Abstract. Aim: To assess the diagnostic accuracy and radiation dose of split-bolus multidetector-row computed tomography (MDCT) protocol in the detection and characterization of focal liver lesions in oncologic patients. Patients and Methods: We retrospectively analyzed triphasic CT at initial diagnosis and follow-up split-bolus 64-detector row CT protocol in 48 oncologic patients with focal liver lesions. Split-bolus MDCT protocol by i.v. injection of two bolus of contrast medium combines hepatic arterial phase (HAP) and hepatic enhancement during portal venous phase (PVP) in a single pass. First bolus: 75-90 mL at 2.0 mL/sec to obtain adequate hepatic enhancement during the PVP; second bolus: 60 mL/sec at 3.5 mL/sec to ensure HAP. Each bolus is followed by 20 mL of saline solution at the same flow rate. Sensitivity, specificity, positive predictive value and negative predictive value of split-bolus MDCT protocol were calculated for detection and characterization of liver lesions. The effective radiation dose (ED) was calculated using dose-length product (DLP) values in mSv determined using a conversion factor. Results: compared to triphasic-MDCT, split-bolus MDCT protocol confirmed all the 210 lesions identified and characterized by triphasic-MDCT technique, unchanged during the follow-up. The mean ED was 27.8±6 mSv for chest-abdomen-pelvis biphasic split-bolus MDCT and 45.7±13.6 mSv for triphasic-MDCT. Conclusion: The diagnostic efficacy of split-bolus protocol is comparable to that of triphasic protocol at MDCT with a reduction in radiation dose of approximately 35-40%.

The liver is the organ most commonly affected by metastatic disease, which arises most frequently from primary sites in the colon, breast, lung, pancreas and stomach (1). In clinical practice, accurate detection and characterization of focal liver lesions at the time of diagnosis or during the course of treatment is essential for patient management.

Triphasic hepatic arterial phase (HAP), portal venous phase (PVP) and delayed phase (DP) multidetector-row computed tomography (MDCT) is the preferred technique for the detection and characterization of a wide range of liver lesions (2-4). General screening for liver disease is well-performed with helical CT during the PVP to detect hypovascular lesions.

The split-bolus protocol is an innovative technique consisting of splitting intravenous contrast medium into two or three boluses and combining phase images (HAP and PVP) in a single scan, and it is used in several CT applications, with a significant reduction of dose radiation to the patient (5-9). To our knowledge, in the literature there exist no studies regarding the application of this technique in the evaluation of focal liver lesions. We implemented the split-bolus MDCT technique for the detection and characterization of focal liver lesions in oncologic patients.
We assessed the diagnostic efficacy of the split-bolus technique comparing the results with those of triphasic-MDCT technique in the evaluation of focal liver lesions in order to propose this technique both for diagnosis and follow-up of oncologic patients.

Patients and Methods

Study design and patients. A retrospective analysis of split-bolus MDCT data of patients consecutively referred from January 2012 to December 2013 was performed in our study. Written informed consent for split-bolus MDCT protocol was obtained from each patient.

Forty-eight oncologic patients (23 males and 25 females; age range=42-80 years, mean age=63.3 years; weight range=60 and 75 kg, mean weight=68 kg), with 296 focal liver lesions detected by an initial triphasic-MDCT examination, underwent split-bolus MDCT scanning of the chest, abdomen and pelvis 6-12 months after their initial CT examination as a part of their follow-up. No patient had cardiovascular insufficiency or liver cirrhosis.

All patients had known extrahepatic histologically-confirmed primary cancer: colorectal cancer (n=13), lung cancer (n=15), breast cancer (n=9), pancreatic cancer (n=3), gastric cancer (n=7) and melanoma (n=1).

To determine the benign or malignant nature of a focal liver lesion, we considered the typical features at triphasic-MDCT, at ultrasound or magnetic resonance imaging and their behavior on sequential imaging studies.

Because the patients had chemotherapy after initial triphasic-MDCT, in order to perform a correct comparison of the results of triphasic (representing the patient baseline study) and split-bolus (representing the follow-up evaluation) MDCT techniques, we only included focal liver lesions unchanged in size and appearance (benign, malignant and indeterminate lesions) in our analysis. Malignant lesions that grew, became smaller or disappeared over time at split-bolus MDCT follow-up evaluation were excluded.

Scanning protocols. At initial triphasic and follow-up split-bolus MDCT, all patients were scanned with a Philips Brilliance 64-detector row scanner (Philips Healthcare, Best, the Netherlands). Triphasic-MDCT: This protocol consisted of unenhanced images and a HAP (started 35-40 s after the injection of the contrast medium or 20 s after threshold of 150 HU in the thoraco-abdominal aorta by using bolus tracking technique) of the upper abdomen, a PVP started 40 s after the end of HAP acquisition of the chest, abdomen and pelvis and a DP (5 minutes after the start of injection) of the upper abdomen. Nonionic iodinated contrast medium (Iopamidolo, Iopamiro 370 mgI/ml; Bracco, Milano, Italy and Iopromide, Ultravist 370 mgI/ml Schering AG, Berlin, Germany) was injected in a quantity ranging from 120 ml to 150 ml at a rate of 4 ml/s from an antecubital vein using an 18-gauge needle.

Split-bolus MDCT: This protocol consisted of unenhanced low-milliamperes scans of the upper abdomen and a single acquisition of the chest, abdomen and pelvis after i.v. injection of a maximum of 150 ml of contrast medium (as described above), split by an automatic power injector (Stelland CT; Medrad, Indianola, PA, USA) into two boli (Figure 1).

The dose of contrast medium for the first bolus, injection duration and times were established on the basis of literature data (10-12) and broad clinical experience. For our patients (weight ranging from 60 to 75 kg), we obtained an adequate hepatic enhancement during PVP by administering the first bolus of contrast medium (1.2 ml/kg) at a fixed flow rate of 2 ml/s, and with an injection duration ranging from 37 to 45 s. In addition, optimal patient bodyweight-tailored dose of contrast medium for the liver was determined based on a definition of the dose which can give adequate hepatic enhancement (more than 50 HU increase from unenhanced baseline HU of the liver) during PVP (13, 14). HAP occurs about 35 s after the start of i.v. injection of a bolus of 60 ml of contrast medium at 3.5 ml/s.

Using the scout film, a scan range from the pulmonary apex to the pubic symphysis was determined. Then a circular region of interest of the bolus tracking technique (raising the threshold value at 500 HU) was placed in the descending aorta. Approximately at the end of the second bolus injection of contrast medium, the scan started cranio-caudally after a delay of at least 6 s from the arrival of the contrast medium in the aorta. The inherent 6 s delay in the bolus tracking technique is necessary in order to move the scan table to the start of the scan, give breath-hold instructions to the patient, and tune the gantry parameters.

A single contrast-enhanced acquisition was carried out, resulting in a simultaneous contrast enhancement of the arterial and venous systems.

For triphasic and split-bolus MDCT protocol, the following acquisition parameters were used: slice thickness 2.5 mm; gantry rotation speed 0.75 s; reconstruction index 1.25; pitch: 0.935:1; 120 kVp and 200-400 mAs. Automatic tube current modulation was used to minimize radiation exposure. MDCT examinations were completed with sagittal, coronal and curved multiplanar reconstructions.

Images were transferred to an external workstation (Advantage Workstation 4.2 from GE Healthcare, Milwaukee, Wisconsin, USA; and Magic View from Philips Medical Systems, Best, the Netherlands) and stored in image archiving and communication system (PACS; Agfa Impax RIS Healthcare, Mortsel, Belgium, EU).

Image analysis. All CT images were transported from local digital media to a viewing station (Advantage Workstation 4.2; Magicview) and were blindly reviewed by two radiologists (M.S., A.D.A) with more than 10 years of experience in interpreting body CT images, and who independently analyzed triphasic and split-bolus CT.

Attenuation of the aorta, main portal vein and right lobe of the liver were measured by a circular region of interest without major vascular structures, at combined HAP/hepatic enhancement during PVP on split-bolus scans and at HAP and PVP on triphasic-MDCT scans.

The appearance of each lesion at split-bolus MDCT was described on the basis of the attenuation and homogeneity of the lesion in comparison with aorta, relating to the triphasic CT findings (2, 4, 15-18).

After describing the state of each lesion in each phase, the pattern of enhancement over time of each lesion was described as a three-part pattern name that incorporated the appearance of the lesion in each phase (HAP, PVP, DP) of the triphasic CT technique (e.g. hypo-/hyper-hypo-) and as a two part pattern name that incorporated the appearance of the lesion in the combined HAP/hepatic enhancement during PVP on split-bolus protocol (e.g. hypo-hypo-).

The comparative analysis between the two protocols was performed only on lesions that did not change in number and size between the initial triphasic and follow-up split-bolus MDCT.

The radiation dose to the patient and the number of images to be analyzed with split-bolus (including DP) and triphasic-MDCT protocol were determined and the results were compared.
deviations (SDs) of attenuation CT values, Student’s also assessed. For comparative analysis of the averages and standard specificity, positive predictive value and negative predictive value were detection and characterization of focal liver lesions, sensitivity, substantial agreement; $k\geq0.80$, excellent agreement (20, 21). For the agreement; $0.41\leq k\leq0.60$, moderate agreement; $0.61\leq k\leq0.80$, liver lesions was evaluated using weighted $k$ statistics, with a $k$ value on the following: $k$ value $<0.2$, poor agreement; $0.2\leq k\leq0.4$, fair agreement; $0.41\leq k\leq0.60$, moderate agreement; $0.61\leq k\leq0.80$, substantial agreement; $k>0.80$, excellent agreement (20, 21). The detection and characterization of focal liver lesions, sensitivity, specificity, positive predictive value, negative predictive value were also assessed. For comparative analysis of the averages and standard deviations (SDs) of attenuation CT values, Student’s $t$-test was used: a $p$-value less than 0.05 was considered statistically significant.

Results

Forty-eight patients underwent initial triphasic (n=48 examinations) and follow-up split-bolus (n=48 examinations) MDCT protocol, with a total of 96 chest, abdominal and pelvic MDCT examinations. Focal liver lesion size varied from 5 mm to 47 mm. No significant differences were shown at combined HAP/hepatic enhancement during PVP of split-bolus MDCT compared to HAP and PVP of triphasic-MDCT with respect to peak enhancement of the aorta, main portal vein and liver parenchyma (Figure 2).

The mean attenuation value of the aorta at split-bolus MDCT was not significantly different from that of the standard multiphase protocol at HAP (354.16 HU±43.65 vs. 375.76 HU±42.86 respectively; $p<0.05$).

The attenuation value of the main portal vein at split-bolus MDCT was not significantly different from that of the standard MDCT triphasic protocol at PVP (210.25 HU±23.08 vs. 227.28 HU±28.19, respectively; $p<0.05$).

The mean attenuation value of the liver parenchyma at split-bolus MDCT was not significantly different from that of the MDCT triphasic protocol at PVP (118.1 HU±12.9 vs. 112.3 HU±12.8, respectively; $p<0.05$).

Image analysis and comparison of the triphasic and split-bolus MDCT protocols, were performed on 234 lesions [typical hemangiomas (n=11), atypical hemangiomas (n=3), cysts (n=88), hypovascular (n=105) and hypervascular (n=3) metastasis, and indeterminded (≤5 mm) lesions (n=24)], not changed in size and appearance on initial triphasic and split-bolus MDCT examination. Split-bolus MDCT technique confirmed all 234 of the lesions identified by MDCT triphasic technique with a sensitivity, specificity, positive predictive value, negative predictive value of 100% and a weighted $k$ value of 1 (0.8≤$k$≤1, excellent agreement).

Similarly to triphasic-MDCT, the split-bolus MDCT technique was not able to characterize the small lesions with a size $\leq5$ mm (indeterminate lesions).

Some representative images of the liver lesions included in the study for comparison of triphasic and split-bolus CT findings are reported in Figures 3-7.

A significant reduction of the radiation dose was obtained by the split-bolus MDCT technique (mean dose 27.8±6 mSv) with respect to triphasic-MDCT (mean dose 45.7±13.6 mSv) ($p<0.05$).

The split-bolus MDCT technique leads to a significant reduction in the number of images to be analyzed with respect to triphasic-MDCT (the mean number of images was 665.6±81.1 for split-bolus and 1069.1±318.6 for triphasic-MDCT; $p<0.05$).

Discussion

Differentiation between benign and malignant focal liver lesions in patients with known primary extra-hepatic malignancy is essential in order to avoid inappropriate diagnosis and unnecessary surgery or chemotherapy (1). Although triphasic spiral CT has gained acceptance as the preferred technique for the evaluation of a wide range of liver lesions (2-4), in the initial and follow-up computed tomographic scans, some authors consider PVP imaging of
hepatic enhancement only adequate for detecting hypovascular hepatic lesions (22, 23).

Considering the radiation dose to the patient due to the triphasic CT technique and to the repeated CT scans during the follow-up, we implemented an innovative split-bolus MDCT protocol that, compared to monophasic injection of contrast medium used for triphasic or PVP acquisition, has the advantage of combining the HAP and the PVP hepatic enhancement in a single acquisition allowing identification of both hypo- and hypervascular focal liver lesions.

To better evaluate the split-bolus CT protocol reported in our study, it is essential to know the enhancement peak of main portal vein and liver related to patient weight, determined by the first bolus of contrast medium. As reported in literature (11), patient weight is correlated to enhancement peak of main portal vein and liver. With 40 and 45 s of injection duration, in patients with weight ranging from 60 to 70 kg, the enhancement peak of the main portal vein was 212.4±20.4 and 206.5±19.2 HU and that of the liver was 59.8±9.6 and 58.9±7.8 HU, respectively.

In our study, with a fixed flow rate of 2 ml/s, and an injection duration time ranging from 37 to 45 s, by first bolus (1.2 ml/Kg), we obtained an attenuation in HU of the liver parenchyma and the main portal vein similar to that of the standard triphasic-MDCT protocol. In addition, optimal patient bodyweight-tailored dose of the first bolus of contrast medium for the liver was determined based on the dose providing adequate hepatic enhancement (more than 50 HU increase from unenhanced baseline HU of the liver) during the hepatic parenchymal phase (13, 14). A second bolus of 60 ml of contrast medium, at 3.5 ml/s ensured an adequate HAP demonstrating the hypervascular lesions.

The split-bolus technique had high accuracy (excellent agreement) in the detection and characterization of focal liver lesions: this technique detected and characterized all 234 lesions detected by the triphasic MDCT-technique.

For both triphasic and split-bolus MDCT techniques, the intrinsic limitations common to CT remain: as reported in the literature, focal lesions of small size (≤5 mm) are indeterminate (2, 9, 24).

Our study has certain limitations. Firstly, the study groups were relatively small. Our preliminary study, with a relatively small group, confirmed the diagnostic performance of this technique, although further studies with a larger number of patients should be performed. Secondly, we evaluated the results of split-bolus MDCT technique subsequent to chemotherapy, and some lesions changed both in size and appearance. We overcame this limitation by not analyzing the lesions that grew, became smaller or disappeared over time in the comparison.

Our study using split-bolus MDCT protocol included an additional DP to make the results comparable with those of triphasic-MDCT.
Figure 3. Initial triple-phase computed tomography (CT) of hepatic cysts in arterial phase (a), venous phase (b), and delayed phase (c). Single-pass 64 detector-row CT at 6-month follow-up with split-bolus intravenous contrast medium technique (d) and delayed phase at 5 min (e) show similar patterns.
Figure 4. Initial triple-phase computed tomography (CT) of hepatic sub-capsular (segment VII) typical hemangioma with a peripheral globular enhancement in arterial phase (a), venous phase (b), and delayed phase (c). Single-pass 64 detector-row CT at 6-month follow-up with split-bolus intravenous contrast medium technique (d) and delayed phase at 5 min (e) demonstrates similar patterns (peripheral enhancement that extends toward the center).
Figure 5. Initial triple-phase computed tomography (CT) of hepatic subcapsular (segment IV) atypical hemangioma with rapid flow in arterial phase (a), venous phase (b), and delayed phase (c). Single-pass 64 detector-row CT at 6-month follow-up with split-bolus intravenous contrast medium technique (d) and delayed phase at 5 min (e) shows similar patterns.
Figure 6. Initial triple phase computed tomography (CT) of a hypodense liver metastasis in patient with colorectal cancer in arterial phase (a), venous phase (b), and delayed phase (c). Single-pass 64 detector-row CT at 6-month follow-up with split-bolus intravenous contrast medium technique (d) and delayed phase at 5 min (e) show similar appearance and same size.
Figure 7. Initial triple phase computed tomography (CT) of a hyperdense liver metastasis in patient with gastric cancer in arterial phase (a), venous phase (b), and delayed phase (c). Single-pass 64 detector-row CT at 6-month follow-up with split-bolus intravenous contrast medium technique (d) and delayed phase at 5 min (e) show similar appearance and same size.
In conclusion, this preliminary study demonstrates the effectiveness of split-bolus MDCT technique in the evaluation of focal liver lesions in oncologic patients. Split-bolus MDCT technique confirmed the results of initial triphasic-MDCT, with a significant reduction in radiation dose (approximately 35-40%) to the patient and a significant decrease in the number of images to be analyzed, in data storage and costs. Moreover, the split-bolus technique optimized the results of PVP, allowing the detection of both hypo- and hypervascular focal liver lesions.

Our preliminary study demonstrates that the designed split-bolus MDCT technique can be proposed as an alternative to the triphasic technique and to PVP acquisition as initial and follow-up CT examination of oncologic patients. Furthermore, if the data of split-bolus MDCT are confirmed in a large series, it will potentially represent a valid tool in the clinical work-up of oncologic patients, in addition to other diagnostic modalities such as 18F-fluorodeoxyglucose positron-emission tomography.

References