

# Defining the Modalities of Intravenous Contrast Application During the Diagnostics of Hepatic Metastases with Computerized Tomography

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## ABSTRACT

**Introduction:** The liver is the biggest human abdominal parenchymal organ; it weights approximately 1500 grams and is located in the right hypochondrium, under the diaphragm. Liver is able to perform multiple functions also by means of the rich dual vascularization: hepatic arterial system and the portal vein system, between which exists a short circuit (shunt) and free mixture inside the sinusoid, whilst the two flows drain in the same vein system. The discovery of CT and its application in practice fundamentally changes the importance of diagnostic methods for hepatobiliary lesions. **Patients and methods:** During a 4-year period, 984 patients suspected with liver or biliary tract disease were explored with CT. 117 of these patients were analyzed with liver metastases. Examinations of the liver was performed in dorsal decubitus and in absolute apnea with spiral movement of the table and in denominations of 1 and 5 mm. Siemens MSCT 64 and 6 tier apparatuses enable short scanning time with almost immediate reconstruction, which offers all the necessary elements required for carrying out certain protocols. **Results:** The average density of metastatic lesions is about 20 HU smaller than normal liver parenchyma. Metastasis with necrosis are more hypodense (30-50 HU smaller than normal liver parenchyma), whilst necrotic metastases with smaller dimensions are almost isodense with normal parenchyma. However, metastases with diameter between 4 to 6 cm are completely isodense and will remain so even after the application of I.V. contrast. The average more frequent size according to most authors, as well as according to our material (148 patients or 90%) was 2-3 cm in transversal diameter.

**Key words:** CT, metastasis, contrast medium.

## 1. INTRODUCTION

The liver is the biggest human abdominal parenchymal organ; it weights approximately 1500 grams and is located in the right hypochondrium, under the diaphragm. Because of the possibility of external and internal secretion, the liver is an important endocrine and exocrine gland between the digestive tract and the blood stream, which means a rich laboratory with a large number of functions. This large number of functions (metabolic, detoxifying and hemodynamic) conditions quite complicated structure of the liver:

- Polygonal shaped parenchymal cells,
- Reticuloendothelial tissue (stromal and Kupffer cells) through which passes the sinusoids,
- Biliary tract.

Liver is able to perform multiple functions also by means of the rich dual

vascularization: hepatic arterial system and the portal vein system, between which exists a short circuit (shunt) and free mixture inside the sinusoid, whilst the two flows draining the same vein system. It is important the fact that the blood circulation in the liver is very changeable and that determines its activity.

The discovery of CT and its application in practice fundamentally changes the importance of diagnostic methods for hepatobiliary lesions. Being simple, quick and painless, CT quickly took its place in the diagnostics of pathological changes in the liver and becomes the leader in this field of diagnostics. Nonetheless, except when there was the presence of calcification and adipose tissue, CT data of hepatic solid masses were in most cases nonspecific. However, with the application of contrast, initially in the form of infusion and afterwards in bolus injection, it was enabled the eval-

uation of vascularity and in some cases even the histopathological determination of the liver mass.

Among the methods for determining the real liver status in occurrences/appearances of metastases, CT occupies the first place.

## 2. OBJECTIVE

Clarification of basic dilemma in oncology:

- Safe presence of secondary deposits,
- Stage of development,
- The extent of lesion, and
- The possibility of adequate control after giving the therapy

## 3. MATERIAL AND METHODS

During a 4-year period, 984 patients suspected with liver or biliary tract disease were explored with CT. Out of them 117 of these patients were analyzed with liver metastases. Examinations of the liver was performed in dorsal decubitus and in absolute apnea with spiral movement of the table and in denominations of 1 and 5 mm. Siemens MSCT 64 and 6 tier apparatuses enable short scanning time with almost immediate reconstruction, which offers all the necessary elements required for carrying out certain protocols.

After the performing of unenhanced examination there was applied the intravenous contrast in quantity of 1-1.5 ml/PT in one of the forearm veins at the time of 15 seconds. Having in consideration that the strengthening of contrast in the liver depends on the spatial distribution of contrast medium (CM) and that 4 factors affect the volume distribution:

- The volume of plasma space,
- The volume of interstitial space,
- Endothelial membrane permeability,
- CM features and method of application.

We can easily come to conclusion that the only function that can be changed is the selection of contrast medium and modalities of its application. These two factors not that they only have an direct effect but likewise have an indirect effect on the quality of post contrast scan because the arrival time of the contrast in the designated layer depends on several factors:

- CM quantity and application speed. We have used a manual application of about 6-7 ml/sec. The amount of applied CM and the application speed affect in plasma osmolarity hence the bolus injection causes a faster diffusion in the body's interstitial space rather than CM infusion.
- CM osmotic pressure. The concentration of iodine in the vascular system depends on the osmotic pressure of CM, whose diffusion from the plasma sector in the interstitial space is often passive phenomenon that depends on the osmotic gradient. For this reason hyperosmotic CM have faster and greater diffusion towards the interstitial space and consequently bigger concentration.
- Place of application of CM. It must be as proximal as possible to gain a proper concentration. Injections in the palm or forearm level have more dispersion in venous spaces and therefore the distal application that can be performed is the cubital vein.

Scanning is performed after 15, 30, 45 seconds, 1, 2 and 5 minutes after the start of the application of CM in that layer.

If the pathological process has required exploration in several layers, there was used multiple bolus technique.

This is a modified method of angioscanning proposed by Wegener in 1980, and complemented by Matthieuin 1983 and is used in the greatest number of cases.

This scanning method is proved to be adequate for the patient since it allows sufficient time for normal respiration between two scans. If slices would be done at a faster rhythm then there would be a risk that not the same respiratory amplitudes will form, by taking us away from previously set slices.

In all patients with positive data, where it was possible were collected diagnostic biopsy certificates.

## 4. RESULTS

**Density:** In unenhanced scans the metastases in most cases manifest as round or oval hypodense areas. Only in some cases were presented as spotted calcification (31 cases or 18%), which sometimes are visible even in classic abdomen radiography.

The average density of metastatic lesions is about 20 HU smaller than normal liver parenchyma. Metastasis with necrosis are more hypodense (30-50) HU smaller than normal liver parenchyma), whilst necrotic metastases with smaller dimensions are almost isodense with normal parenchyma. However, metastases with diameter between 4 to 6 cm are completely isodense and will remain so even after the application of I.V. contrast. In the steatotic liver, metastases can appear hypodense (due to hypodense surrounding parenchyma).

**Structure.** Liver metastasis can be manifested in a wide range. According to the rule metastasis without necrosis has a homogeneous structure, but necrotic metastases in most cases have low density which goes from the periphery to the center. So the peripheral ring that we see often becomes even more apparent after the application of contrast while the central part shows the attenuation values of the fluid which change very little after the application of contrast.

In CT there is no typical data for different histological types of metastasis, which means that based on the CT characteristics it is difficult to determine the origin or type of primary tumor.

**Size:** The average more frequent size according to most authors, as well as according to our material (148 patients or 90%) was 2-3 cm in transversal diameter. Very small metastases particularly those solitary can be anticipated along with large multifocal or isodense ones contours. Depending on the differences in density between liver neoplastic and the normal tissue, metastases contours can be more or less clear. Unclear contours are partly a result of the partial volume effect which can reduce the difference between healthy and pathologic tissue. In some cases large metastases can cause the liver waveform contours and this in isodense metastasis may be the only sign in CT that shows its existence.

**The imbibition of contrast:** In literature there are different opinions on the contrast application values with the aim of the best opacification of metastatic changes. I.V. bolus in some cases leads to increased difference of contrast between

Authors	No. of patients	Technique	1	2	3	4	5
Moss et al.	61	Bolus	16%	58%	26%	3%	13%
Scherer et al.	20	Bolus	20%	40%	40%	0%	/
Prando et al.	10	Bolus	20% / 10%	10% / 10%	70% / 80%	10% / 10%	20% / 0%
Our results	117	Bolus	7%	19%	74%	18%	6%

Legend:

1. Good appearance in unenhanced scans
2. Equally good appearances in unenhanced scans as in those after the contrast application
3. Good appearance after the contrast application
4. Appearance only after the contrast application
5. Appearance only in unenhanced scans

Table 1. The impact of contrast medium in the appearance of liver metastases

	MacCarthy	Fruhling	Friedman	Scherer	Biello	Personal
Authors	et al.	Et al.	et al.	and assoc.	et al.	results
Time	18	30	30	30	18	2
Number	32	55	107	62	92	264
Diagnosis with CT	unlimited expansive lesions	unlimited expansive lesions	metastases	metastases	tumors	metastases
Type of data	metastases	metastases	meta and others	metastases	tu.sol.primand sec.	metastases
Type of study	retrospective	prospective	retrospective	prospective	retrospective	retrospective
Positive results	6/7–86%	17/17–18%	15/20–75%	45/62–73%	44/55–80%	170/175–97%
Negative results	22/25–88%	30/38–79%	84/87–97%	/	35/37–95%	93/94–98.9%
False positive results	3/25–12%	8/32–21%	3/87–3.5%	/	2/37–5%	1/94–1.1%
False negative results	1/7–14%	5/20–25%	5/20–25%	/	11/55–20%	5/175–3%

Table 2. Diagnostic precision with CT in metastasis, respectively in liver solid tumors

metastasis and normal liver tissue but the stances of the authors about this are different (Table 1).

**Diagnostic accuracy:** The diagnostic sensitivity of CT in confirmation of liver metastasis is different by different authors due to the use of different scanning times and varies from 75–97% accuracy (Table 2 and 3).

To reduce these false negative or false positive results in our material are responsible two factors:

- The short exposure time enables scanning in full apnea that brings possible artifacts as a consequence of minimum respiratory movements.
- This short time of exposure enables dynamic monitoring of contrast imbibition from lesions in which case is enabled the visualization of isodense lesions.

**Hepatic diagnosis of hepatic masses:** Based on the results shown, it is evident that CT is an exceptional method for detection of hepatic masses. However in literature there are some controversial thoughts and discussions on the possibility of accurate differentiation of hepatic masses, particularly of primary and secondary neoplastic lesions. With the analysis of pre and post contrast scans in metastases in our material, we were able to diagnose intrahepatic expansive masses with great accuracy because of the large number of specific features.

#### a) Pre contrast scans

##### Metastases

- Multiple lesions more than 10 in number;
- Characteristic lesions with characteristic signs:
  - Decrease of attenuation values from the periphery towards the center;
  - Intra tumorous multiple calcification.

#### b) Post contrast scans

According to the subtraction of attenuation values in function of time, after the application of contrast, it is confirmed that in the liver appear four types of (2) tumorous time - dense metric curves:

- Type 1: The curve significantly elevates and in gradual manner drops and thus remains around zero in the second minute;
- Type 2: Curve elevates and drops very quickly;
- Type 3: There is no evident elevation or dropping;
- Type 4: The curve drops fast and then in gradual manner elevates.

Types 1 and 2 are further divided into three groups depending on the localization and form of imbibition within the mass:

- Diffused and homogeneous through mass;

	I			II			TOTAL	
	IA	IB	IC	IIA	IIB	IIC	III	IV
Hepatoma	0	5	0	54	6	3	17	4
Metastases	0	7	3	6	49	7	32	13
Hemangioma	3	11	2	0	0	0	0	0
Cholangioma	0	0	0	0	0	0	6	1
Abcess	0	0	0	0	13	0	0	0
Other Lesions	0	0	0	0	0	4	2	5
Expansive								
Subtotal	3	23	26	60	68	14		
TOTAL		31			142		57	23

Table 3. Type of contrast imbibition in intrahepatic lesions

PRE CONTRAST SCANS								
	No. of tumors	Tumor density		Density lob. Reduction	Ring hypo density	Protrusion		Calcification
	> 10	Iso	Hyper			Manifested	Restrained	
HCC	11 / 9.5%	13 / 11%	31 / 27%	41 / 36%	34 / 29%	14 / 12%	19 / 17%	9 / 8%
METASTASES	134 / 80%	4 / 2%	0	0	0	2 / 1 %	11 / 6%	31 / 18%
POST CONTRAST SCANS								
	Ring imbibition	Size reduction	Special drawing		Imbibition with bolus		Liver Cirrhosis	
			Edge nodes	as "donuts"	Transitional dif.	Transitional perif.	Confirmed	Suspicious
HCC	11 / 12%	19 / 21%	0	0	51 / 57%	16 / 17%	17 / 19%	8 / 9%
METASTASES	63 / 54%	0	34 / 30%	19 / 16%	11 / 9%	57 / 49%	3 / 2%	1 / 0.9%

Table 4. Diagnostic differentiation between hepatocellular carcinoma and metastasis

- Circular or punctiform in the peripheral.
- Septate or punctiform within the mass.

Imbibition results from the bolus in intrahepatic lesions in our material are shown in Table 4 which systematizes the contrast imbibition type.

#### Primary tumor

The use of rapid CT apparatus enabled the determination of the vascularity and contrast imbibition only after rapid application of the contrast in the bolus. Analysis of the length of the period and the contrast imbibition distribution confirmed that the largest number of tumors showed intensive, fast, diffuse and inhomogeneous imbibition by type 2a.

#### Metastasis

Multiple tumors or tumors of different sizes suggest neoplastic lesions particularly when imbibition calcifications are present in the form of type 2bi.e. rapid transit imbibition in the form of a peripheral ring with nodular edges.

Using the defined and mentioned criteria there was offered a tabular presentation of differential changes between hepatocellular carcinoma and metastasis.

## 4. DISCUSSION

Table 1 shows that some authors agree, which was confirmed by our material as well that is a small number of metastases which can be diagnosed only after the application of contrast. However, the percentage in our material was significantly greater, but by taking into account the number of cases analyzed. Reasons for this phenomenon can be:

- \* The use of new-generation apparatuses with very short time of exposure and better spatial and dense metric differentiation.
- \* Using the most appropriate method for the application of contrast and scanning time.
- \* Strict criteria of classification.
- \* The largest number of patients in the initial phase, non-manifesting phase of occurrence of metastases.

Taking into consideration that metastasis (as well as other liver diseases) in the highest number of cases in CT is manifested with changing of density, the question arises of the existence of the connection between the measured density and histologic data, which means vascularization scale of pathologic change.

While some authors believe that inexpensive vascular processes after the application of contrast the density is greater than in tumors and hypodense metastases (2, 7, 18), other authors (20) consider that vascularization and intensity of den-

sification have no relations between them.

CT is superior method in presenting density changes of the liver parenchyma. Given that the vast majority of diffusive and focal hepatic lesions leads to alterations of density of the liver parenchyma in the hypodense and hyper dense form or with a mixed density, then a large number of liver diseases can be accurately identified and classified from the unenhanced scans, normally by using the apparatus adequately (fast scanning, absolute apnea), by using the spiral scanning (up to visualization of lesion), and with precise analysis of every scan.

However, in patients where the unenhanced scanning is normal and is inconsistent with positive clinical data by using previous examinations such as ultrasound or examinations with radionuclides, at that point, it is necessary the application of I.V. Contrast for verification of the suspicious lesions in unenhanced scanning and classification of the type of lesion. Due to the vascular configuration i.e. double afferent flow, fast change of contrast imbibition as in the normal liver as well as in the diffusive (inflammatory and degenerative) and focal lesions (benign and malign neoplasms) it is possible only with the use of fast scans after the fast application of the contrast in bolus.

## 5. CONCLUSION

We should mention the fact that the histological construction do not condition the manner and the extent of contrast imbibition of the lesion, therefore the one hand liver metastases in different primary tumors after the application of contrast provide same images, whilst on the other hand after application of contrast metastasis of the same primary tumors in different patients show completely different dense metric values.

- **Author's contribution:** author and all co-authors of this paper have contributed in all phases if it's preparing. Final proof reading was made by first author.
- **Conflict of interest:** none declared.

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