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

Arben Kutllovci¹,², Halit Ymeri¹,², Drita Zogaj²,³, Skender Kutllovci⁴, Dukagjin Zogaj¹
¹University Clinical Center of Kosova, Prishtina, Kosova
²Faculty of medicine, University of Prishtina, Prishtina, Kosova
³National Institute of Public Health of Kosova, Prishtina, Kosova
⁴Medical Group, Consulting, Prishtina, Kosova

Corresponding author: Arben Kutllovci, MD. ORCID ID: http://orcid.org/0000-0001-6058-9521. E-mail: arben_kutllovci@hotmail.com

doi: 10.5455/aim.2016.24.25-29
ACTA INFORM MED. 2016 FEB; 24(1): 25-29
Received: 11 November 2015 • Accepted: 29 December 2015

© 2016 Arben Kutllovci, Halit Ymeri, Drita Zogaj, Skender Kutllovci, Dukagjin Zogaj
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

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 sinusoïds,
• 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 evalu-
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 inhibition 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
Defining the Modalities of Intravenous Contrast Application

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;

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

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

| Time | Number | Diagnosis with CT | Type of data | Type of study | Positive results | Negative results | False positive results | False negative results |
|------|--------|-------------------|--------------|---------------|------------------|------------------|------------------------|------------------------|
| 18   | 32     | unlimited expan - sive lesions | metastases | retrospective | 6/7–66% | 22/25–88% | 3/5–12% | 1/7–14% |
| 30   | 55     | unlimited expan - sive lesions | metastases | prospective | 17/17–18% | 30/38–79% | 8/32–21% | 5/20–25% |
| 30   | 107    | metastases | meta and others | retrospective | 30/30–100% | 84/87–97% | 3/8–7% | 5/20–25% |
| 18   | 62     | metastases | tumors | prospective | 18/18–100% | 45/62–73% | / | / |
| 2    | 92     | metastases | tu.so. | retrospective | 2/2–100% | 44/55–80% | / | / |
| 264  |         | metastases | prim.and | retrospective | 2/2–100% | 170/175–97% | 35/37–95% | 1/94–1.1% |

Table 3. Type of contrast imbibition in intrahepatic lesions

| Type of data | IA | IB | IC | IIA | IIB | IIC | III | IV | TOTAL |
|--------------|----|----|----|-----|-----|-----|-----|----|-------|
| Hepatoma     | 0  | 5  | 0  | 54  | 0   | 0   | 0   | 17 | 89    |
| Metastases   | 0  | 7  | 3  | 6   | 49  | 7   | 32  | 13 | 117   |
| Hemangioma   | 3  | 11 | 2  | 0   | 0   | 0   | 0   | 0  | 16    |
| Cholangioma  | 0  | 0  | 0  | 0   | 0   | 0   | 6   | 1  | 7     |
| Abcess       | 0  | 0  | 0  | 13  | 0   | 0   | 0   | 0  | 13    |
| Other Lesions| 0  | 0  | 0  | 0   | 0   | 0   | 4   | 2  | 11    |
| Subtotal     | 3  | 23 | 26 | 60  | 68  | 14  | 57  | 23 | 253   |

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:

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;

Original Paper / Acta Inform Med. 2016 Feb; 24(1): 25-29
Defining the Modalities of Intravenous Contrast Application

### Table 4. Diagnostic differentiation between hepatocellular carcinoma and metastasis

| No. of Tumors | Tumor Density | Density lob. Reduction | Ring hypo density | Protrusion | Calcification |
|---------------|---------------|------------------------|-------------------|------------|--------------|
| HCC 11 / 9.5% | > 10          | Iso 13 / 11%           | 31 / 27%          | 41 / 36%   | 14 / 12%     | 19 / 17%     | 9 / 8%         |
| METASTASES    | 134 / 80%     | 4 / 2%                 | 0                 | 0          | 2 / 1%       | 11 / 6%      | 31 / 18%       |

| Ring imbibition | Size reduction | Special drawing | Imbibition with bolus | Liver Cirrhosis |
|-----------------|----------------|-----------------|-----------------------|----------------|
| HCC             | 11 / 12%       | 19 / 21%        | 0                     | 0              |
| METASTASES      | 63 / 54%       | 0               | 34 / 30%              | 19 / 16%       |

**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:

- As a result of new-generation apparatus 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 densification 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.

**REFERENCES**

1. Robinson PJ. Imaging liver metastases: current limitations and future prospects. Br J Radiol. 2000; 73: 234-41.
2. Sica GT, Ji H, Ros PR. CT and MR imaging of hepatic metastases. AJR Am J Roentgenol. 2000; 174: 691-8.
3. Glover C, Douse P, Kane P. et al. Accuracy of investigations for asymptomatic colorectal liver metastases. Dis Colon Rectum.
4. Teefey SA, Hildebolt CC, Dehdashri F et al. Detection of primary hepatic malignancy in liver transplant candidates: prospective comparison of CT, MR imaging, US, and PET. Radiology. 2003; 226: 533-42.

5. Paulson EK. Evaluation of the liver for metastatic disease. Semin Liver Dis. 2001; 21: 225-36.

6. Valis C, Andia E, Sanchez A. et al. Hepatic metastases from colorectal cancer: preoperative detection and assessment of resectability with helical CT. Radiology. 2001; 218(1): 55-60.

7. Furuse J, Nagase M, Ishii H. et al. Contrast enhancement patterns of hepatic tumors during the vascular phase using coded harmonic imaging and Levovist to differentiate hepatocellular carcinoma from other focal lesions. Br J Radiol. 2003; 76: 385-92.

8. Francis IR, Cohan RH, McNulty NJ. et al. Multidetector CT of the liver and hepatic neoplasms: effect of multiphase imaging on tumor conspicuity and vascular enhancement. AJR Am J Roentgenol. 2003; 180: 1217-24.

9. Saini S. Imaging of hepatobiliary tract. N Engl J Med. 1997; 336: 1889-94.

10. Bissoli E, Bison L, Gioulis E. et al. Multislice CT fluoroscopy: technical principles, clinical applications and dosimetry. Radiol Clin North Am. 1998; 36: 287-97.

11. Hahn PF, Saini S. Liver-specific MR imaging contrast agents. Radiol Clin North Am. 2003; 41: 51-65.

12. Zealley IA, Skehan SJ, Rawlinson J. et al. Selection of patients for resection of hepatic metastases: improved detection of extrahepatic disease with FDG PET. Radiographics. 2001; 21: S55-S69.

13. Zeeley IA, Schaefer, Rawlinson J. et al. Combined functional and structural evaluation of cancer patients with a hybrid camera-based PET/CT system using (18)F-FDG. J Nucl Med. 2002; 43: 1129-36.

14. Yao SZ, Zhang CQ, Chen J. et al. Clinical evaluation of 18F-FDE PET-CT in detecting malignant liver tumors. Yi Ji Jun Yi Da Xue Xue Bao. 2003; 23: 1214-16 (in Chinese).

15. Yang M, Martin DR, Karabulut N. et al. Comparison of MR and PET imaging for the evaluation of liver metastases. J Magn Reson Imaging. 2003; 17: 343-9.

16. Semelka RC, Cance WG, Marcos HB. et al. Liver metastases: comparison of current MR techniques and spiral CT during arterial portography for detection in 20 surgically staged cases. Radiology. 1999; 213: 86-91.

17. Vogt TJ, Schwartz W, Blume S. et al. Preoperative evaluation of malignant liver tumors: comparison of unenhanced and SPIO (Resovist)-enhanced MR imaging with biplanar CTA and intraoperative US. Eur Radiol. 2003; 13: 262-72.

18. Kinkel K, Lu Y, Both M. et al. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. Radiology. 2002; 224: 748-56.

19. Schultz JF, Bell JD, Goldstein RM. et al. Hepatic tumor imaging using iron oxide MR1: comparison with computed tomography, clinical impact, and cost analysis. Ann Surg Oncol. 1999; 6: 691-8.

20. Lai DT, Fullham M, Stephen MS. et al. The role of whole-body perfusion emission tomography with [18F] fluorodeoxyglucose in identifying operable colorectal cancer metastases to the liver. Arch Surg. 1996; 13: 703-7.

21. Desai DC, Zervos EE, Arnold MW. et al. Positron emission tomography affects surgical management in recurrent colorectal cancer patients. Ann Surg Oncol. 2003; 10: 59-64.

22. Arguedas MR, Chen VK, Eloubeidi MA. et al. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. Am J Gastroenterol. 2003; 98: 679-90.

23. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making. 1993; 13: 322-38.

24. Sorensen R, Maglaser C, Campagna P. et al. Usefulness of alpha-fetoprotein in the diagnosis of hepatocellular carcinoma. Anticancer Res. 2003; 23: 1747-53.

25. Donckier V, Van Laethem JL, Goldman S. et al. [F-18] fluorodeoxyglucose positron emission tomography as a tool for early recognition of incomplete tumor destruction after radiofrequency ablation for liver metastases. J Surg Oncol. 2003; 84: 215-23.

26. Ohtomo K, Ito Y, Yoshikawa K. et al. Hepatocellular carcinoma and cavernous hemangioma: differentiation with MR imaging. Efficacy of T2 values at 0.35 and 1.5 T. Radiology. 1992; 188: 621-3.

27. Quin SF, Benjamin GG. Hepatic cavernous hemangiomas: simple diagnostic sign with dynamic bolus CT. Radiology. 1992; 182: 545-8.

28. McFarland EG, Mayo-Smith WW, Saini S. et al. Hepatic hemangiomas and malignant tumors: improved differentiation with heavily T2-weighted conventional spin-echo MR imaging. Radiology. 1994; 193: 43-7.

29. Middleton ML. Scintigraphic evaluation of hepatic mass lesions: emphasis on hemangioma detection. Semin Nucl Med. 1996; 26: 4-15.