의학석사 학위논문

Therapeutic response assessment using 3D ultrasound in hepatic metastasis from colon cancer:

Application of personalized 3D-printed tumor model using CT images

삼차원 초음파를 이용한 대장암 간전이의 치료 반응 평가

환자 맞춤형 삼차원 프린트 종양 모델을 이용한 연구

2016 년 8 월

서울대학교 대학원

의학과 영상의학 전공

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Therapeutic response assessment using 3D ultrasound in hepatic metastasis from colon cancer: Application of personalized 3D-printed tumor model using CT images

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이 논문을 의학석사 학위논문으로 제출함
2016년 4월

서울대학교 대학원
의학과 영상의학 전공
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최예라의 의학석사 학위논문을 인준함
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Abstract

Therapeutic response assessment using 3D ultrasound in hepatic metastasis from colon cancer:

Application of personalized 3D-printed tumor model using CT images

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Introduction: With technological revolution of three-dimensional (3D) printing in medical field, 3D visualization of anatomy and pathologic condition and creation of 3D-printed physical models became accessible in the diagnostic imaging practices. The purpose of this study was to evaluate the accuracy and reliability of 3D US for response evaluation of hepatic metastasis from colon cancer applying of personalized 3D-printed tumor model using CT images.

Methods: Twenty patients with liver metastasis from colorectal cancer who received cytotoxic chemotherapy and underwent CT baseline and after chemotherapy were retrospectively included in this institutional review board-approved study. Personalized 3D-printed ultrasound tumor model were created from CT images. Two radiologists measured the volume of each 3D printing

ultrasound tumor model using 3D US. With the tumor volume from CT as a reference standard, we compared the difference between CT volume and US tumor volume. The mean difference and correlation coefficient between each US volume measurement and the CT volume were analyzed. The response evaluation was based on RECIST criteria.

Results: There were 10 patients of response group and 10 patients of non-response group. With the tumor volume from CT as a reference standard, tumor volume measurement using 3D US with 3D-printed tumor model showed no statistically significant difference (7.18 ± 5.44 mL in observer 1 and 8.31 ± 6.32 mL in observer 2 vs 7.42 ± 5.76 mL in CT, $p>0.05$).

3D US provided the high correlation coefficient with the CT volume (r=0.953, observer1; r=0.97, observer2) and with the high inter-observer intraclass correlation (0.978; 0.958-0.988). Regarding response assessment, 3D US was in agreement with CT volume in 17 of the 20 patients in observer 1 and 18 of the 20 patients in observer 2 with excellent inter-observer agreement ($\kappa = 0.961$).

Conclusions: 3D US volumetric measurement applying of personalized 3D-printed tumor model using CT images in hepatic metastasis from colon cancer is accurate and reliable method for the response evaluation in comparison with the tumor volume from CT.

Keywords: 3D ultrasound, 3D-printed tumor model, hepatic metastasis, colon cancer

***Student Number*: 2013-21705**

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LIST OF ABBREVIATION

3D = Three-dimensional

CT = Computed Tomography

MR = Magnetic Resonance

US = Ultrasonography

RECIST = Response Evaluation Criteria in Solid Tumors

INTRODUCTION

Colorectal carcinoma is one of the most common cancers worldwide and presenting high mortality rates due to relatively early manifestation and high incidence of distant metastases. Liver is the predominant site of metastases, as the initial site in 30% of distant metastases [1]. In the unresectable metastatic colorectal carcinoma, the first-line palliative chemotherapy consists of combination chemotherapy with 5- fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX) and 5-FU/LV/irinotecan (FOLFIRI) [2]. Evaluation of the liver metastases after chemotherapy is important to guide treatment and to make possible more effective salvage treatment that prolongs survival [3]. Currently, the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) is most widely used to assess the response to treatment for solid tumors, based on measurement of the longest diameter of the target lesions [4]. However, there are several problems in unidimensional measurement, such as difficulty in determining diameter of irregular and conglomerate mass, discrepancies in scan planes leading to measurement error, and interobserver variability [5, 6].

Quantification of tumor burden using volumetric image acquisition from computed tomography (CT) or magnetic resonance (MR) has become issue in place of uni- or bidimensional measurement [7-11]. 3D volumetric measurement has advantages in better quantification of total tumor burden, more accurate assessment of tumor change, and better measurement of irregular mass [5]. With recent advances of three-dimensional ultrasound (3D US) and its various clinical

applications of volumetric measurement, oncologic measurement using 3D US also has been suggested [12-15]. In comparison of CT or MR, US is more readily available and has no radiation hazard. Thus in cancer patients who needs frequent follow-up examinations, 3D US can be a useful method for monitoring treatment response. However, many studies about volume measurement using 3D US were experimental or *in vitro* phantom studies, because of limited sonographic window using 3D transducer associated with various patient's anatomy and position as well as respiratory motion [12, 14, 16-20].

With technological revolution of 3D printing in medical field, 3D visualization of anatomy and pathologic condition and creation of 3D-printed physical models became accessible in the diagnostic imaging practices [21-25]. Furthermore, radiologic 3D modeling technology can produce patient-tailored tumor model utilizing CT information. In this study, we developed 3D-printing hepatic tumor models from patients' CT data for the first time which are adequate for US evaluation. The purpose of this study was to evaluate the accuracy and reliability of 3D US for evaluation of hepatic metastasis from colon cancer using 3D-printing patient-tailored tumor models from CT images.

MATERIALS AND METHODS

Patient Selection and Study Protocol

This retrospective study was approved by our institutional review board, and the informed consent was waived. From January 2014 to July 2014, 94 patients were pathologically confirmed colon cancer with liver metastasis. The exclusion criteria included patients who received surgical resection or target therapy (n = 21), unavailable for evaluation of baseline or follow-up CT (n =7), and the size of target lesion less than 1 cm or more than 5 cm (n = 46).

Finally, 20 patients (17 men and 3 women, mean age, 58.4 years ± 9.5; age range, 42–74 years) who received cytotoxic chemotherapy including infusional 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) and underwent baseline and follow-up CT were included in our study. Baseline CT was obtained mean 13 days (median 6, 0-42 days) before the start of the initial chemotherapy. Post-chemotherapy CT was obtained mean 11.4 days (median 10, 3-27 days) after the start of the fourth cycle of chemotherapy. **Figure 1** shows a flowchart of the study population and the study protocol.

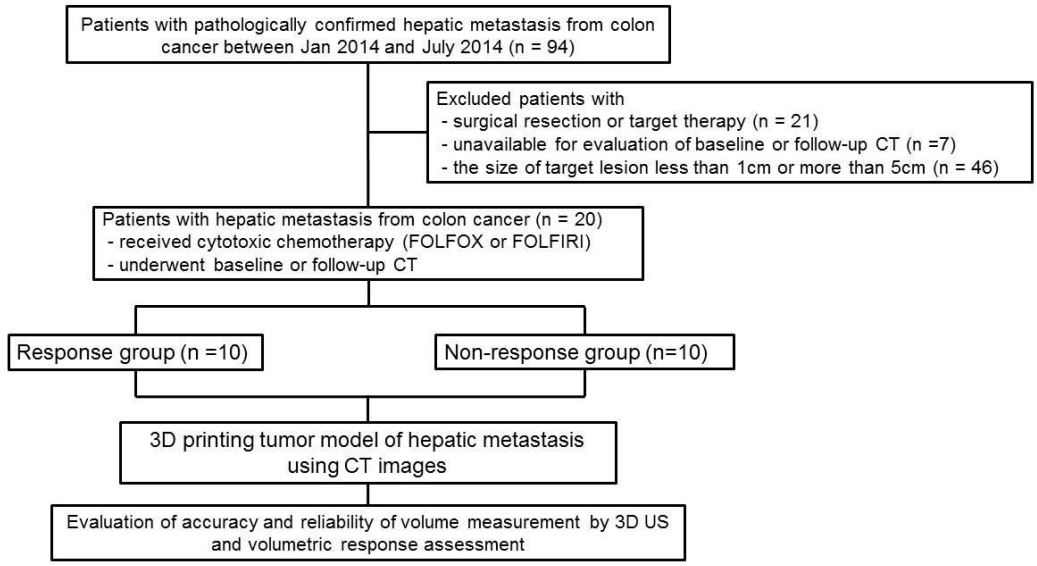


Figure 1. Study flowchart of patient selection and phantom construction

CT Examination

CT examinations were performed by using the following CT scanners: Discovery CT750 HD (64-channel scanner, GE Healthcare, Milwaukee, WI, USA) in 4 patients, Brilliance 64 (64-channel scanner, Philips Healthcare, Cleveland, OH, USA) in 10 patients, Sensation 16 (16-channel scanner, Siemens Medical Solutions, Erlangen, Germany) in 5 patients, LightSpeed Ultra (8-channel scanner, GE Healthcare, Milwaukee, WI, USA) in one patient. For 8-, 16-, and 64-detector CT examinations, detector collimations of 1.25, 0.75, and 0.625 mm, respectively, were used. A section thickness of 3.0-3.2 mm with 2.5 to 3-mm reconstruction interval, a field of view of 300-370 mm, a gantry rotation time of 0.5 s, an effective amperage setting of 150-200 mAs, and a peak voltage of 120 kVp were used for all CT scanners. All patients underwent dual-phase CT during the late arterial and portal venous phases. For dynamic phase imaging, a fixed dose of 1.5 ml of nonionic contrast material (iopromide [370 mg of iodine permilimeter], Ultravist 370; Schering, Berlin, Germany) per kilogram of body weight (555 mgI/kg) was injected at a rate of 2.0-4.0 mL/sec using a power injector (Multilevel CT; Medrad, Indianola, PA, USA).

Response Evaluation

The response evaluation was based on the change of the largest tumor diameter on the CT scan between baseline and after chemotherapy. Two radiologists (J.H.K., Y.R.C.) evaluated the baseline CT and post-chemotherapy CT images after fourth cycle which means 60 days interval with consensus. The overall response was

determined using the revised RECIST guideline (version 1.1) [4]. According to the RECIST guidelines, patients with complete response (CR) and partial response (PR) were categorized into the response group and patients with stable disease (SD) and progressive disease (PD) were categorized into the non-response group. Among the target tumor lesions in the patients of both response and non-response group, in order to construct 3D-printing phantom and obtain appropriate acoustic window on 3D US, tumors less than 1 cm and more than 5 cm in diameter were excluded in this study. A total of 40 target lesions from each pre- and post-chemotherapy CT scan of 20 patients were selected.

3D printing hepatic tumor model

For fabricating 3D printing hepatic tumor model, we initially segmented tumor volume and made phantom mold from CT data using in-house software program and then, the volume files were converted to stereolithography files (STL) of mesh structures. After that, the STL files were transformed into printable code format using MakerWare 3.9 (Makerbot, New York, NY, US). A total of 40 tumor phantom molds of 20 patients at a 1:1 scale was produced with the MakerBot Replicator 2X 3D printer (Makerbot, New York, NY, US). After finishing above steps, the silicone material mixed with graphite powder for echogenicity was cast into the tumor phantom mold. The time spent for overall procedure was within 5 hours per 1 case. **Figure 2** shows a flowchart of the 3D printing hepatic tumor model.

One radiologist (Y.R.C, with 4 years of clinical experience in abdominal imaging) measured the regions of interest (ROI) of the representative target

metastatic mass in the liver on the portal-phase images. PC-based in-house software (MISSTA - medical imaging solution for segmentation and texture analysis) reconstructed 3-dimensional volume-rendering model and calculated its volume automatically with the input of ROI information. ROIs were delineated around the boundary of the tumor in each axial CT images. The section thicknesses of all CT scans were 2.5mm to 3mm. To minimize measurement errors, we used mean value of three measurements in the different day of same representative mass. PC-based in-house software (MISSTA) was used for lesion segmentation with automated quantification of the tumor volume implemented with a dedicated C++ language with MFC (Microsoft Foundation Classes, Microsoft, Redmond, Wash).

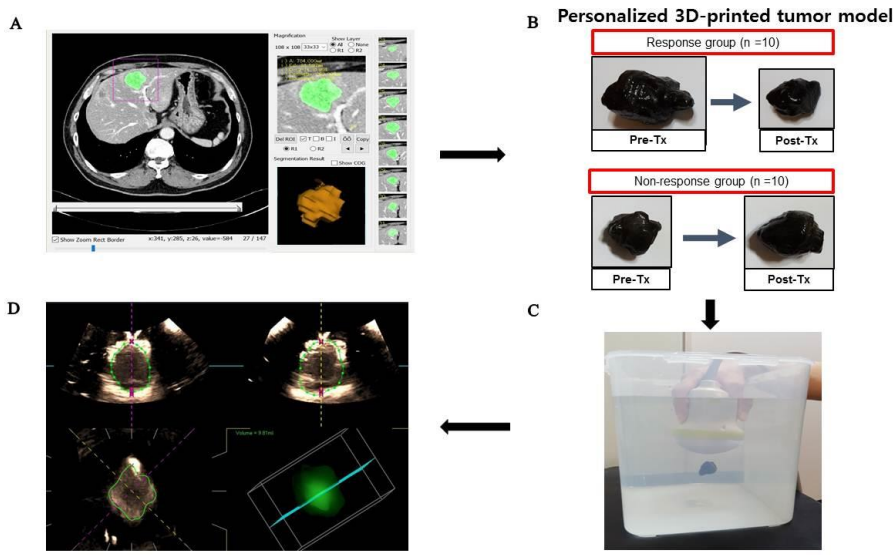


Figure 2. Study process flowsheet

A) Screenshot of the in-house program of segmentation and 3-dimensional volume-rendering reconstruction of the tumor. B) A 3D-printed phantom constructed by the software and 3D printer. C) Experimental setting for sonographic volume measurement of the phantom using 3D-transducer scanning through an automated sweeping movement. D) Volume measurement of the phantom. Manual outlining of the boundaries of the tumor phantom at 8 images of transverse (upper left) or longitudinal (upper right) plane. Then, boundaries at coronal plane (lower left) and 3D reconstructed image and its volume (lower right) were automatically generated by the built-in software of the ultrasound unit.

Tumor volume measurement using 3D-US

Two radiologists (B.Y.H., Y.R.C. with 7 and 4 years of experience in abdominal imaging) performed scanning using an US unit (Aplio 500; Toshiba Medical, Otawara, Japan) equipped with PVT-375BT, 3.5 MHz curved 2D-transducer and PVT-375MV, 3.5 MHz mechanical convex 3D-transducer involving the following parameters: a dynamic range of 65; a gain of 85; a frame rate of 25 fps; and a depth of 10 cm in 2D-transducer, a dynamic range of 65; a gain of 89; a frame rate of 30 fps; and a depth of 9 cm in 3D-transducer.

After each phantom was fixed with a fine thread in the center of container filled with distilled water, the volume transducers were dipped in the water and placed over 2 cm above the phantom. On the grey-scale 2D US, the phantom was imaged using the maximum transverse plane. Then, the radiologist adjusted size and position of the volume of interest (VOI) to contain the phantom. During an automated sweeping movement through predetermined sweeping angle 75°, the radiologist held on the transducer to avoid movement. Volumetric measurement for each phantom was performed on the US unit with the analysis software. The software allowed display on the monitor simultaneously in three different 2D perpendicular planes. One 2D plane was selected, and a rotation axis that passed through the center of a tumor to be measured was set on the 2D image. The outer boundary of a tumor was manually drawn on the 2D image, and then the volume data were rotated on the rotation axis by 22.5° to produce the next 2D image. Because each rotation step took 22.5°, each measurement required eight rotation steps, thus manual drawing of the boundaries on 2D images was performed a total

of eight times (**Figure 2**). In addition to the tumor volume measurement on US, we estimated volume of the phantom by calculation using the ellipsoid volume formula, $V = \frac{4}{3}\pi r_1 r_2 r_3$, where r_1, r_2, and r_3 are half the diameters on each x, y, z planes by 2D US. The reference volume of the phantom was automatically calculated and indicated on the PC-based in-house software (MISSTA) that was used for modelling 3D phantoms with CT images. The actual volume of 3D-printed phantoms was measured using the water displacement method and compared with reference volume from CT images.

Statistical analysis

To evaluate the accuracy of volume measurement by two observers and volume estimation using diameters, mean difference and standard deviation of difference between measured volume and reference volume were calculated. The limits of agreement and 95% confidence intervals were determined using the methods published by Bland and Altman [26]. The inter-observer variability of volume measurement on 3D US was evaluated by the intraclass correlation coefficient (ICC) and limits of agreement. An ICC > 0.7 was considered to be indicative of an excellent reliability correlation. Comparison of 3D US volume analysis and RECIST (unidimensional) guidelines in determining response to treatment was performed using kappa statistics. The kappa value of inter-observer agreement was assigned as follows: less than 0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, good; and more than 0.81, excellent. A *p* value less than 0.05 was considered to indicate a statistically significant difference. Statistical analyses were

performed with Statistical Package for Social Science (SPSS version 19.0 for Microsoft Windows) and Medcalc (version 16.2.1, Medcalc Software, Mariakerke, Belgium) statistical software.

RESULTS

There were 10 patients of response group and 10 patients of non-response group with a total of 40 target lesions on baseline and post-chemotherapy CT scans. There were 7 men (mean age, 58.7 years) and 3 women (mean age, 54.3 years) in the response group and 10 men (mean age, 59.4 years) in the non-response group. Lesion diameters ranged from 10.6 to 33.8 mm (mean 21.8 ± 6.5 mm). In the response group, mean diameter decreased from 26.9 ± 5.3 mm to 16.1 ± 3.2 mm after chemotherapy. In the non-response group, mean diameter changed from 21.5 ± 6.7 mm to 22.8 ± 5.9 mm after chemotherapy.

There was no technical failure to create personalized 3D-printed ultrasound tumor model. The volume of 3D-printed phantoms using the water displacement method was 7.44 ± 5.80 mL (mean ± SD) and the reference volume from CT images was 7.42 ± 5.76 mL (mean ± SD). There was no statistically significant difference between tumor volumes and actual phantom volumes ($p>0.05$).

Accuracy and reliability of volumetric US

The reference tumor volume from CT images was 7.42 ± 5.76 mL (mean ± SD).

The tumor volume measurement by observer 1 and 2 using 3D US were 7.18 ± 5.44 mL and 8.31 ± 6.32 mL, respectively. With the tumor volume from CT as a reference standard, tumor volume measurement using 3D US with 3D-printed

tumor model showed no statistically significant difference (p>0.05). The estimated tumor volume calculated by the ellipsoid volume formula $V = \frac{4}{3}\pi r_1 r_2 r_3$ using half the diameters on each x, y, z planes by 2D US was 9.10 ± 8.47 mL.

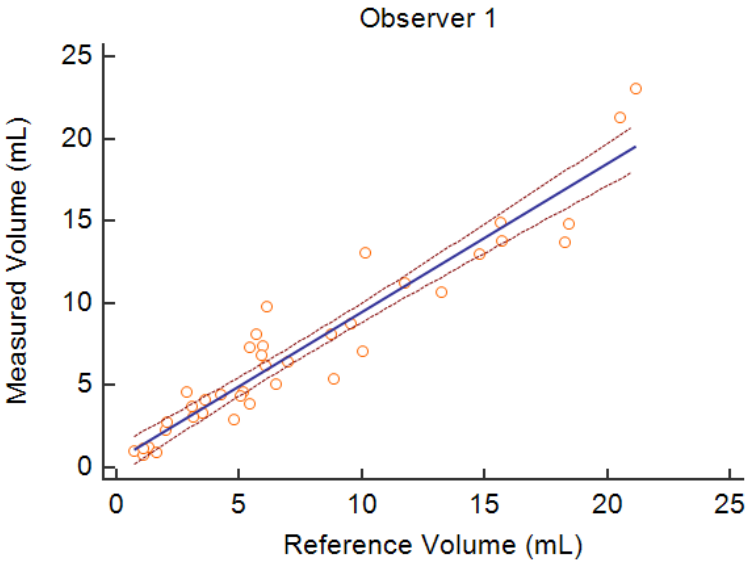
The tumor volume measurement on 3D US showed better correlation with the actual volume of the phantoms than estimated tumor volume by ellipsoid formula on 2D US. The values of correlation coefficients (r) were 0.953, 0.97, and 0.945 for 3D US measurement by observer 1, 2, and estimated volume by ellipsoid formula, respectively. In addition, mean difference and the limits of agreement were smaller in the measured volume than in the estimated volume. For the measured volume by 3D US, mean difference from reference tumor volume were -0.24 ± 1.75 mL (mean ± SD) by observer 1, and 0.89 ± 1.58 mL by observer 2. For the estimated volume from 2D diameters, mean difference was 1.69 ± 3.56 mL. Limits of agreement were from -3.66 mL to 3.19 mL and from -2.21 mL to 3.99 mL respectively in the observer 1 and 2, whereas, from -5.29 mL to 8.66 mL in the estimated volume from 2D diameters **(Table 1)**. **Figure 3** summarizes the mean difference and the correlation coefficient between tumor volume measurement on 3D US and estimated volume from 2D US against the true volume of tumor phantoms. Regarding reliability of the volume measurement on 3D US by two observers, excellent reliability correlation was observed. The ICC value was 0.978 (95% CI, 0.958-0.988).

	Measured Volume (observer 1)	**Measured Volume (observer 2)**	**Estimated volume from 2D diameters ($V = \frac{4}{3}\pi r_1 r_2 r_3$)**
Mean volume[a]	7.18 ± 5.44	8.31 ± 6.32	9.10 ± 8.47
Mean difference from reference volume (95% CI)	-0.24 (-0.79 to 0.32)	0.89 (0.38 to 1.40)	1.69 (0.55 to 2.82)
SD of differences between measured volume and reference volume	1.75	1.58	3.56
Upper limit of agreement	3.19 (2.23 to 4.15)	3.99 (3.12 to 4.86)	8.66 (6.70 to 10.62)
Lower limit of agreement	-3.66 (-4.63 to -2.70)	-2.21 (-3.08 to 1.34)	-5.29 (-7.25 to 3.33)

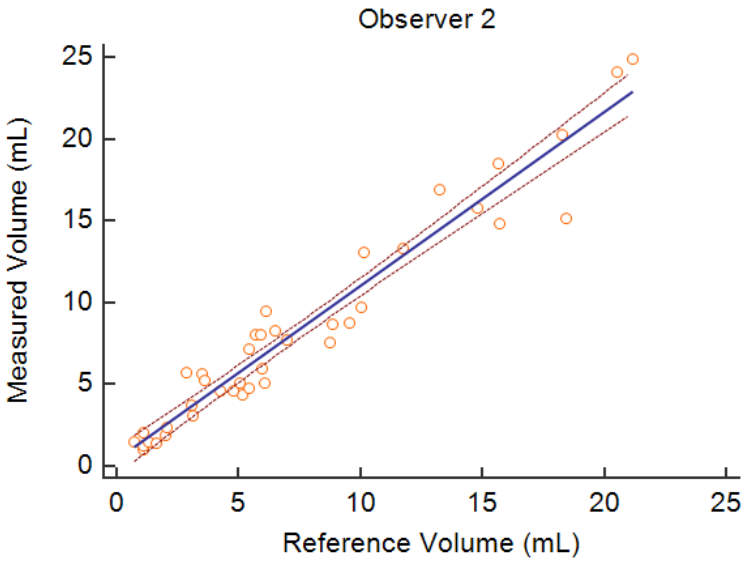
[a] The mean reference volume was **7.42 ± 5.76 mL**

Table 1. Comparison of measured volume using three-dimensional ultrasound and estimated volume from 2D diameters ($V = \frac{4}{3}\pi r_1 r_2 r_3$) with the true volume of tumor phantoms

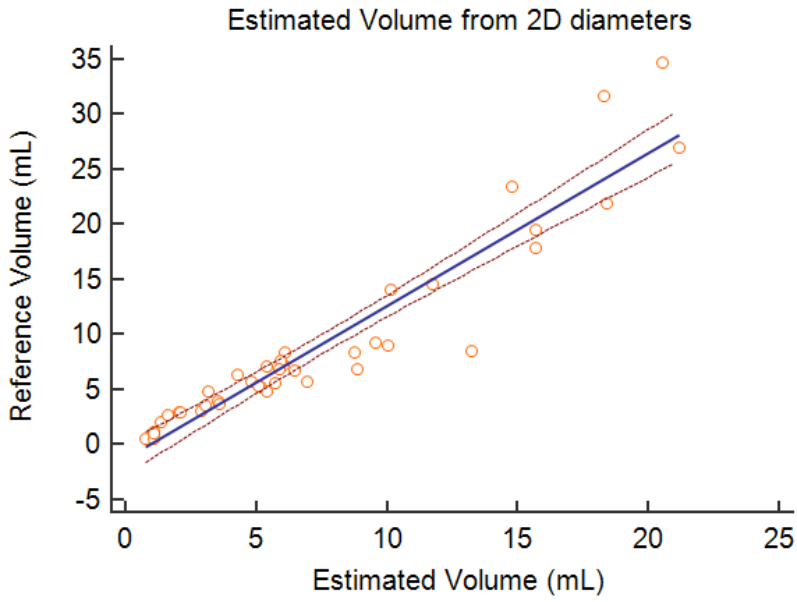
(A)


Observer 1
Measured Volume (mL)
Reference Volume (mL)
0
5
10
15
20
25

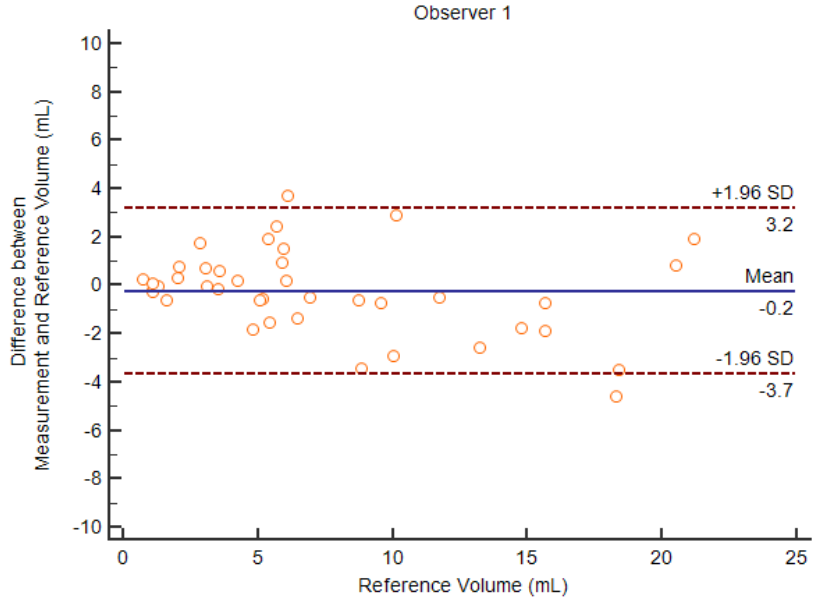
(B)


Observer 2
Measured Volume (mL)
Reference Volume (mL)
0
5
10
15
20
25

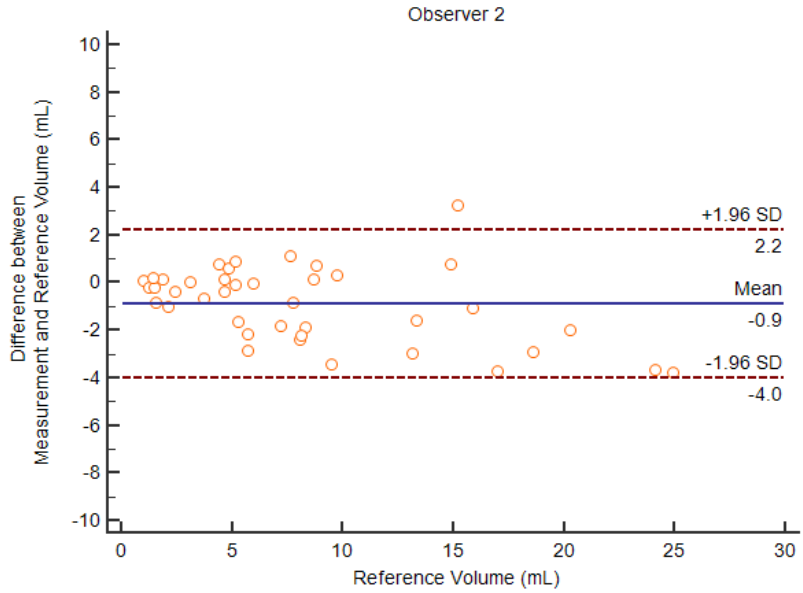
(C)


Estimated Volume from 2D diameters
Reference Volume (mL)
Estimated Volume (mL)
35
30
25
20
15
10
5
0
-5
0
5
10
15
20
25

(D)


Observer 1
Difference between Measurement and Reference Volume (mL)
Reference Volume (mL)
+1.96 SD
3.2
Mean
-0.2
-1.96 SD
-3.7
10
8
6
4
2
0
-2
-4
-6
-8
-10
0
5
10
15
20
25

(E)



(F)

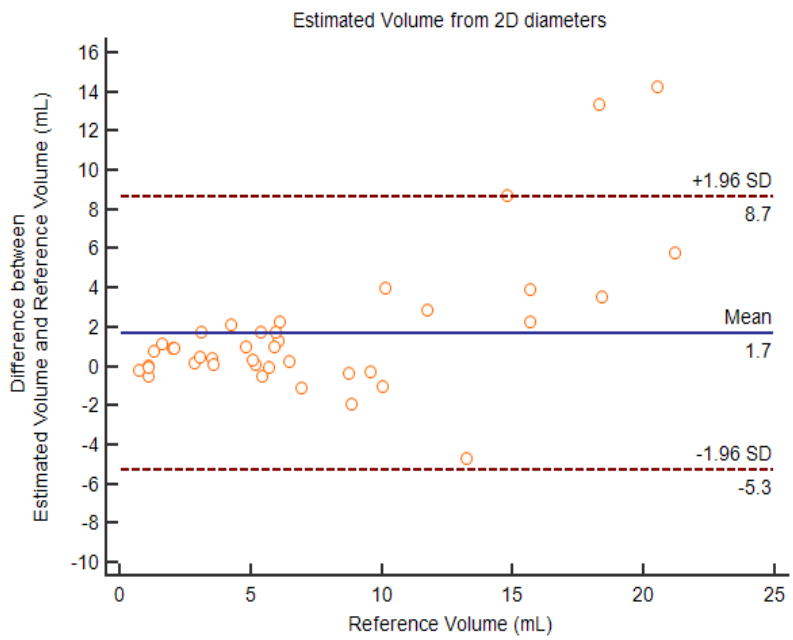


Figure 3. Comparison of measured volume using three-dimensional ultrasound and estimated volume from 2D diameters (V=π/6 abc) with the

true volume of tumor phantoms

A-C) Scatter diagrams of true volume vs volumetric measurement (by observer 1 and 2) and estimated volume from 2D diameters. The values of correlation coefficients (r) are 0.953, 0.97, and 0.945 for observer 1, observer 2, and the estimated volume

D-E) Plots of difference between the volume measurement and estimation against the true volume. The 95% limits of agreement (mean difference ± 1.96 SD) calculated using the Bland and Altman method were indicated as dashed line

Treatment response evaluation

For ten patients of response group and other ten patients of no-response group, changes in unidimensional diameter of target lesions on CT, changes in volume of corresponding target lesions on CT, and on 3D US uisng personalized 3D-printed tumor model using CT images were compared (**Table 2**). The average of absolute values of percentage change in diameter on pre- and post-chemotherapy CT was 33.27%, whereas percentage change in CT volume was 64.0%. In the response group, the average 43.49% decrease in diameter on CT was observed, whereas 71.42% decrease in volume on CT. In the no-response group, the average 10.15% increase in diameter on CT was demonstrated, while 22.33% increase in volume on CT.

Regarding RECIST criteria, 10 patients of PR have been included in the response group, and 8 patients with SD and 2 patients with PD have been included in the no-response group. For therapeutic response assessment using volumetric measurement, unidimensional RECIST criteria was extrapolated to volume. Thus, partial response represented greater than 65% reduction in volume, disease progression represented greater than 73% increase in tumor volume, and stable disease indicated less than 65% reduction to less than 73% increase in tumor volume [27]. After applying volumetric criteria, two patients with PR in the response group changed to SD, and one patient with SD in the no-response group changed to PD based on CT volume. Overall, downstage in three patients according to the RECIST criteria, and change to no-response group in two patients were observed after volumetric response evaluation.

In comparison to the response evaluation based on CT volume, response evaluation based on volume measurement on 3D US using personalized 3D-printed tumor model was concordant in 17 out of 20 patients for observer 1, and 18 out of 20 patients for observer 2. The inter-observer agreement was excellent ($\kappa = 0.961$). In terms of response versus non-response group, CT volume and 3D US volume measurement were identical in 19 out of 20 patients for both observers.

No.	Unidimensional RECIST Criteria*				Volumetric Criteria**											
					CT volume				3D US volumetric US (R1)				3D US volumetric US (R2)			
	Baseline (cm)	Post-Tx. (cm)	Change (%)	Criteria	Baseline (mL)	Post-Tx. (mL)	Change	Criteria	Baseline (mL)	Post-Tx. (mL)	Change	Criteria	Baseline (mL)	Post-Tx.	Change	Criteria
1	1.8	1	44.5% D	PR	5.15	1.06	79.4% D	PR	4.63	0.8	82.7% D	PR	4.38	1.27	71.0% D	PR
2	3.3	1.8	45.5% D	PR	15.65	3.12	80.1% D	PR	14.94	3.1	79.3% D	PR	18.57	3.1	83.3% D	PR
3	2.2	1.5	31.8% D	PR	6.46	2.86	55.8% D	SD	5.13	4.63	9.7% D	SD	8.32	5.72	31.3% D	SD
4	4	1.5	62.5% D	PR	20.5	2.0	90.2% D	PR	21.33	2.32	89.1% D	PR	24.14	1.88	22.1% D	PR
5	3.3	2	39.4% D	PR	18.27	4.24	76.8% D	PR	13.7	4.45	67.5% D	PR	20.25	4.62	77.2% D	PR
6	3.4	2.3	32.4% D	PR	18.4	5.92	67.8% D	PR	14.89	7.42	50.2% D	SD	15.16	5.97	60.6% D	SD
7	2.4	1.4	41.7% D	PR	5.41	1.31	75.7% D	PR	3.91	1.3	66.8% D	PR	4.83	1.51	68.7% D	PR
8	2.7	1.4	48.1% D	PR	6.04	1.61	73.4% D	PR	6.22	0.98	84.2% D	PR	5.12	1.43	72.1% D	PR
9	3	2.1	30% D	PR	8.74	4.79	45.2% D	SD	8.12	2.98	63.3% D	SD	7.62	4.65	39.0% D	SD
10	3.9	1.6	59.0% D	PR	10.14	3.06	69.8% D	PR	13.07	3.78	71.1% D	PR	13.12	3.73	71.6% D	PR
11	2.9	2.4	17.2% D	SD	10.02	5.04	49.7% D	SD	7.12	4.41	38.1% D	SD	9.72	5.13	47.2% D	SD
12	2.8	3.3	17.9% I	SD	11.74	14.75	25.7% I	SD	11.25	12.98	15.4% I	SD	13.33	15.84	18.8% I	SD
13	3.3	2.8	15.2% D	SD	15.66	21.16	35.1% I	SD	13.81	23.1	67.3% I	SD	14.86	24.93	67.8% I	SD
14	1.2	1.8	50% I	PD	1.09	2.06	89.7% I	PD	0.91	2.82	209.9% I	PD	1.02	2.43	138.2% I	PD
15	2.8	2.0	28.6% D	SD	9.53	3.57	62.6% D	SD	8.82	4.19	52.5% D	SD	8.82	5.24	40.6% D	SD
16	2.4	2.4	0%	SD	5.69	5.39	5.2% D	SD	8.14	7.34	9.8% D	SD	8.07	7.18	11.0% D	SD
17	1.6	1.8	12.5% I	SD	6.09	5.87	3.6% D	SD	9.79	6.83	30.2% D	SD	9.5	8.1	14.7% D	SD
18	1.1	1.2	9.1% I	SD	0.72	1.09	50.1% D	SD	1	1.16	16% I	SD	1.54	2.1	36.4% I	SD
19	1.6	2.7	68.8% I	PD	3.5	8.85	153.2% I	PD	3.38	5.4	59.8% I	SD	5.69	8.7	52.9% I	SD
20	2.6	2.8	7.7% I	SD	6.94	13.24	90.8% I	PD	6.45	10.7	65.9% I	SD	7.77	16.96	118.3% I	PD

Table 2. Changes in pre- and post-chemotherapy diameters of the target lesion on CT and volumes of the phantoms on 3D US, and corresponding

response evaluation according to the unidimensional (1D) RECIST criteria and three-dimensional (3D) volumetric criteria

DISCUSSION

We found that, with the tumor volume from CT as a reference standard, tumor volume measurement using 3D US with personalized 3D-printed tumor model from CT images showed no statistically significant difference (7.18 ± 5.44 mL in observer 1 and 8.31 ± 6.32 mL in observer 2 vs 7.42 ± 5.76 mL in CT, $p>0.05$). In addition, 3D US provided the high correlation coefficient with the CT volume ($r=0.953$, observer1; $r=0.97$, observer2) and the high inter-observer intraclass correlation (0.978; 0.958-0.988). Regarding response assessment, the percentage change in CT volume was greater than the percentage change in diameter on on pre- and post-chemotherapy CT (64.0% vs 33.27%). 3D US with personalized 3D-printed tumor model was in agreement with CT volume in 17 of the 20 patients in observer 1 and 18 of the 20 patients in observer 2 with good to excellent inter-observer agreement (kappa = 0.742 and 0.833, respectively).

Previous studies about volumetric tumor measurement of 3D US used manually made phantoms such as pieces of ham or condoms filled with water, or tissue phantoms made by using chicken or pork [12, 18, 19]. In this study, we firstly reconstructed the hepatic tumor applying of personalized tumor model using CT images of each patients, utilizing the recently developed 3D printing technology. Our study results showed that volume measurement by 3D US has no statistically significant difference compared to the tumor volume measured using CT, providing high value of correlation coefficient as well as high inter-reader agreement. The absolute measurement error from CT volume was -0.24 ± 1.75 mL

(mean ± SD) and 0.89 ± 1.58 mL (mean ± SD) for observer 1 and 2, respectively. The measurement error and the limits of agreement for measured volume with 3D US were lower than that for calculated volume from 2D US diameters according to ellipsoid formula. These results are concordant with the results of previous similar studies [12, 18, 19, 28, 29]. The absolute measurement error in the previous study by Park et al. was 2.6 mL ± 0.2 mL (mean ± SD) and volume measurements of two observers showed high agreement using US phantom made of 20 ham pieces (8.6 ~ 10.5 mL) [12]. Their study emphasized the scanning conditions such as position of US focus and tumor depth for accuracy of volumetric tumor measurement with 3D US. In our study, all phantoms were located in 2 cm deep from the transducer and focus was at the same level as the phantoms, which was considered as optimal scanning condition of 3D US. Xu et al. demonstrated that the volume measurement error of 3D US was 0.3% ± 3.3% in regular phantoms, -0.4% ± 3.7% in irregular phantoms, and 0.9% ± 11.3% in liver tumor, respectively, as compared with -5.3 ± 9.4%, 13.6 ± 28.0%, and 15.3 ± 37.3% for two-dimensional ultrasound, respectively. They also showed great inter-observer and intra-observer reproducibility both *in vitro* and *in vivo* [18]. In their *in vivo* study conducted in 68 liver tumors, the true volumes of the tumors were measured using the method of water displacement. However, 31 liver tumors were unsuccessful in measurement of true volume due to various reasons including tumor rupture or bleeding, inability to separate tumor from liver tissue, and unresectability of the tumor. In contrast, using 3D printing technology, we could reconstruct personalized hepatic tumor phantoms utilizing each patient's CT data, thus know the true volume of tumor without surgical resection. Furthermore, we could evaluate the change in volume of

the hepatic tumor after treatment.

With technological revolution of 3D printing in the medical field, 3D visualization of anatomy and pathologic condition and creation of 3D-printed physical models became accessible in the diagnostic imaging practices [21-25]. In many cases, the 3D modeling has been applied for patients with complex disease or anatomy in the preoperative setting. Recently, personalized or realistic experimental phantoms were constructed for validation of new imaging techniques. Burfeindt et al. proposed a 3D-printed phantom for use in preclinical experimental microwave imaging techniques which was derived from an MRI of a human subject [30]. In their study, the interior structure and dielectric properties of the phantoms were very similar to realistic breast tissue, which was possible with 3D printing technology. In the recent study by Ehler et al., it was determined that the use of patient specific phantoms created using a 3D printer for dosimetric verification of intensity-modulated radiation therapy (IMRT) was feasible [31]. They constructed soft-tissue equivalent 3D printed phantom using an anthropomorphic phantom as a 'patient', and dosimetric calculations and measurement were compared in the anthropomorphic phantom and 3D printed phantom. In the present study, we reconstructed hepatic tumor models utilizing CT information to validate 3D US quality and to investigate volumetric criteria in the patients with chemotherapy. Thus, compared with the other phantom studies regarding 3D US, our patient-tailored hepatic tumor models can simulate the real tumor morphology and changes according to the treatment.

Although the revised RECIST guideline (version 1.1) is most widely used to assess the response to treatment for solid tumors, its limitations associated with

unidimensional measurement such as difficulty in determining diameter of irregular or conglomerated lesions have been dilemma in the radiological as well as clinical field [5, 6]. Instead, volumetric response evaluation using volumetric image acquisition from CT or MR has gained a much interest and acceptance in place of uni- or bi-dimensional methods [7-11]. 3D volumetric measurement has advantages in better quantification of total tumor burden, more accurate assessment of tumor change, and better measurement of irregular mass [5]. However, there has been lack of studies about accuracy and reliability of volumetric response evaluation and no established volumetric criteria currently. In this study, compared to the unidimensional RECIST criteria, volumetric criteria based on CT volume made change in response evaluation in 15% (3/20) of patients (PR to SD in two patients, SD to PD in one patient), and change in group in 10% (2/20) of patients (response group to no-response group). Our discordance rate of 15% was similar to or slightly higher than those of previous studies comparing volumetric measurement against uni-dimensional measurements [3, 5]. The study published by Fang et al. demonstrated that volumetric evaluation showed good agreement with RECIST (κ=0.779) and discordance rate was 13.3% (6/45) [3]. In their study, 3 SD changed to PR, 1 PR and 2 PD changed to SD after applying volumetric evaluation. They explained that disproportionate asymmetrical change of tumors while maintaining longitudinal diameter accounted for SD by RECIST while PR by volumetric evaluation. On the contrary, 2 patients with PR by RECIST were considered as SD by volumetric assessment in our study. This could be explained that although larger change in volume than in longitudinal diameter was observed in the study, volumetric criteria derived from extrapolation of unidimensional criteria was much

wider range for stable disease, i.e. 65% reduction to 73% increase. Therefore, a new validated volumetric guideline is needed rather than simple transformation using volumetric formula of RECIST unidimensional criteria.

With advances in 3D US technology, it has been reported that 3D US is accurate and reliable for volume measurement in the various field [12, 32-36]. In comparison of CT or MR, US is more readily available and has no radiation hazard. Thus in cancer patients who needs frequent follow-up examinations, 3D US can be a useful method for monitoring treatment response. However, many studies about volume measurement using 3D US have been experimental or *in vitro* phantom studies, because of limited sonographic window using 3D transducer associated with various patient's anatomy and position as well as respiratory motion [12, 14, 16-20]. In this study, we reconstructed CT-based personalized tumor lesions for each patient via recently developed 3D printing technology. Therefore, in comparison to the volumetric measurement using CT data, we could assess the accuracy and reliability of volumetric assessment on 3D US and therapeutic evaluation for each patient under chemotherapy due to hepatic metastases from colon cancer.

Our study has several limitations. First, small sample size gives us difficulty for testing of correlation between measurement and reference value of the tumor volume in terms of statistical reliability and generalization. Second, because we did not understand the acoustic characteristics of the 3D-printed phantoms made up of silicone and graphite powder, measurement error owing to the thick echogenicity at the interface between phantom and water was inevitable. Despite the high inter-observer agreement (ICC=0.978) in 3D US measurement, different

individual tendency to measure was observed, especially during the manual outlining of the boundaries on 2D images of eight planes on US units. At the thick echogenic borders of the phantoms, observer 2 drew relatively larger boundaries compared to the observer 1, and volume of the phantoms were generally larger in observer 2 (8.31 ± 6.32 mL) than in observer 1 (7.18 ± 5.44 mL). For optimal visualization of phantoms on 3D US and reducing bias in subjective measures, further study with in-depth knowledge of acoustic characteristics of variable materials used for 3D printing is needed.

In conclusion, 3D US volumetric measurements applying of personalized 3D-printed tumor model using CT images in hepatic metastasis from colon cancer are accurate and reliable method for the response evaluation in comparison with the tumor volume from CT. With the advantages of accessibility, high cost-effectiveness, and no radiation hazard in comparison with CT and MRI, 3D US would be useful in the volumetric treatment response evaluation in the cancer patients.

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국문 초록

삼차원 초음파를 이용한 대장암 간전이의 치료 반응 평가

환자 맞춤형 삼차원 프린트 종양 모델을 이용한 연구

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서론: 의학 분야에서 3 차원 프린트 기술의 발전으로 해부학 및 병적 컨디션의 삼차원 구상화와 3 차원 프린트된 생체 모델의 이용이 진단 영상의학 분야에서 가능해졌다. 본 연구에서는 대장암의 간전이 환자의 전산화 단순촬영(CT) 영상을 이용하여 3 차원 프린터로 제작한 종양 모델을 이용하여 삼차원 초음파의 정확도와 신뢰도에 대한 연구를 시행하였다.

방법: 20 명의 대장암의 간전이로 항암 화학 요법을 받고 화학 요법 전과 후에 CT 검사를 시행 받은 환자들을 후향적으로 모집하였다. 환자들의 CT 영상으로 삼차원 프린터를 이용하여 환자 맞춤형 초음파 종양 모델을 제작하였다. 두 명의 영상의학과 의사가 삼차원 초음파로 삼차원

프린팅 종양 모델의 부피를 각각 측정하였다. CT 영상에서 얻은 종양 모델의 부피를 기준 부피로 하여 초음파에서 측정한 부피를 비교하여 평균 차이와 상관 관계를 분석하였다. 종양 치료 반응 평가는 RECIST criteria 를 기준으로 분석하였다.

결과: 10 명의 치료 반응군과 10 명의 치료 무반응군을 대상으로 분석하였다. CT 에서 얻은 종양의 부피를 기준으로 하여 삼차원 프린팅 종양 모델의 삼차원 초음파를 이용한 측정 부피를 통계적으로 유의한 차이가 없었다. (7.18 ± 5.44 m (측정자 1) 과 8.31 ± 6.32 mL (측정자 2) 대 7.42 ± 5.76 mL (CT 부피), p>0.05). 삼차원 초음파는 CT 부피와 높은 상관관계를 보였으며 (r=0.953, 측정자 1; r=0.97, 측정자 2), 측정자간에도 높은 상관 관계를 보였다 (Intraclass correlation=0.978; 0.958−0.988). 치료 반응 평가에 있어서 삼차원 초음파는 CT 부피와 비교하여 측정자 1 에서 20 명 중 17 에서, 측정자 2 에서 20 명 중 18 에서에서 일치하였고, 측정자간의 높은 합의도를 보였다 (kappa = 0.961)

결론: 대장암의 간전이 환자에서 환자 맞춤형 삼차원 프린팅 종양 모델의 삼차원 초음파를 이용한 부피 측정은 CT 에서 얻은 부피와 비교하였을 때 치료 반응 평가에 정확하고 신뢰 있는 방법이다.

주요어 : 삼차원 초음파, 삼차원 프린팅 종양 모델, 대장암 간전이

학 번 : 2013−21705