions in MEN syndrome

8. Doppman JL. Multiple endocrine syndromes—a nightmare for the endocrinologic radiologist. Seminars in roentgenology. 1985; 20(1):7–16. PMID: 2857507

9. Scarsbrook AF, Thakker RV, Wass JA, Gleeson FV, Phillips RR. Multiple endocrine neoplasia: spectrum of radiologic appearances and discussion of a multitechnique imaging approach. Radiographics: a review publication of the Radiological Society of North America, Inc. 2006; 26(2):433–51.

10. Terminani B, Gibril F, Doppman JL, Reynolds JC, Stewart CA, Sulliff VE, et al. Distinguishing small hepatic hemangiomas from vascular liver metastases in gastrinoma: use of a somatostatin-receptor scintigraphic agent. Radiology. 1997; 202(1):151–8. https://doi.org/10.1148/radiology.202.1.8988205 PMID: 8988205

11. Castroneves LA, Coura Filho G, de Freitas RMC, Salles R, Moyses RA, Lopez RVM, et al. Comparison of 68Ga PET/CT to Other Imaging Studies in Medullary Thyroid Cancer: Superiority in Detecting Bone Metastases. J Clin Endocrinol Metab. 2018; 103(9):3250–9. https://doi.org/10.1210/jc.2018-00193 PMID: 29846642

12. Raue F, Frank-Raue K. Long-Term Follow-up in Medullary Thyroid Carcinoma. Recent results in cancer research Fortschritte der Krebsforschung Prog dans les recherches sur le cancer. 2015; 204:207–25. https://doi.org/10.1007/978-3-319-22542-5_10 PMID: 26494391

13. Giraudet AL, Vanel D, Leboulleux S, Auperin A, Dromain C, Chami L, et al. Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. J Clin Endocrinol Metab. 2007; 92(11):4185–90. https://doi.org/10.1210/jc.2007-0211 PMID: 17726071

14. Giraudet AL, Taieb D. PET imaging for thyroid cancers: Current status and future directions. Annales d’endocrinologie. 2017; 78(1):38–42. https://doi.org/10.1016/j.anj.endo.2016.10.002 PMID: 27989550

15. Tamm EP, Kim EE, Ng CS. Imaging of neuroendocrine tumors. Hematology/oncology clinics of North America. 2007; 21(3):409–32. vii. https://doi.org/10.1016/j.hoc.2007.04.006 PMID: 17548032

16. Thakker RV. Multiple endocrine neoplasia—syndromes of the twentieth century. J Clin Endocrinol Metab. 1998; 83(8):2617–20. https://doi.org/10.1210/jcem.83.8.5045 PMID: 9709920

17. Weber HC, Venzon DJ, Lin JT, Fishbein VA, Orbuch M, Strader DB, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology. 1995; 108(6):1637–49. PMID: 7783837

18. Imperiale A, Greget M, Chabrier G, Keoman y J, Rust E, Detour J, et al. Solitary hepatic metastasis from medullary thyroid carcinoma with persistent elevated calcitonin levels: high value of the integrated use of imaging techniques. AJR American journal of roentgenology. 2007; 189(3):748–52. https://doi.org/10.2214/ajr.189.3.1890748 PMID: 17673130

19. Ball DW. Medullary thyroid cancer: monitoring and therapy. Endocrinology and metabolism clinics of North America. 2007; 36(3):823–37, viii. https://doi.org/10.1016/j.ecl.2007.04.001 PMID: 17673130

20. D’Souza SL, Elmunzer BJ, Scheiman JM. Long-term follow-up of asymptomatic pancreatic neuroendocrine tumors in multiple endocrine neoplasia type I syndrome. Journal of clinical gastroenterology. 2014; 48(5):458–61. https://doi.org/10.1097/MCG.0000000000000062 PMID: 24356459

21. Sundin A, Vuillermie MP, Kaltssas G, Plockinger U. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: radiological examinations. Neuroendocrinology. 2009; 90(2):167–83. https://doi.org/10.1159/000184855 PMID: 19077417

22. Buetow PC, Parrino TV, Buck JL, Pantongrag-Brown L, Ros PR, Dachman AH, et al. Islet cell tumors of the pancreas: pathologic-imaging correlation among size, necrosis and cysts, calcification, malignant behavior, and functional status. AJR American journal of roentgenology. 1995; 165(5):1175–9. https://doi.org/10.2214/ajr.165.5.7572498 PMID: 7572498

23. Fidler JL, Johnson CD. Imaging of neuroendocrine tumors of the pancreas. International journal of gastrointestinal cancer. 2001; 30(1–2):73–85. PMID: 12489582

24. Fromigue J, De Baere T, Baudin E, Dromain C, Leboulleux S, Schlumberger M. Chemoembolization for liver metastases from medullary thyroid carcinoma. J Clin Endocrinol Metab. 2006; 91(7):2496–9. https://doi.org/10.1210/jc.2005-2401 PMID: 16608897

25. Ganeshan D, Paulson E, Duran C, Cabanillas ME, Busaidy NL, Charnsangavej C. Current update on medullary thyroid carcinoma. AJR American journal of roentgenology. 2013; 201(6):W667–76. https://doi.org/10.2214/AJR.12.12370 PMID: 24261394

26. Wells SA Jr., Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid: official journal of the American Thyroid Association. 2015; 25(6):567–610.

27. Schlumberger M, Bostofft L, Dralle H, Jarzab B, Pacini F, Smit JW. 2012 European thyroid association guidelines for metastatic medullary thyroid cancer. European thyroid journal. 2012; 1(1):5–14. https://doi.org/10.1159/000336977 PMID: 24782992
28. McDonnell CH 3rd, Fishman EK, Zerhouni EA. CT demonstration of calcified liver metastases in medullary thyroid carcinoma. Journal of computer assisted tomography. 1986; 10(6):976–8. PMID: 3782568

29. Bankoff MS, Tuckman GA, Scarborough D. CT appearance of liver metastases from medullary carcinoma of the thyroid. Journal of computer assisted tomography. 1987; 11(6):1102–3. PMID: 2890675

30. Soyer P, Gueye C, Somville E, Laissy JP, Scherrer A. MR diagnosis of hepatic metastases from neuroendocrine tumors versus hemangiomas: relative merits of dynamic gadolinium chelate-enhanced gradient-recalled echo and unenhanced spin-echo images. AJR American journal of roentgenology. 1995; 165(6):1407–13. https://doi.org/10.2214/ajr.165.6.7484575 PMID: 7484575

31. Berger JF, Laissy JP, Limot O, Henry-Feugeas MC, Cadot G, Mignon M, et al. Differentiation between multiple liver hemangiomas and liver metastases of gastrinomas: value of enhanced MRI. Journal of computer assisted tomography. 1996; 20(3):349–55. PMID: 8626888

32. Klotz T, Montoril PF, Da Ines D, Petitcolin V, Joubert-Zakey J, Garcia JM. Hepatic haemangioma: common and uncommon imaging features. Diagnostic and interventional imaging. 2013; 94(9):849–59. https://doi.org/10.1016/j.diii.2013.04.008 PMID: 23796395

33. Harman M, Nart D, Acar T, Elmas N. Primary mesenchymal liver tumors: radiological spectrum, differential diagnosis, and pathologic correlation. Abdominal imaging. 2014.

34. Corrias G, Monti S, Horvat N, Tang L, Basturk O, Saba L, et al. Imaging features of malignant abdominal neuroendocrine tumors with rare presentation. Clin Imaging. 2018; 51:59–64. https://doi.org/10.1016/j.clinimag.2018.02.004 PMID: 29448120

35. Belousova E, Karmazanovskiy G, Kriger A, Kalinin D, Mannelli L, Glotov A, et al. enhanced MDCT in patients with pancreatic neuroendocrine tumours: correlation with pathological findings and diagnostic performance in differentiation between tumour grades Clin Radiol. 2017; 72(2):150–8. https://doi.org/10.1016/j.crad.2016.10.021 PMID: 27890421

36. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001; 86(12):5658–71. https://doi.org/10.1210/jcem.86.12.7139416

37. Bodei L, Kidd MS, Singh A, van der Zwan WA, Severi S, Drozdov IA, et al. PRRT genomic signature in blood for prediction of (177)Lu-octreotate efficacy. Eur J Nucl Med Mol Imaging. 2018; 45(7):1155–69. https://doi.org/10.1007/s00259-018-3967-6 PMID: 29484451

38. Jimenez C. Treatment for Patients With Malignant Pheochromocytomas and Paragangliomas: A Perspective From the Hallmarks of Cancer. Front Endocrinol (Lausanne). 2018; 9:277.

39. Bodei L KM, Singh A, van der Zwan WA, Severi S, Drozdov IA, et al. PRRT genomic signature in blood for prediction of 177Lu-octreotate efficacy. Eur J Nucl Med Mol Imaging. 2018; 45(7):1155–69. https://doi.org/10.1007/s00259-018-3967-6 PMID: 29484451

40. Capdevila J, Bodei L, Davies P, Gorbounova V, Jensen RT, Kniege U, et al. Unmet Medical Needs in Metastatic Lung and Digestive Neuroendocrine Neoplasms. Neuroendocrinology. 2018; 28.

41. Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. Radiographics: a review publication of the Radiological Society of North America, Inc. 2015; 35(2):500–16.

42. Chiti A, Fantl S, Savelli G, Romeo A, Bellanova B, Rodari M, et al. Comparison of somatostatin receptor imaging, computed tomography and ultrasound in the clinical management of neuroendocrine gastro-entero-pancreatic tumours. European journal of nuclear medicine. 1998; 25(10):1396–403. PMID: 9818279