COMPARISON OF HEPATIC METASTASES FROM CARCINOID AND PANCREATIC ENDOCRINE TUMORS: HELICAL TRIPHASIC CT FINDINGS

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Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NET) represent a rare subclass of all gastrointestinal tumors. Because their aggressiveness and growth patterns vary greatly, from nearly benign to highly malignant, their classification is in continuous development: the revised Word Health Organization (WHO) classification [1] has characterize GEP-NET into:

- Well-differentiated endocrine tumors,
- Well-differentiated endocrine carcinomas,
- Poorly differentiated endocrine carcinomas.

Due to slow progress, carcinoid patients may have non-specific abdominal pain and diarrhoea for several years before diagnosis. Many patients get increased abdominal pain attacks with time, and approximately 40% are discovered at emergency surgery for intestinal obstruction. In other patients the diagnosis is settled after detection of liver metastases, sometimes together with features of the carcinoid syndrome, which initially may be discrete with flush induced after intake of certain food or alcohol [6].

The most common symptom in fact is flushing, occurring in up to 94% of patients. Flushing has been linked to several factors including serotonin, tachykinins, and histamine. It can be provoked by cheese, wine, nuts, and stress. Diarrhea is the next most common manifestation of carcinoid syndrome, occurring in 80% of patients. Other symptoms include bronchial constriction and wheezing, abdominal pain, and pellagra (niacin deficiency). Carcinoid heart disease develops in 40% to 50% of patients with the syndrome. It's characterized by plaquelike deposits of fibrous tissue on the tricuspid and pulmonary valves and the endocardium. Plaque formation causes endocardial thickening, which in turn causes retraction and fixation of the valves, leading to valvular dysfunction. This disease predominantly affects the right side of the heart, as the lungs are able to deactivate the serotonin before entering the left atrium. However, left-sided disease has been reporter.

The detection of GEP-NET metastases can be done with different techniques and so the sensitivities of detection of liver metastases vary on the basis of technique chosen. A recent study shows that they may be detected using US, SRS, CT, and MR with sensitivities of 46% [10], 49,3%, 78,5%, and 95,2% respectively [11].

In literature radiological differences between hepatic lesions of CTum and PET populations are not clearly underlined; moreover consensus is not easily found to distinguishing radiological CT findings presentation of lesions; some authors in facts recently considered that CT can not differentiate liver metastases due to NET from any other malignant tumors [12]. This is due to the variability of behavior of these lesions; in fact they are generally well vascularised and best depicted during i.v. contrast enhancement in the portal venous inflow phase where they show up as high attenuating lesions in the non-enhanced normal liver.

As with the primary tumor, carcinoid metastases are usually of low density on noncontrast CT [2]; they are typically lesions and so well visualized as avidly enhancing masses during the early (arterial) phase of multiphasic contrast-enhanced CT.

Hollett and colleagues [19] showed that the HAP (hepatic arterial dominant phase) images improved conspicuity in 39% of patients with a variety of metastatic lesions usually considered to be hypervascular. They demonstrated also that HAP imaging should be performed in patients suspected of having metastatic carcinoid to the liver, because approximately two-thirds of carcinoid metastases were either uniformly or heterogeneously hyperattenuating during the HAP, approximately one-third of lesions were most conspicuous during the HAP, and approximately one-sixth of lesions were visible only during the HAP. In approximately one-third of patients, the HAP images, which showed more lesions than either the non-contrast phase or the PVP, were judged to be best for overall lesion detection [14].

Purpose

Due to the extreme variability and insidious presentation of GPNET (Gastropancreatic neuroendocrine tumors) hepatic metastases are present at time of diagnosis in a considerable percentage of cases. Because presence of liver involvement and number of lesions are recognize as independent prognostic factors, their detection is of tremendous importance. MR imaging has been shown the most sensitive imaging modality for liver metastases including neuroendocrine liver metastases but CT still plays a major role in oncologic patients, for sur-

veillance and detection. However few study exists regarding CT findings of liver metastases from NET. Therefore the aime of our works was first to describe morphologic features and vascular behavior of carcinoid and pancreatic metastases, second to look for differences between carcinoid and TEP metastases and last to identify a best phase for detection of metastases.

Materials and methods

Flow chart

We retrospectively evaluated a list of 1015 patients hospitalized in the pancreatic unit of Beaujon hospital – Paris – France. We excluded 937 patients for the following reasons: patients evaluated before 2004 (year of PACS Imaging installation) (n = 505); patients with other associated tumors (n = 10); already treated (n = 61); without CT exams (n = 28), without abdominal CT (n = 127) or without correct triphasic CT exam (n = 11); without hepatic metastases (n = 136) and with other endocrine tumors or not identified endocrine tumors (n = 59).

Target population

Over a period of 64 months (January 2004 – December 2009) we used the PACS system of our hospital to retrospectively analyze patients who had previously untreated liver metastases originated from carcinoid or pancreatic endocrine tumors.

We identified 78 consecutive patients (35 women and 43 men, mean age, 55,7 years min 20 Max 81 years old; 13,36 standard deviation) referred for CT evaluation of secondary neoplastic involvement of the liver. All patients had a histological diagnosis of pancreatic endocrine tumors or carcinoid tumors based on histological analysis of specimens from either the primary site or the liver.

Diagnostic confirmations

The diagnosis of primary neuroendocrine tumors carcinoid (n = 33) or pancreatic (n = 45) was histological. In all patients the most part of lesions allowed the typical malignant behavior at triphasic CT. However some lesions presented an atypical behavior (FNH-like behavior); in this case malignant behavior was confirmed on follow-up with evidence of an increase in size, the apparition of a portal venous wash out or with a complementary exam (MRI).

FNH-like lesions

On the basis of observed data we noted a group of 20 patients with the presence of 51 hepatic metastases mimicking FNH-like nodules defined as nodules with well-defined contours and with a homogeneous arterial enhancement without portal venous washout. We analyzed this group focusing our attention on sex of patients, primitive tumor, size and number of FNH-like lesions, technique of confirmation of malignant nature of these lesions.

Results

Characteristics of patients

The characteristics of the 78 remaining patients enrolled into this retrospective study are listed in table 1. Briefly, the studied population included 43 men (55 %) and 35 women (45 %). The mean +/- SD age was 55,8 +/- 13.1 years, range: 20–81 years (men 57,9 +/- 14,3 range 20-81, women 53,2 +/- 11,9 range 33-78) at the time of first complete imaging work-up of metastatic disease.

Concerning primary, 42 % arose from the pancreas (33 patients) and 58 % arose from the ileum (45 patients); The primitive tumour had been removed at time of imaging in 35 (45 %) cases, including 16 cases (48,5%) in the carcinoid tumour group and 19 cases (42 %) in the pancreatic endocrine tumour group. Metastases revealed the malignancy in 21 (7%) cases.

Synchronous and metachronous metastases were observed in 48 (62 %) and 30 (38 %) patients respectively.

Morphological characteristics and enhancement behavior of liver metastases

Metastases showed heterogeneous contrast intake in 56 patients (72 %), including 28 patients (85 %) with carcinoid tumour and 28 (62 %) patients with pancreatic endocrine tumour. Cystic components and target sign were found respectively in 59 (76 %) and 34 (44%) patients, including 28 / 11 (85% / 33%) patients with carcinoid tumour and 31/23 (65 % / 51 %) patients with pancreatic endocrine tumour.

Enhancement pattern

Liver metastases presented the classic washin /washout pattern in 37% of cases. The three next frequent pattern were hyper-isointense (20,1 %), iso-hypointense (17,2 %) and hypo-hypointense (15,7 %).

Single pattern was seen in 38 patients whereas 40 patients showed metastases with multiple patterns. Among those patients with multiple pattern, the 2 most frequent associations were first hyper-isointense and hyper-hypointense pattern (20,7 %) and second iso-hypointense and hyper-hypointense pattern (15,9 %).

Best phase for detection

In 50 (64%) of 78 patients, lesions were more conspicuous and better defined on contrast-enhan-

ced arterial phase. Difference between both arterial and portal phase were much more obvious in PET group where the arterial phase was the best phase in up to 80 % of cases.

FNH-like lesion

51 FNH-likes lesions were depicted in 20 patients (9 men, 11 women). Mean ± SD size was 9.7 cm ± 2.6 cm. The primitive tumour was a carcinoid in 5 cases and a PET in 15 cases. Confirmation of the malignant nature of the lesions was obtained by change in appearance and/or size in 16 cases, surgery in 1 cases and other technique (MRI, DWI) in 3 cases.

Discussion

To our knowledge, our series is the largest series of liver metastases secondary to neuroendocrine tumors (NET) evaluated on MDCT that has been reported in the literature. Despite the fact that MR imaging has been shown the most sensitive imaging modality for liver metastases including neuroendocrine liver metastases, CT plays a major role in diagnosing liver metastases as it is currently performed in oncologic patients for surveillance and in patients with various abdominal symptoms [24, 25]. Interestingly, we have found a limited number of articles that have focused on CT findings of liver metastases from NET [8, 10, 11, 14, 16, 25, 26]. It is generally known that most neuroendocrine liver metastases are hypervascular but prevalence of this pattern and the others has not been described. Thus, we aimed to describe the different CT patterns of neuroendocrine liver metastases in patients with endocrine tumors of the pancreas and carcinoid tumors.

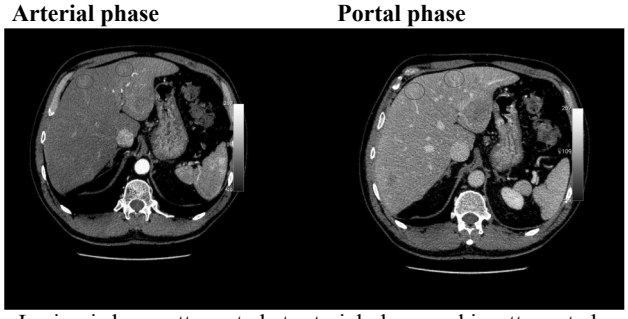
Our study based on analysis of 559 lesions, confirms that most neuroendocrine liver metastases were hypervascular (69%) on arterial phase imaging and hypo-attenuated (73%) on portal venous phase. However, only 37% of the lesions shared these two findings. Besides this typical appearance, the second most common pattern was composed of neuroendocrine liver metastases that were hypervascular on arterial phase imaging but did not exhibit wash-out (25%). This finding which has already been described in Dromain's paper suggests that the wash-out sign has a low sensitivity in neuroendocrine liver metastases [24]. Other neuroendocrine liver metastases were not hypervascular on arterial phase imaging but were hypo-attenuated (33%) on portal venous phase. These various presentations reinforce the complementary role of portal-venous phase imaging.

It is usually considered that neuroendocrine liver metastases from pancreatic tumors and from carcinoid tumors have a similar presentation [12]. Our results disagree with this statement as we have seen that lesions from carcinoid tumors (87.5%) are more often hypo-attenuated on portal venous phase than those from pancreatic tumors (56%). Indeed, this explains why we have found that liver metastases from carcinoid tumors were best seen on portal venous-phase in 58%, conversely to liver metastases from pancreatic tumors which were best seen on arterial phase MDCT in most (80%) cases. In a series of hypervascular liver metastases from various origin (breast carcinoma, neuroendocrine tumor, melanoma, renal cell carcinoma, and thyroid carcinoma) more lesions were detected on portal venous phase imaging [26]. These authors have also demonstrated that combination of unenhanced plus portal venous phase images allowed detection of statistically significantly more hypervascular liver metastases than combination of arterial phase plus portal venous images [26]. In a series of 31 patients with proved carcinoid liver metastases, more lesions (although not significant) were detected on portal venous phases [14]. Then, hypervascularity on arterial phase imaging when present is a key finding in neuroendocrine liver metastases. Yet, neuroendocrine liver metastases may lack hypervascularity. In these cases, portal venous phase is especially helpful for detection and characterization.

Interestingly, we have seen liver metastases that had a focal nodular hyperplasia-like appearance in 23/78 patients. We are not aware of any published data on this topic. We defined FNH-like lesion as lesions that were isoattenuating on unenhanced CT scan, hypervascular and homogeneous on arterial phase imaging and iso-attenuating on portal-venous phase. As small FNHs may lack central scar, we did not consider this finding for FNH-like lesions. One could argue that FNHs may coexist in patients with liver metastases and these lesions could be benign ones. Yet most of our FNH-like lesions were confirmed as liver metastases either on pathology or on significant increase on follow-up or significant decrease under treatment. We want to stress this new pattern as its recognition may change patient management.

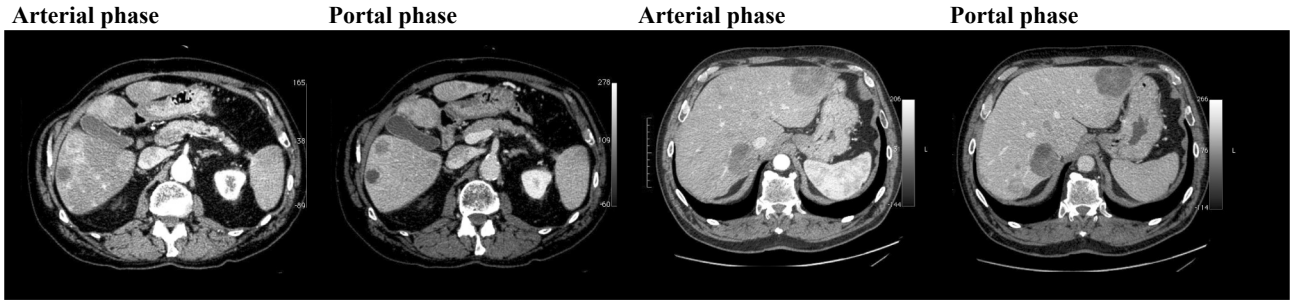
Our study has limitations. First, our study design was retrospective, but we selected all consecutive patients diagnosed with liver metastases from NET who had MDCT, which limits the possibility of sampling bias. Furthermore all patients had the same CT protocol which strengthens the results. Second, not all patients had pathologic confirmation of their neuroendocrine liver metastases. As most patients

have diffuse liver involvement, surgical resection is performed in a minority of the cases and this could have biases our results. Third, we did not perform independent readings of CT examinations. Our intent was not to primarily assess which phase was best in neuroendocrine liver metastases but rather to describe in a large series of neuroendocrine liver metastases originating from pancreatic tumors and carcinoid tumors.



Lesion is hyperattenuated at arterial phase and isoattenuated at portal venous phase without portal venous washout.

Fig. 1. *Typical behavior of FNH-like nodules.*



First typical pattern of endocrine metastases . Note hypervascular enhancement at arterial phase and the hypovascular washout at portal venous phase.

Second typical pattern of endocrine metastases. Note that lesions of smaller size can be detected only by visualisation of portal venous washout.

Fig. 2. *Vascular Patterns*

Table 1

	Pattern of enhancement among 78 patients					
	Arterial phase	*Portal phase*	*Freq. Pattern*	% Pattern	*PET*	*Carcinoid*
1	hyperintense	hypointense	50	37,3%	29	21
2	hyperintense	isointense	27	20,1%	20	7
3	isointense	hypointense	23	17,2%	10	13
4	hypointense	hypointense	21	15,7%	8	13
5	hyperintense	hyperintense	7	5,2%	5	2
6	isointense	isointense	3	2,2%	1	2
7	hypointense	isointense	1	0,7%	0	1
8	hypointense	hypointense	1	0,7%	1	0
9	isointense	hyperintense	1	0,7%	0	1
			134	100%	74	60

Conclusion

In conclusion, our large series shows that a minority of patients had neuroendocrine liver metastases that were hypervascular on arterial phase imaging and hypo-attenuating on portal venous phase. Recognition of the other patterns is mandatory. We have also shown for the first time that these metastases could have FNH-like appearance.

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VALOAREA EXAMINĂRII PRIN TOMOGRAFIE COMPUTERIZATĂ ÎN DIAGNOSTICUL PANCREATITEI ACUTE

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Introducere. Pancreatita acută, greu de diagnosticat în primele momente din cauza factorilor etiologici multipli, fiziopatogenezei complexe, necesită un raționament medical privind diagnosticul de urgență, fiind necesară o decizie rapidă, formulată după o evaluare clinică, de laborator şi imagistică. La aplicarea unui tratament timpuriu, pancreatita acută evoluează favorabil şi doar în 20% din cazuri boala are o evoluție severă, degenerând în pancreatită necrotico-hemoragică. O valoare indiscutabilă în determinarea gradului de extindere a procesului inflamator pancreatic îl au examinările imagistice.

Scopul studiului: evaluarea tomografiei computerizate (TC) spiralate în diagnosticul pancreatitei acute.

Materiale şi metode. Pentru aprecierea valorii metodelor imagistice de diagnostic (ecografie abdominală și tomografie computerizată) în aprecierea gradului de extindere a procesului inflamator pancreatic, am considerat utilă analiza retrospectivă a 47 de pacienți care s-au adresat în departamentul de urgență al IMSP Centrul Științifico-Practic de Medicină Urgentă din municipiul Chișinău.

Concluzii. Se înregistrează o incidență sporită a pancreatitei acute la persoanele apte de muncă, cu o răspândire mai înaltă în regiunea de Centru a republicii, cu prevalare în localitățile urbane. Diagnosticul pancreatitei acute trebuie definitivat în primele 48 de ore de la debutul bolii, pentru preîn-