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The ability of consecutive phases of multiphase spiral CT to detect liver metastases

Przydatność poszczególnych faz wielofazowej spiralnej tomografii komputerowej w wykrywaniu przerzutów nowotworowych do wątroby.

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Summary

Background: In view of the constant progress in methods of treating liver metastases, new standards for radiological examinations must be developed. The purpose of this study was to evaluate the ability of sequential phases of multiphase spiral CT (sCT) to detect liver metastases and their segmental localization.

Material/Methods: sCT was performed on 100 patients with hepatic metastases. sCT included unenhanced scans (NC) and those of the hepatic arterial-dominant (HAP), portal venous-dominant (PVP), and equilibrium phases (EP). In each phase, the number, size of detectable lesions, and the accuracy of the topographic report of lesion location in liver segments were evaluated. Patients with primary cancer of the gastrointestinal tract constituted almost 70% of the group.

Results: A total of 354 liver metastases were detected by sCT. PVP revealed 346 (97.7%), HAP 298 (84.2%), and EP 241 (68.1%) secondary lesions. NC scans revealed 195 metastases (55.1%) when evaluated in the 'abdominal window'. The exact localization of metastases in liver segments was established in PVP in 88% of cases, in HAP 76%, in EP 70%, and in the NC phase in 71% of cases. Lesion diameter ranged from 4 to 127 mm (median: 21 mm). Lesions of more than 30 mm in diameter were clearly detectable in each phase of the CT examination.

Conclusions: PVP in sCT has the highest sensitivity in detecting liver metastases and contributes to the most adequate segmental localization. In the standard diagnosis of liver metastases, biphasic examination including HAP and PVP should be performed.

Key words: multiphase sCT • liver metastases • localization in liver segments

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Introduction

Cancer metastases involving the liver are a common problem in oncology because they are second only to regional lymph nodes as a site of dissemination. This is a result of the dual blood supply from both the systemic and splanchnic systems, but also because of the presence of local humoral factors promoting neoplastic cell growth [1]. The capacity of forming secondary lesions in the liver depends on the histological type and the localization of the primary tumor. Neoplasms of the gastrointestinal tract, drained by the portal vein system, give rise to liver metastases most

frequently, followed by breast and pulmonary cancers. The frequency of liver metastases is 20 times higher than that of primary liver tumors [1,2].

Patients with liver metastases not undergoing surgery survive on average no more than one year from the time of diagnosis [3,4]. Over the last decade the therapeutic approach to metastatic lesions has changed dramatically, particularly due to surgical resections, thermal therapies, percutaneous ablative therapies, chemoembolization, and orthotopic liver transplantation [1,3,4,5]. The possibility of a radical treatment of liver metastases depends on their number, size, and segmental location, as well as on their relation to vascular structures [3]. New standards for radiological examinations have been developed due to the constant progress in the methods of treatment of liver metastases.

The widely used methods for liver imaging are ultrasonography (US), computerized tomography (CT), and magnetic resonance imaging (MRI). In US, liver metastases have nonspecific appearance as hypoechoic, hyperechoic, or of mixed echogenicity [4]. The sensitivity for overall tumor detection ranges from 57% to 92%, whereas sensitivity decreases to 20% for lesions less than 1 cm in diameter [6,7].

Both CT and MR imaging, particularly contrast-enhanced imaging, have been successfully used for hepatic lesion detection [8,9]. Results of studies of MR imaging have suggested that this technique might improve the conspicuity of liver lesions [10]. New generations of CT scanners facilitate performing dynamic examinations, CT angiography (angio-CT), and three-dimensional reconstructions. Focal liver lesions show variable enhancement patterns, and administration of iodine contrast material in different phases of sCT is useful in visualizing the vascularity of liver tumors [2,3,11–15]. The use of i.v. contrast media administered with mechanical power injectors increases the sensitivity of focal lesion detection and can only be achieved if good scanning techniques are applied. Spiral CT is a relatively noninvasive method for the detection of hepatic lesions, with generally good results for lesion detection [16].

Multiphase examinations are not a part of the standard procedure of liver diagnostics in many hospitals. Moreover, CT examinations frequently consist of scans without contrast medium and/or with manual contrast injection, which produce only non-contrast and equilibrium phase images. The purpose of this study was to evaluate the sensitivity of each of the consecutive phases of multiphase sCT in the detection of liver metastases and in their exact localization to specific hepatic segments.

Materials and methods

212 patients with focal liver lesions detected by US underwent multiphase sCT of the liver with a HiSpeed scanner (GE) at the Radiology Department of the University of Gdansk in the period of March 1999 to December 2001. From this group, 100 cancer patients with liver metastases and oncological history with the primary tumor confirmed pathologically were chosen for further study. Three independent observers (JP, AZ, and ES) performed a prospective analysis of multiphase sCT images. Multiphase sCT included the non-contrast phase (NC), the hepatic arterial-dominant phase (HAP), the portal venous-dominant phase (PVP), and the equilibrium phase (EP). The thickness of the examined sections was 5 mm, pitch 1.5:1, matrix 512x512, and the exposure parameters were 120 kV and 210 mA. Spiral imaging of the entire liver was performed during the administration of 120 ml of iodinated contrast medium at a rate of 4 ml/sec through an 20 G venous catheter positioned in an antecubital vein using a power injector (Medrad). The onset of HAP was reached within 20–25 seconds (average: 22 sec.) after the beginning of contrast administration, PVP after 55–60 sec., and EP after 180 sec.

Metastases were confirmed histopathologically in 31 patients, and a diagnosis of secondary neoplasm was made in the remaining 69 patients on the basis of the subsequent clinical course and other imaging examinations. The group was comprised of 53 women and 47 men aged 38–78 years (median age: 57 years). Table 1 presents the localization of the primary tumors in the studied group. Patients with cancers of the gastrointestinal tract constituted approximately 70% of the group, the remaining subgroup including patients with pulmonary and breast cancers. Five patients had other types of neoplasms: melanoma, intestinal carcinoid, renal cancer, soft tissue sarcoma, and ovarian cancer. In the present study, liver lesions showing progression in consecutive radiological examinations or regression in the course of chemotherapy were identified as metastatic. Partial response to treatment (regression), defined according to the WHO criteria, is a more than 50% reduction in total tumor load of all measurable lesions determined by two observations not less than 4 weeks apart. Progressive disease is a more than 25% increase in the size of one or more measurable lesions [17].

Each of the observers independently determined the number of lesions visible in each phase and the adequacy of lesion localization to specific hepatic segments. The localization of lesions was determined through analysis of all phases, and three-dimensional reconstructions were accepted as references. The anatomical classification of liver segments by Coinaud [18], modified by Bismuth [19], was accepted as the reference.

To evaluate the correctness of the study protocol, the consistency of the results obtained by the individual observers was verified using kappa statistics (Cohen's test) [20]. The sensitivities of the different phases in detecting liver metastases (percentage of lesions detected) were compared by the chi-squared test.

Table 1. Studied group of 100 patients according to primary tumor site.
Tabela 1. Pierwotna lokalizacja nowotworu w grupie 100 chorych z przerzutami do wątroby.

Primary tumor by type	Number of patients
Colorectal cancer	53
Pancreatic and gastric cancer	15
Pulmonary cancer and carcinoid	15
Breast cancer	12
Other neoplasms	5

Table 2. Number of lesions by primary tumor site of all 354 liver lesions studied.
Tabela 2. Liczba przerzutów do wątroby w poszczególnych typach nowotworów pierwotnych.

Primary tumor	Number of metastases [range]	Percentage
Colorectal cancer	201 [1-7]	56.8%
Pancreatic and gastric cancer	82 [3-19]	23.2%
Pulmonary cancer and carcinoid	24 [1-5]	6.8%
Breast cancer	36 [1-7]	10.2%
Other neoplasms	11 [1-4]	3%

Table 3. Number of visible and invisible lesions in consecutive phases of sCT.
Tabela 3. Liczba widocznych i niewidocznych ognisk w poszczególnych fazach badania sTK.

Number of lesions	NC	HAP	PVP	EP	NC+EP	HAP+PVP
Visible	195 (55.1%)	298 (84.2%)	346 (97.7%)	241 (68.1%)	265 (74.9%)	353 (99.7%)
Invisible	159 (44.9%)	56 (15.8%)	8 (2.3%)	113 (31.9%)	89 (25.1%)	1 (0.03%)

Results

Comparison of the results obtained by the independent observers revealed high and very high values of the kappa statistics. The values ranged from 0.65 to 0.95 in the evaluation of the consistency in lesion localization in subsequent phases of the CT examination. Evaluation of the consistency in lesion counts in consecutive phases gave a kappa value of 0.8–0.97. The high consistency of the results obtained by the three observers (JP, AZ, and ES) proved the proposed study protocol to be adequate and repeatable.

A total of 354 secondary lesions were detected in the analyzed patients. Individual patients were found to have from 1 to 19 metastases (median: 3). Metastases from gastrointestinal tract neoplasms (colorectal, pancreatic, and gastric cancers) constituted 80% of the detected lesions in the liver. Table 2 shows the number of metastases according to the primary tumor site.

Diameters of lesions ranged from 4 to 127 mm (median: 21 mm). Half of all metastases detected were less than 20 mm in diameter.

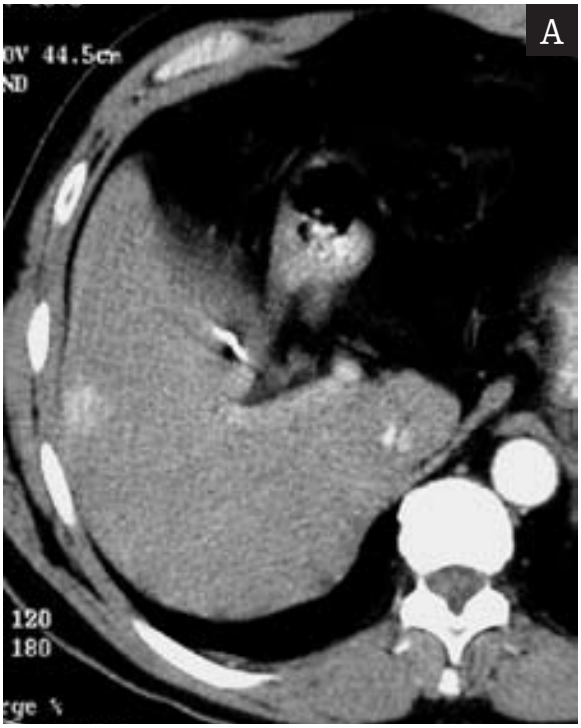
PVP revealed 346 of the 354 metastases found (97.7%), HAP 298 (84.2%), whereas EP showed 241 lesions, which is 68.1% of the metastases detected in all phases of the study. NC assessed in the 'abdominal window' gave the correct diagnosis of metastases in 55.1% cases (195 lesions) and in the 'cerebral window' it showed 64.1% correct diagnoses (227 of 354 lesions). Table 3 shows the ability to reveal metastases in subsequent phases. The differences between the efficacies of PVP and HAP (97.7 % vs. 84.2%), HAP and EP (84.2% vs. 68.1%), and EP and NC 'abdominal window' (68.1% vs. 55.1%) are statistically significant (chi-squared test, $p<0.001$).

Combined HAP and PVP failed to reveal only 1 metastasis (colorectal cancer), but it was successful in visualizing 99.7% of all lesions (353 of 354). Forty-eight lesions were visible only in PVP, which included metastases of less than 20 mm in diameter, originating from pancreatic cancer (32 lesions), followed by gastric (9 lesions) and colon cancer (7 lesions). Seven metastases (from renal cell carcinoma, soft tissue sarcoma, and pulmonary carcinoid) constituted 2% of all lesions and were detected exclusively in HAP. The combination of NC and EP did not reveal 25% of all metastases (89 of 354 lesions). The difference in the sensitivities of HAP+PVP and NC+EP was statistically significant (chi-squared test, $p<0.001$). Additionally, statistically significant differences were found between the sensitivities in revealing metastases in PVP versus NC+EP and in HAP versus NC+EP (chi-squared test, $p<0.001$ and $p=0.002$, respectively). Lesions of more than 30 mm in diameter were clearly visible in all sCT phases.

The exact localization of lesions in liver segments was confirmed by sequential phases in the following percentages of cases: PVP 88%, HAP 76%, EP 70%, and NC 75%. The differences between the sensitivity of PVP and those of the other phases (HAP, EP and NC) in the localization of lesions to specific hepatic segments were statistically significant (chi-squared test, $p<0.001$).

Discussion

Multiphase spiral computerized tomography has a high efficacy in the detection of focal liver lesions [3,11,21–24]. The administration of iodine contrast material for the visualization of liver tumors in different phases of sCT permits an assessment of the vascularity of those lesions. The hepatic arterial-dominant phase (HAP) displays the aorta, the hepatic artery and its branches, as well as focal lesions supplied by these vessels. Most neoplasms and tumor-like conditions, e.g. hepatocellular carcinoma, focal nodular hyperplasia of the liver, arteriovenous shunts, and metastases mainly from renal and thyroid cancers, endocrine tumors, sarcomas, and melanoma, are called hypervascular lesions [12–15,25] because they receive a greater arterial blood supply than the surrounding liver tissue. Hypervascular lesions are well visualized in HAP as hyperdense foci. In a subsequent phase of the examination, the portal venous-dominant phase (PVP), the above lesions may not be visualized or have reduced visibility [11,13,25]. This poor visibi-



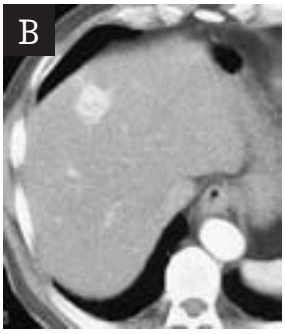
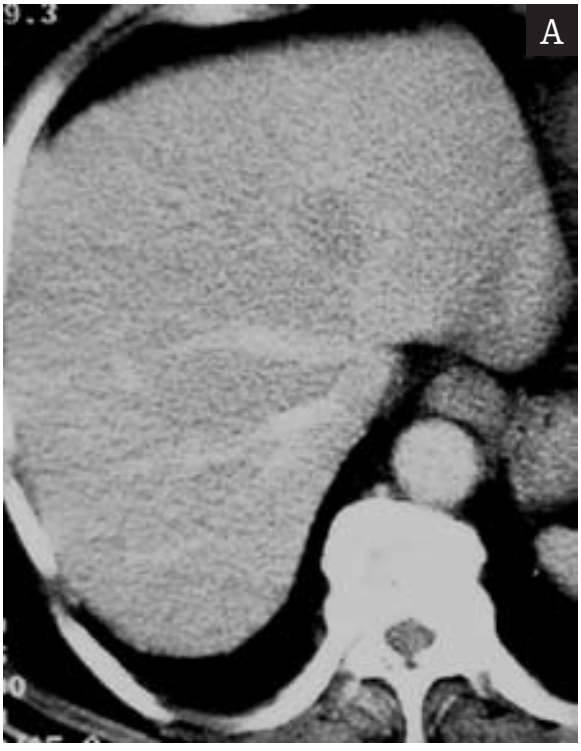


Figure 1a, b. Metastases from a pulmonary carcinoid. These lesions were visualized only in HAP images and correctly recognized in segments V (Fig. 1a) and IV (Fig. 1b).

Rycina 1a, b. Przerzuty rakowiaka płuca do wątroby widoczne były jedynie w fazie tętniczej wątrobowej. Prawidłowo oceniono lokalizację zmiany w segmencie V wątroby (ryc. 1a) i w segmencie IV (ryc. 1b).



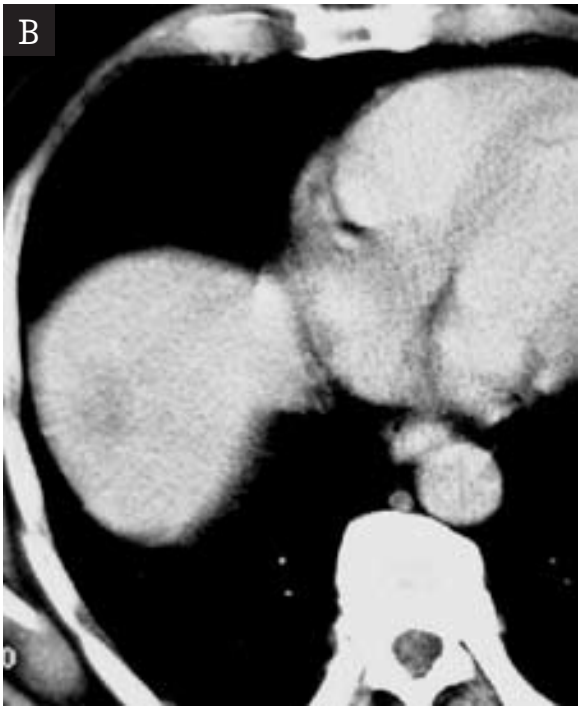


Figure 2a, b. Metastases from breast cancer visible only in transverse PVP scans of the liver. These lesions were correctly recognized in segments IV (Fig. 2a) and VIII (Fig. 2b)

Rycina 2a, b. Przerzuty raka piersi do wątroby były widoczne tylko w fazie żylnej wrotnej. Poprawnie opisano lokalizację ogniska w segmencie IV (ryc. 2a) i w segmencie VIII (ryc. 2b).

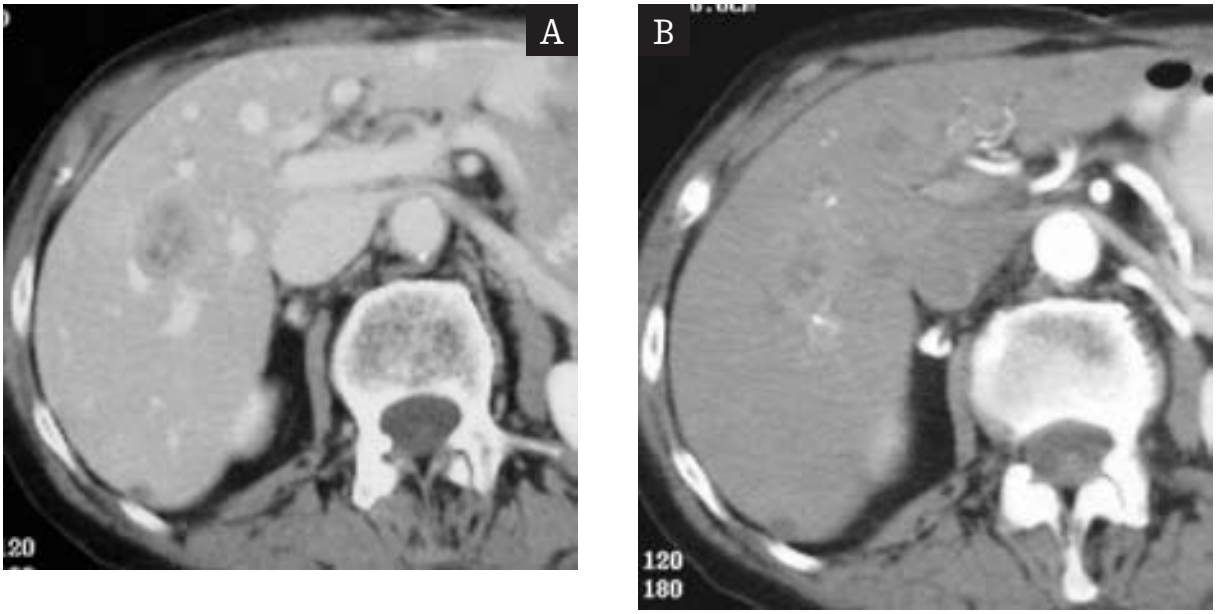


Figure 3a, b. Metastasis from colon cancer clearly visible in PVP scan and correctly recognized in segment VIII of the liver (Fig 3a). This lesion was not detected in HAP images (Fig 3 b). A cyst was detected in each phase in segment VII of the liver.

Rycina 13a, b. Przerzut raka okrężnicy do wątroby najlepiej widoczny w fazie żylnej wrotnej (ryc. 3a). Prawidłowo oceniono lokalizację zmiany w segmencie VIII wątroby. Zmiana ta nie została wykryta w fazie tętniczej wątrobowej (ryc. 3b). Torbiel w segmencie VII wątroby była dobrze widoczna we wszystkich fazach badania.

lity is caused by the effects of early contrast wash-out from the lesions and the progressive enhancement of the liver parenchyma due to equilibration between the lesion and the liver. This renders a differential diagnosis extremely difficult. The enhancement of the liver is stronger than that of hypovascular lesions during both the arterial and portal phases [1,25]. Metastases with a less intensive supply, e.g. from the gastrointestinal tract or pulmonary and breast cancer, are usually visible as less perfused regions compared with the enhanced liver parenchyma [1,11,13]. Only the border of hypervascular metastases can receive mainly portal blood; during PVP these metastases thus show a peripheral ring of enhancement [1,11]. Hypervascular lesions with the persistent effect of enhancement in PVP may be demonstrated as hyperdense foci. The equilibrium phase (EP) produces a uniform enhancement of the vascular structures and liver parenchyma. With this, less perfused regions may be identified.

Hypervascular lesions are better visualized in HAP [12,14,15], so they become relatively more enhanced than the surrounding liver parenchyma within the first 20–40 seconds after beginning continuous infusion of the contrast medium [12,13,21–24]. PVP may not reveal the presence of hypervascular metastases due to their level of enhancement being similar to that of the normal hepatic tissue [26]. Hypovascular lesions, which include most types of metastases (from a primary GI tract tumor), are visible as regions of hypoperfusion: foci of hypodensity compared with the surrounding liver tissue. This is caused by their low enhancement [23,24,26].

The role of HAP in detecting hepatocellular carcinoma and hypervascular metastases is renowned [2,4,14,15,22,27,28]. According to Hollet et al. [22], the efficacy of HAP is highest of all the phases. The authors also state that 37% of neoplastic foci in liver with diameter not greater than 15 mm can be demonstrated in HAP only. Oliver et al. [24] report that this also concerns larger lesions, but less frequently. Bonaldi et al. [14], however, report that 8% of metastases are detected in HAP only. Our results are similar to the ones published by Sheafor et al. [13], who studied the efficacy of triphase sCT in the detection of metastases from breast carcinoma and found that 2–4% of lesions are revealed in the arterial-dominant phase only. In our study, 2% of lesions were detected exclusively in HAP, and these were metastases from renal cancer, sarcoma, and carcinoid (Fig. 1a, b). The lower sensitivity of HAP demonstrated in our report compared with those of other authors [13,14,22,24] is due to the low number of hypervascular metastases (3% of analyzed lesions). In the presented report, all hypervascular metastases (11) were revealed in the arterial-dominant phase, and 67% of them (7 of 11 lesions) were visualized exclusively in this phase. This result proves the high sensitivity of HAP in the detection of metastases with a rich vascular supply. Research by Erik et al. [15] demonstrates the high sensitivity and specificity of HAP in the diagnosis of secondary carcinoid lesions. In our study, 3 of 4 carcinoid metastases were visible only in HAP, and their diameter did not exceed 20 mm, whereas the fourth secondary focus of carcinoid of 40 mm in diameter was clearly detectable in all phases of the examination. However, for metastases from renal cell carcinoma, commonly thought of as hypervascular, the value of multiphase scanning is seriously questioned by Raptopoulos et al. [26]. They show that combining the PVP and NC scans detected as many lesions as combining PVP and HAP images. But the majority of patients studied by Raptopoulos et al.[26] received immunotherapy before examination, which could alter the biological and radiological properties of the neoplastic tissue.

Most lesions (343) considered in our study were metastases from the gastrointestinal tract, lung and breast cancers (97%), characterized by a scant vascular supply. In our study, 346 lesions were well visible in PVP and 342 of them were hypovascular. Forty-eight of the hypovascular metastases were detected exclusively in PVP (Fig. 2a, b). Our results are therefore compatible with the other reports where PVP was considered as the best method of visualization of these lesions [11,13,23,24]. As for hypovascular metastases, HAP images do not add significant information to PVP scanning of the liver, and the sensitivity of PVP in the detection of these lesions reached 99.7% in our study (Fig. 3a, b).

Sheafor et al. [13] consider PVP as the optimal diagnostic phase in detecting metastases from breast cancer and argue that only a small percentage of breast tumors are of hypervascular type. Blake et al. [21] studied this phenomenon in cases of metastases from malignant melanoma. The authors stated that only the biphasic CT examination, including PVP and HAP or PVP and NC, produced a significant rate of secondary lesion detection. In the same study, the ability of EP in detecting focal liver lesions was strikingly low. Our study likewise revealed low sensitivity of EP and NC both individually and combined (25% of lesions were not recognized) in detecting liver metastases. On the other hand, PVP and HAP performed in combination allow detecting as much as 100% of secondary lesions, which is consistent with the results of Blake et al. [21].

Some authors report that CT arterioportography (CTAP) produces the highest sensitivity, both in the detection and the localization of metastases to specific hepatic segments [2,29,30]. This is of particular value in cases of lesions of less than 10 mm size [29,30].

We found that PVP is the phase which best demonstrates the division of the liver into individual segments thanks to the optimal enhancement of the venous structures. This is consistent with data found in literature [29–31]. Our report also demonstrated the utility of PVP in the most accurate assessment of the localization of lesions in individual liver segments (88% correct topographic reports). Similar efficacy of HAP and NC scans in the evaluation of the segmental localization of lesions is due to the analogous images of venous vessels, which in both phases are visible as hypodense bands. EP was seen to cause the most problems in evaluating the exact location of metastases, since all vascular structures are equally enhanced in this phase of the examination.

Conclusions

The portal venous-dominant phase shows the highest sensitivity in the detection and localization of hepatic metastases to specific liver segments. PVP combined with HAP increases the sensitivity of hypervascular metastases diagnosis. EP and NC combined do not improve diagnosis compared with PVP and HAP performed separately. Biphasic examination including HAP and PVP should be performed as a standard in the diagnostics of liver metastases.

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