Semi-automatic Volumetric Measurement of Treatment Response in Hepatocellular Carcinoma After Trans-arterial Chemoembolization

JOHANNES BUDJAN[1*], ELKE A. SAUTER[1*], JOHN N. MORELLI[2], MARCO NOLDEN[3], ANDREAS FETZER[3], LOTHAR PILZ[4], MIRIAM REICHERT[1], THERESA BRANDT[3], JAN HANSMANN[1], STEFAN HANEDER[5], NILS RATHMANN[1], STEFFEN J. DIEHL[1], HANS-PETER MEINZER[3], STEFAN O. SCHOENBERG[1] and ULRIKE I. ATTENBERGER[1]

[1]*Department of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany;*
[2]*St. John's Medical Center, Tulsa, OK, U.S.A.;*
[3]*Division of Medical and Biological Informatics, German Cancer Research Centre, Heidelberg, Germany;*
[4]*Department of Biostatistics, University Medical Center Mannheim, Medical Faculty Mannheim, Mannheim, Germany;*
[5]*University Hospital of Cologne, Institute of Diagnostic and Interventional Radiology, University of Cologne, Cologne, Germany*

Abstract. *Aim: To perform a quantitative, volumetric analysis of therapeutic effects of trans-arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC) patients. Patients and Methods: Entire tumor volume and a subset of hypervascular tumor portions were analyzed pre- and post-TACE in magnetic resonance imaging datasets of 22 HCC patients using a semi-automated segmentation and evaluation tool from the Medical Imaging Interaction Toolkit. Results were compared to mRECIST measurements and inter-reader variability was assessed. Results: Mean total tumor volume increased statistical significantly after TACE (84.6 ml pre- vs. 97.1 ml post-TACE, p=0.03) while hypervascular tumor volume decreased from 9.1 ml pre- to 3.7 ml post-TACE (p=0.0001). Likewise, mRECIST diameters decreased significantly after therapy (44.2 vs. 15.4 mm). In the inter-reader assessment, overlap errors were 12.3-17.7% for entire and 36.3-64.2% for the enhancing tumor volume. Conclusion: Quantification of therapeutic changes after TACE therapy is feasible using a semi-automated segmentation and evaluation tool. Following TACE, hypervascular tumor volume decreases significantly.*

Hepatocellular carcinoma (HCC) is the third most common cause of death from cancer worldwide and the sixth most common cancer overall (1). Less than 30% of HCC patients are eligible for definitive resection and/or liver transplantation (2). As such, minimally-invasive techniques such as percutaneous ablation and transarterial chemoembolization (TACE) have become an important option in the management of HCC (3). TACE is now considered the treatment of choice in patients with Barcelona Clinic Liver Cancer (BCLC) intermediate-stage HCC (4) and has shown promising results in the treatment of advanced HCC (5).

With the development of minimal-invasive techniques for the treatment of HCC, monitoring of therapeutic response has become increasingly important. The Response Evaluation Criteria of Solid Tumors (RECIST) criteria for tumor response evaluation was established in 2000 and proposed response assessment through measurement of the largest tumor diameter (6). However, a 2009 study by Forner *et al.* showed that the RECIST criteria were ineffective for monitoring response to loco-regional HCC therapy, as RECIST does not account for the extent of tumor necrosis (7). Modified RECIST (mRECIST) criteria, specific to HCC, were proposed in 2010 focusing on assessment of the extent of arterial phase contrast enhancement (8). The mRECIST

*These Authors contributed equally to this study.

Correspondence to: Dr. Johannes Budjan, Department of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. Tel: +49 06213832276, Fax: +49 06213833817, e-mail: johannes.budjan@umm.de

Key Words: Trans-arterial chemoembolization, therapy assessment, mRECIST, volumetry.

and European Association for the Study of the Liver (EASL) criteria have subsequently been shown to be more effective in predicting survival than assessments incorporating only measurements of tumor size (9).

Although the mRECIST criteria represent an improvement over prior standards, mRECIST evaluations still rely upon a one-dimensional measurement performed on three-dimensional MR or CT datasets. It is reasonable to assume, and has been shown in other applications, that volumetric measurements are more accurate than one-dimensional size assessments in determination of therapeutic response (10-12). In this context, 3D segmentation is the most accurate approach to obtain volumetric data. With respect to the above discussion, this consists of distinguishing a liver mass from the hepatic parenchyma on a CT or MR image or an arterially-enhancing portion of tumor from surrounding areas of non-enhancement. While segmentation can be readily performed by radiologists, technologists, or other observers, manual segmentation of a mass or organ on numerous axial 2D slices, as required for volumetric measurements, is cumbersome and time-consuming (13). Semi-automated techniques have shown to be less time-intensive and generally more reliable than manual or fully-automated segmentations (13-16). The Medical Imaging Interaction Toolkit (MITK) is free, open-source imaging software (17, 18). A voxel-based segmentation tool with support of manual delineation such as region growing and slice interpolation is provided as part of this software package; the implementation of which is described in detail elsewhere in the literature (17).

The aim of this study was to evaluate therapy response after TACE therapy in HCC patients using the segmentation MITK workflow for the analysis of MR examinations. The results were compared to mRECIST measurements.

Patients and Methods

The requirement of informed consent for this retrospective analysis was waived by the local institutional research board (Medizinische Ethikkommission II, 2008-338N-MA). Twenty-two consecutive patients (17 men and 5 women) with known hepatocellular carcinoma who were set to undergo TACE therapy and received a pre- and post-interventional magnetic resonance imaging (MRI) examination in-house were included from November 28th 2005 to March 3rd 2011. Mean patient age was 68 years (range=51 to 80 years). Mean time of MRI examination prior to TACE therapy was 2.5 weeks (range=0-13 weeks). Mean follow-up interval after TACE therapy was 5.5 weeks (range=2-12 weeks).

MR Imaging. Prior and after TACE therapy, all patients underwent an MRI examination with a standardized protocol on a single 1.5T MR-system (MAGNETOM AVANTO 32×76, Siemens Healthcare Sector, Erlangen, Germany). The protocol included coronal and axial T2 weighted half Fourier acquisition single-shot turbo spin-echo sequences as well as diffusion weighted imaging. Pre- and post-contrast T1-weighted sequences following gadolinium administration (0.1 mmol/kg body weight) were obtained. A 6-channel body-array coil was utilized in combination with 6 elements of the spine matrix coil for signal reception. 3D Volume-Interpolated Breathhold Examination (VIBE) sequences (TR/TE 5.5/1.93 ms, FA 30˚, acquisition time 21.1 sec, matrix 384x188, FoV 370×265, slice thickness 3 mm, voxel size 1.0×1.4×3 mm^3, parallel imaging factor 2) were used to acquire pre-contrast and multi-phase dynamic images. For multi-phase dynamic imaging, VIBE sequences were obtained at 25 sec (arterial phase), 59 sec (venous phase), and 80 sec (portal-venous phase) after injection.

Transarterial chemoembolization (TACE). All TACE procedures were performed by one interventional radiologist (SJD) with 15 years of experience in trans-arterial therapy of liver lesions. The details of the technique utilized for these procedures have been previously described (19). In all cases, TACE was performed with drug-eluting beads (DC Bead, Biocompatibles, United Kingdom).

Image analysis. For each of the 22 patients, Digital Imaging and Communications in Medicine (DICOM) files from the pre- and post-treatment MR examinations were exported to an offline workstation where they were analyzed with the Medical Imaging Interaction Toolkit (MITK; German Cancer Research Center Division of Medical and Biological Informatics; www.mitk.org). The primary index lesion was selected in this assessment. The primary index lesion was defined as the lesion first targeted during the TACE therapy, often corresponding to the largest lesion (20). Lesion assessment was performed by a MD candidate who was directly supervised by an experienced user of this software package. The semi-automated segmentation tool was used to outline the tumor margins on each available slice of the arterial phase T1 weighted images as described previously (17). In an analogous manner, the enhancing portions of the dominant tumor on all available slices of the arterial phase images were selected (Figure 1). Care was taken to exclude hemorrhagic areas without arterial enhancement by comparing native and arterial phase T1 images visually. Selection of hyperintense areas was supported by an interactive threshold tool. Additionally, the primary index lesions were measured pre- and post-therapy by the experienced interventional radiologist (SJD) according to mRECIST criteria.

Inter-reader assessment. For the inter-reader variability assessment, the pre- and post-treatment tumor volumes and volumes of maximal enhancement were additionally assessed by 4 independent radiologists using the MITK software in a single, randomly chosen patient. The radiologists had 4, 6, 6, and 10 years of experience in abdominal imaging. The radiologists had no previous experience in using the MITK software and were instructed by the same MD candidate who performed the lesion assessment for all patients. Overlap error was calculated between each pair of radiologists as well as the MD candidate on a voxel-by-voxel basis. Overlap error is derived from the Tanimoto coefficient and quantifies overlap between volumes A and B on a per voxel basis as $C_T=|A \cap B|/|A \cup B|$ where $(1-C_T)$ corresponds to the overlap error (21). A volumetric overlap error of 0 represents a perfect segmentation while a value of 100 indicates no overlap between the segmentation and reference.

Statistical analysis. Data were collected in Microsoft Excel and statistical analyses were performed with the statistic tool SAS 9.2, 2012 (SAS Institute Inc., Cary, NC, USA). Means and standard

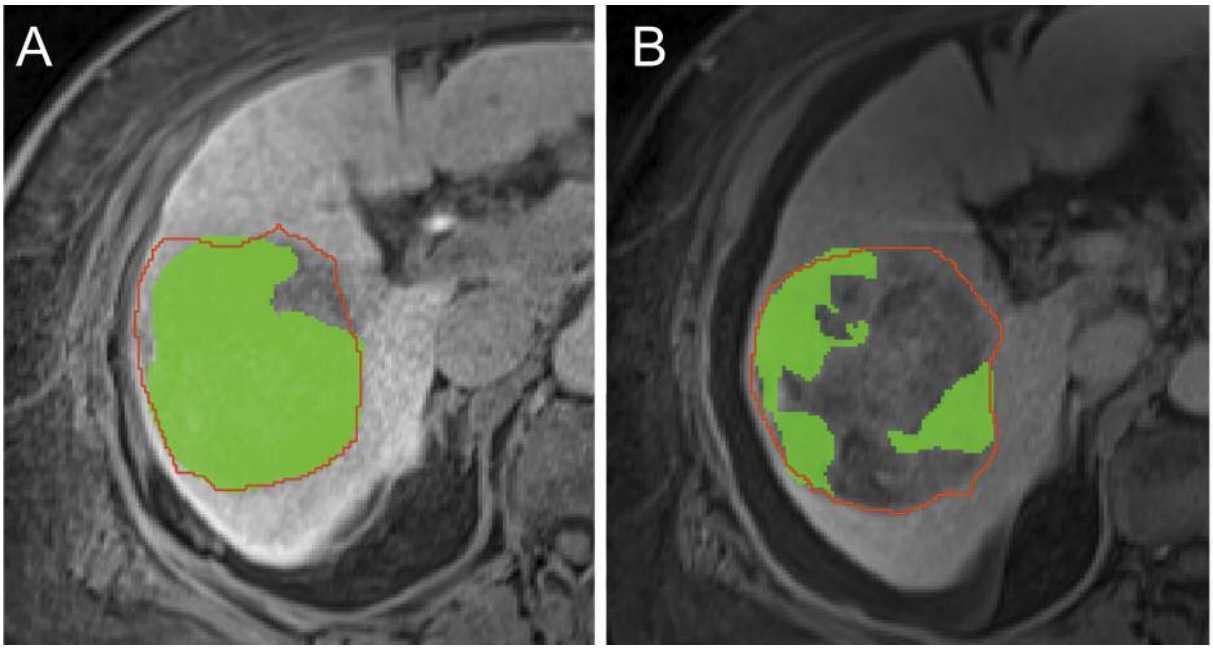

Figure 1. *Illustration of changes of the total tumor volume as well as the hypervascular areas from pre- (A) to post-treatment (B). A clear decrease especially of the hypervascular tumor parts (green areas) can be seen from the pre- to the post-treatment images, while overall tumor area is stable.*

deviations and medians of liver tumor volumes and volumes of maximal tumor enhancement were calculated pre- and post-treatment for each reader. Ratios between post- and pre-treatment values were calculated. Means are given±standard deviations (S.D.). Since most of the distributions of the small samples were skewed, Wilcoxon tests were utilized to compare these values. Level of significance was set to α=0.05.

Results

TACE procedure was technically successful in all 22 patients and without major complications. Segmentation analyses were performed successfully by all readers using the acquired datasets. Total time for the segmentation of both total tumor and enhancing tumor volumes pre- and post-TACE ranged from 8-14 min per patient.

Volumetric measurements and inter-reader assessment. The mean pre-treatment tumor volume (±StDev) was 84.6±128.3 mL. The mean post-treatment tumor volume was 97.1±175.2 ml (median 27.4 ml, skewed distribution). This was statistically significantly higher than the pre-contrast volume (p=0.03) (Figure 2a).The mean pre-treatment volume of arterial-phase enhancing tumor was 9.1±8.8 ml. The mean post-treatment volume of arterial-phase enhancing tumor was 3.7±11.7 ml (median 1.0 ml), which was significantly lower than the mean pre-contrast volume (p=0.0001, Figure 2b). The mean ratio of the total tumor volume before/after TACE was 1.03±1.38. The mean ratio of the hypervascular volume of the tumor before/after TACE was 0.38±0.83.

mRECIST. As determined by the experienced interventional radiologist, the mean pre-treatment diameter of arterial enhancing viable tumor was 44.2±23.6 mm, median 38 mm. The mean post-treatment viable tumor diameter was 15.4±24.6 mm, median 2 mm (skewed distribution). In the statistical analysis, a significant difference between the pre- and post-TACE diameter of the viable tumor diameter was found (p<0.0001, Figure 2c). The mean mRECIST diameter ratio before/after TACE was 0.31±0.38. In the comparison of hypervascular tumor volume and mRECIST diameter ratios, no statistically significant difference was found.

Inter-reader assessment. In the inter-reader assessment, overlap errors between the 4 radiologists ranged from 12.3-17.7% for the entire tumor volume and from 36.3-54.0% for the enhancing tumor volume pre TACE. Post-TACE, overlap errors ranged between 12.6-13.8% for the entire tumor volume and 47.8-64.2% for the enhancing tumor volume.

Discussion

Loco-regional therapies such as percutaneous ablation and TACE have emerged as important treatment options in the management of HCC (4). As the goal with these techniques

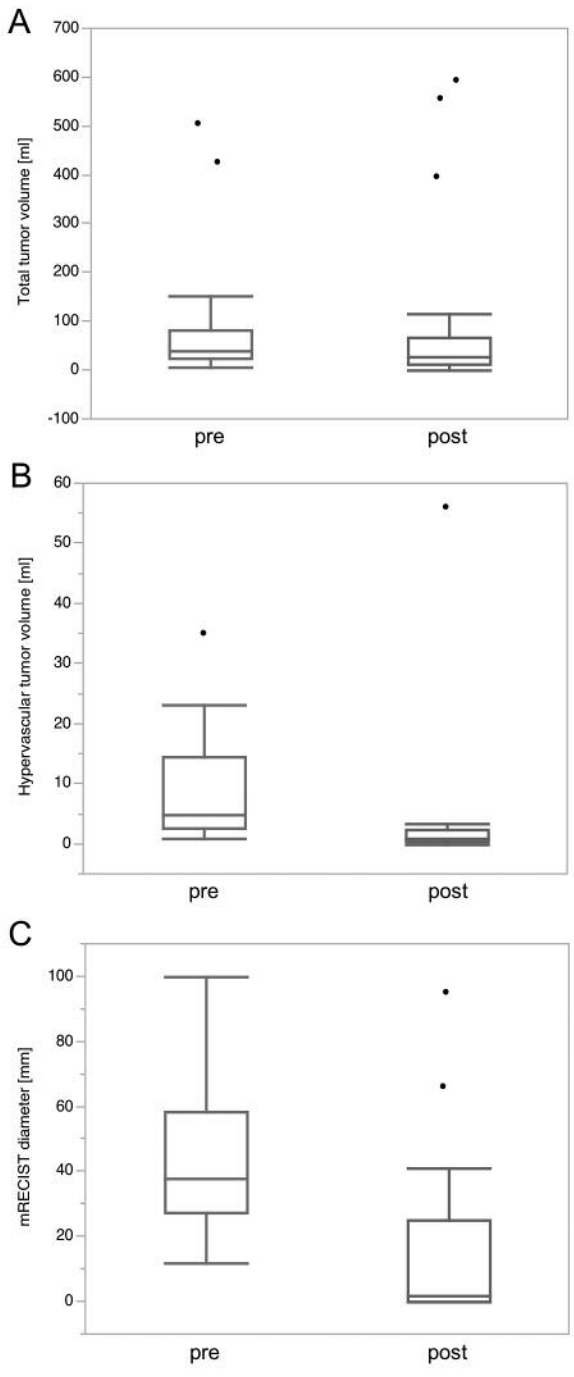

Figure 2. *Boxplots for the variables of overall (A) and hypervascular tumor volume (B) and diameter (as assessed by mRECIST, C) before (left) and after (right) TACE is displayed in this graph.*

is tumor necrosis, that may result in no immediate size reduction of the neoplasm, new methods of identifying therapeutic response on medical images have emerged (8). The present work extends such techniques into volumetric measurements implementing and demonstrating the feasibility of using a semi-automated segmentation and analysis tool to quantify changes in tumor and viable, enhancing tumor volume on MRI following TACE therapy. By applying mRECIST criteria, statistically significant changes in tumor diameter after therapy were found. In the volumetric assessment, only hypervascular tumor proportions showed a significant decrease after TACE therapy, while overall tumor volume even increased. Similar discrepancies regarding changes in total tumor *versus* viable, enhancing tumor diameters were found in previous studies that used two-dimensional measurement techniques (7). This finally led to the implementation of mRECIST criteria for the response assessment of TACE therapy. mRECIST or EASL criteria are currently the methods of choice for evaluating therapeutic response in HCC patients (9, 22). However, they rely on evaluation of residual arterial tumor enhancement utilizing only 1 (mRECIST) or 2 dimensions (EASL). Several prior studies have examined volumetric *versus* single-greatest and two-dimensional measurements in the setting of lung cancer (10, 11, 23) as well as liver (24, 25) and lymph node metastases (26, 27), finding higher accuracy for volumetric measurements. It would stand to reason that volumetric measurements would also be preferable for the assessment of HCC.

One of the primary limitations of volumetric image assessments is the time-requirement necessary to perform manual segmentations. For example, one study found manual liver segmentation to take an average of 25 min per case (13). In that particular study, Hermoye *et al*. examined manual and semi-automated hepatic volumetric MR measurements in living transplant patients with correlation to actual intraoperative graft weight. The semi-automated measurements not only reduced the time required for segmentation to 5 min per case but also improved both accuracy relative to true graft volume and measurement reproducibility. Similar decreases in interpretation time have been shown with semi-automated *versus* manual techniques in other applications (27). Also, the diminished inter-observer variability with semi-automated *versus* manual techniques has been previously demonstrated in metastatic hepatic lesions (28). Kreil *et al*., likewise, examined semi-automated *versus* manual volumetric measurements in post-radiofrequency ablation (RFA) metastatic hepatic lesions, finding semi-automated techniques to correlate relatively-well with manual volumetric measurements for pre-therapy volume calculations and for determination of ablation cavity size following treatment (29). While manual and semi-automated segmentations were not directly compared in our study, the availability of free, open-source semi-automated segmentation tools such as those discussed herein makes the eventual incorporation of volumetric measurements into the daily clinical routine more likely.

In comparison to prior studies, our data suggest a relatively high reproducibility of volumetric hepatic tumor measurements. Calculations of overlap error are one of the most common ways to measure the reproducibility of segmentations (21). For measurements of total tumor volume, the 4 radiologists exhibited a relatively low overlap error of 12-18%, values on the order of those seen with segmentation of the entire liver by CT (21) and lower than those previously seen in a segmentation of hepatic metastatic lesions on CT (30). Measurements of enhancing tumor volume were less reproducible, with overlap errors reaching over 50% pre- and over 60% post-TACE. This higher variability might partly be explainable by differences in software and user differentiation of hemorrhagic and truly arterial hyper-enhancing areas. Additionally, truly arterial enhancing volumes were 10-fold lower than total tumor volumes, leading to relatively high overlap errors despite low absolute differences in volumes. Further improvements in segmentation software will presumably lead to more uniform delineation, especially when further reducing the user's influence in the selection of enhancing tumor portions.

The limitations of the present study include the relatively small sample size. Thus, results herein should be examined in a larger patient cohort, ideally in a prospective study design. This study attempts to translate mRECIST criteria into volumetric measurements; however, mRECIST criteria require identification of several target lesions and summation of the unidimensional diameters of enhancing tumor (8). Likewise, EASL criteria require summation of the two-dimensional diameter products of several target lesions (22). To simplify the computations in the present work, we rely upon measurements of only a primary index lesion. This target-lesion approach has been shown to correlate with disease progression and survival in a large retrospective study (20). Additionally, a recent study found no improvement in survival prediction when using multiple lesion assessment compared to evaluation of a single dominant lesion alone (31). In general, as in the present study, a minority of hepatocellular carcinomas are multifocal. Thus, for a large percentage of patients, multi-target lesion computations would have not been necessary or possible. The interaction time to perform semi-automated volumetric measurements is also a relevant parameter, and is undoubtedly longer than single or two-dimensional measurements. However, this variable was not directly assessed in our work.

Ultimately if volumetric measurements can provide highly relevant clinical data, interaction time with the software becomes a less relevant consideration. Semi-automated segmentation algorithms should also continue to improve, reducing the number of manual corrections and thus interaction time needed.

In summary, this study demonstrates the feasibility of a semi-automated segmentation and analysis tool to quantify therapeutic effects of TACE utilizing volumetric tumor assessments and measurements of enhancing tumor volume. Notably, while total tumor volume slightly increased after TACE therapy, the volume of arterial enhancing tumor areas and mRECIST diameter decreased significantly.

References

1 Huppert P: Current concepts in transarterial chemoembolization of hepatocellular carcinoma. Abdom Imaging *36(6)*: 677-683, 2011.

2 Schwartz M, Roayaie S and Konstadoulakis M: Strategies for the management of hepatocellular carcinoma. Nat Clin Pract Oncol *4(7)*: 424-432, 2007.

3 Lencioni R and Crocetti L: Local-regional treatment of hepatocellular carcinoma. Radiology *262(1)*: 43-58, 2012.

4 Bruix J and Sherman M: Management of hepatocellular carcinoma: An update. Hepatology *53(3)*: 1020-1022, 2011.

5 Pinter M, Hucke F, Graziadei I, Vogel W, Maieron A, Konigsberg R, Stauber R, Grunberger B, Muller C, Kolblinger C, Peck-Radosavljevic M and Sieghart W: Advanced-stage hepatocellular carcinoma: Transarterial chemoembolization *versus* sorafenib. Radiology *263(2)*: 590-599, 2012.

6 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the united states, national cancer institute of canada. J Natl Cancer Inst *92(3)*: 205-216, 2000.

7 Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, Reig M, Bianchi L, Llovet JM and Bruix J: Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: Are response evaluation criteria in solid tumors reliable? Cancer *115(3)*: 616-623, 2009.

8 Lencioni R and Llovet JM: Modified recist (mrecist) assessment for hepatocellular carcinoma. Semin Liver Dis *30(1)*: 52-60, 2010.

9 Shim JH, Lee HC, Kim SO, Shin YM, Kim KM, Lim YS and Suh DJ: Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology *262(2)*: 708-718, 2012.

10 Fraioli F, Bertoletti L, Napoli A, Calabrese FA, Masciangelo R, Cortesi E, Catalano C and Passariello R: Volumetric evaluation of therapy response in patients with lung metastases. Preliminary results with a computer system (cad) and comparison with unidimensional measurements. Radiol Med *111(3)*: 365-375, 2006.

11 Zhao B, Schwartz LH, Moskowitz CS, Ginsberg MS, Rizvi NA and Kris MG: Lung cancer: Computerized quantification of tumor response-initial results. Radiology *241(3)*: 892-898, 2006.

12 Corona-Villalobos CP, Halappa VG, Bonekamp S, Eng J, Reyes D, Cosgrove D, Rastegar N, Pan L, Pawlik TM and Kamel IR: Functional magnetic resonance imaging response of targeted tumor burden and its impact on survival in patients with hepatocellular carcinoma. Invest Radiol *50(4)*: 283-289, 2015.

13 Hermoye L, Laamari-Azjal I, Cao Z, Annet L, Lerut J, Dawant BM and Van Beers BE: Liver segmentation in living liver transplant donors: Comparison of semiautomatic and manual methods. Radiology *234(1)*: 171-178, 2005.

14 Lebenberg J, Buvat I, Garreau M, Casta C, Constantinides C, Cousty J, Cochet A, Jehan-Besson S, Tilmant C, Lefort M, Roullot E, Najman L, Sarry L, Clarysse P, de Cesare A, Lalande A and Frouin F: Comparison of different segmentation approaches without using gold standard. Application to the estimation of the left ventricle ejection fraction from cardiac cine mri sequences. Conf Proc IEEE Eng Med Biol Soc *2011*: 2663-2666, 2011.

15 Buerke B, Puesken M, Muter S, Weckesser M, Gerss J, Heindel W and Wessling J: Measurement accuracy and reproducibility of semiautomated metric and volumetric lymph node analysis in mdct. AJR Am J Roentgenol *195(4)*: 979-985, 2010.

16 Glisson CL, Altamar HO, Herrell SD, Clark P and Galloway RL: Comparison and assessment of semi-automatic image segmentation in computed tomography scans for image-guided kidney surgery. Med Phys *38(11)*: 6265-6274, 2011.

17 Maleike D, Nolden M, Meinzer HP and Wolf I: Interactive segmentation framework of the medical imaging interaction toolkit. Comput Methods Programs Biomed *96(1)*: 72-83, 2009.

18 Nolden M, Zelzer S, Seitel A, Wald D, Muller M, Franz AM, Maleike D, Fangerau M, Baumhauer M, Maier-Hein L, Maier-Hein KH, Meinzer HP and Wolf I: The medical imaging interaction toolkit: Challenges and advances: 10 years of open-source development. Int J Comput Assist Radiol Surg *8(4)*: 607-620, 2013.

19 Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P and Lencioni R: Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: Results of the precision v study. Cardiovasc Intervent Radiol *33(1)*: 41-52, 2010.

20 Riaz A, Miller FH, Kulik LM, Nikolaidis P, Yaghmai V, Lewandowski RJ, Mulcahy MF, Ryu RK, Sato KT, Gupta R, Wang E, Baker T, Abecassis M, Benson AB, 3rd, Nemcek AA, Jr., Omary R and Salem R: Imaging response in the primary index lesion and clinical outcomes following transarterial locoregional therapy for hepatocellular carcinoma. JAMA 303(11): 1062-1069, 2010.

21 Heimann T, van Ginneken B, Styner MA, Arzhaeva Y, Aurich V, Bauer C, Beck A, Becker C, Beichel R, Bekes G, Bello F, Binnig G, Bischof H, Bornik A, Cashman PM, Chi Y, Cordova A, Dawant BM, Fidrich M, Furst JD, Furukawa D, Grenacher L, Hornegger J, Kainmuller D, Kitney RI, Kobatake H, Lamecker H, Lange T, Lee J, Lennon B, Li R, Li S, Meinzer HP, Nemeth G, Raicu DS, Rau AM, van Rikxoort EM, Rousson M, Rusko L, Saddi KA, Schmidt G, Seghers D, Shimizu A, Slagmolen P, Sorantin E, Soza G, Susomboon R, Waite JM, Wimmer A and Wolf I: Comparison and evaluation of methods for liver segmentation from ct datasets. IEEE Trans Med Imaging *28(8)*: 1251-1265, 2009.

22 Gillmore R, Stuart S, Kirkwood A, Hameeduddin A, Woodward N, Burroughs AK and Meyer T: Easl and mrecist responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. J Hepatol *55(6)*: 1309-1316, 2011.

23 Hayes SA, Pietanza MC, O'Driscoll D, Zheng J, Moskowitz CS, Kris MG and Ginsberg MS: Comparison of ct volumetric measurement with recist response in patients with lung cancer. Eur J Radiol *85(3)*: 524-533, 2016.

24 Keil S, Behrendt FF, Stanzel S, Suhling M, Koch A, Bubenzer J, Muhlenbruch G, Mahnken AH, Gunther RW and Das M: Semi-automated measurement of hyperdense, hypodense and heterogeneous hepatic metastasis on standard mdct slices. Comparison of semi-automated and manual measurement of recist and who criteria. Eur Radiol *18(11)*: 2456-2465, 2008.

25 Chapiro J, Duran R, Lin M, Schernthaner RE, Wang Z, Gorodetski B and Geschwind JF: Identifying staging markers for hepatocellular carcinoma before transarterial chemoembolization: Comparison of three-dimensional quantitative *versus* non-three-dimensional imaging markers. Radiology *275(2)*: 438-447, 2015.

26 Fabel M, Bolte H, von Tengg-Kobligk H, Bornemann L, Dicken V, Delorme S, Kauczor HU, Heller M and Biederer J: Semi-automated volumetric analysis of lymph node metastases during follow-up – initial results. Eur Radiol *21(4)*: 683-692, 2011.

27 Fabel M, von Tengg-Kobligk H, Giesel FL, Bornemann L, Dicken V, Kopp-Schneider A, Moser C, Delorme S and Kauczor HU: Semi-automated volumetric analysis of lymph node metastases in patients with malignant melanoma stage iii/iv – a feasibility study. Eur Radiol *18(6)*: 1114-1122, 2008.

28 Bellon E, Feron M, Maes F, Hoe LV, Delaere D, Haven F, Sunaert S, Baert AL, Marchal G and Suetens P: Evaluation of manual vs semi-automated delineation of liver lesions on ct images. Eur Radiol *7(3)*: 432-438, 1997.

29 Keil S, Bruners P, Ohnsorge L, Plumhans C, Behrendt FF, Stanzel S, Suhling M, Gunther RW, Das M and Mahnken AH: Semiautomated *versus* manual evaluation of liver metastases treated by radiofrequency ablation. J Vasc Interv Radiol *21(2)*: 245-251, 2010.

30 Rothe JH, Steffen IG, Lehmkuhl L, Grieser C, Mussler A, Schnapauff D, Stelter L and Denecke T: Volume measurement of liver metastases using multidetector computed tomography: Comparison of lesion diameter and volume segmentation - a phantom study. Rofo *182(12)*: 1082-1090, 2010.

31 Fleckenstein FN, Schernthaner RE, Duran R, Sohn JH, Sahu S, Zhao Y, Hamm B, Gebauer B, Lin M, Geschwind JF and Chapiro J: 3d quantitative tumour burden analysis in patients with hepatocellular carcinoma before tace: Comparing single-lesion *vs*. Multi-lesion imaging biomarkers as predictors of patient survival. Eur Radiol, 2016.

Received June 10, 2016
Revised July 7, 2016
Accepted July 11, 2016