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Comparison of linear, bi-dimensional,  
and volumetric measurements in  
evaluating tumor response of  
hepatocellular carcinoma lesions in the  
arterial and portal venous phases on MRI

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**COMPARISON OF LINEAR, BI-DIMENSIONAL AND VOLUMETRIC  
MEASUREMENTS IN EVALUATING TUMOR RESPONSE OF  
HEPATOCELLULAR CARCINOMA LESIONS IN THE ARTERIAL AND  
PORTAL VENOUS PHASES ON MRI**

by

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Submitted in partial fulfillment of the  
requirements for the degree of  
Master of Science

2015

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## **DEDICATION**

I would like to dedicate this work to my father, Porter Sherman, for his continued support and encouragement throughout the years.

## **ACKNOWLEDGMENTS**

I would like to thank my mentor Dr. Anderson and my readers Dr. Jara and Stacey Hess Pino for their support and guidance during my thesis process. I would like to thank my mother, Sally Sherman, for her grammar skills and her review of my thesis drafts. I would like to thank my husband Tom for driving me to and from BMC at weird hours so I could review images. And I would like to thank Patrick and Dune Raleigh for their ‘tough love’.

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**ABSTRACT**

There are unmet needs in evaluating treatment response of hepatocellular carcinoma in research protocols. Early predictors, such as imaging biomarkers, could allow for earlier judgment of treatment effect. Currently RECIST is the most widely accepted criterion in clinical trials. A modified RECIST (mRECIST) criterion was developed to take into account the unique imaging characteristics of HCC lesions. Much discussion has occurred regarding linear measurements and their appropriateness for evaluating change in tumor burden over time. The simplicity of currently accepted criteria differs with the increasing sophistication of imaging techniques. Tumor volume change on 3D imaging can provide insight into actual action of treatment rather than an estimate of action as shown by linear and bi-dimensional measurements. It was the aim of this study to determine whether linear, bi-dimensional, and volumetric percent changes of HCC lesions, in both the arterial and portal venous phases, are significantly comparable.

27 HCC lesions (identified on 25 subjects) were measured at two timepoints by each method on 3D GRE MRI scans in both phases. Percent change was calculated per

lesion for each measurement type in both the arterial and portal venous phases. Signed rank tests, paired t tests, and comparison of change tests were run to evaluate the data.

Significant differences between the percent changes of linear measurements versus volumetric measurements were observed using a Wilcoxon signed-rank test which showed  $p = 0.0000$ . A simple correlation assessment showed positive correlations for all measurements, with the lowest being correlations 0.8679 for the arterial linear percent change versus the arterial volumetric percent change and 0.8434 for the portal venous linear percent change versus the portal venous volumetric percent change. Differences between percent changes of linear versus bi-dimensional measurements and bi-dimensional versus volumetric measurements were significant as well (Linear versus bi-dimensional  $p = 0.0001$ , bi-dimensional versus volumetric  $p = 0.0004$ ).

To conclude, the differences in the percent changes when comparing the measurement types are statistically significant, particularly when comparing linear and volumetric measurements. Establishing a reproducible volumetric criterion could lead to improvements in the implementation of clinical trials.

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## LIST OF ABBREVIATIONS

A.....	Arterial
ANOVA.....	Analysis of variance
AW.....	Advantage Workstation
cm <sup>3</sup> .....	Centimeters cubed
BMC.....	Boston Medical Center
CT.....	Computed Tomography
GE.....	General Electric
GRE.....	Gradient Echo
HBV.....	Hepatitis B
HCC.....	Hepatocellular carcinoma
HCV.....	Hepatitis C
I-HCC.....	Infiltrative hepatocellular carcinoma
mm.....	Millimeters
mm <sup>2</sup> .....	Millimeters squared
mRECIST.....	Modified Response Evaluation Criteria in Solid Tumors
MRI.....	Magnetic Resonance Imaging
NAFLD.....	Non-alcoholic fatty liver disease
NASH.....	Non-alcoholic steatohepatitis
OLT.....	Orthotopic liver transplantation
OS.....	Overall Survival
PACS.....	Picture archiving communication system

PEI.....	Percutaneous ethanol injection
PPD.....	Product of the perpendicular diameters
PD.....	Progressive Disease
PR.....	Partial Response
Prob.....	Probability
PV.....	Portal Venous
RECIST.....	Response Evaluation Criteria in Solid Tumors
RFA.....	Radiofrequency ablation
SD.....	Stable Disease
SPPD.....	Sum of the products of the perpendicular diameters
TACE.....	Transcatheter arterial chemoembolization
TAE.....	Transarterial embolization
THRIVE.....	T1-weighted high-resolution isotropic volume examination
TTP.....	Time to Progression
US.....	Ultrasound
USA.....	United States of America
WHO.....	World Health Organization

## INTRODUCTION

Hepatocellular Carcinoma (HCC) is the fifth most common tumor type in the world and the most common primary malignancy of the liver. Liver cancer is the third leading cause of cancer-related deaths in the world, more prevalent in men than women.<sup>1,2</sup> The prognosis of a patient with HCC is poor with a five-year survival rate of approximately 12%.<sup>3</sup> The mortality rate has been steadily growing over the last three decades and in the United States (USA) alone the incidence has tripled.<sup>4</sup> This disease has the fastest growing mortality rate of all cancers in the USA and the increase of new cases in younger patients is concerning as the mean age of diagnosis is mid to late 50s.<sup>3,5</sup> The global incidence is heterogeneous and is dependent on risk factor variations throughout the continents; however, the highest burdens are seen in developing countries<sup>2,6</sup>.

HCC begins in hepatocytes, usually arising in the cirrhotic liver.<sup>7</sup> Most cases of HCC develop stepwise from a low-grade dysplastic nodule to a high-grade dysplastic nodule, then to a dysplastic nodule with a focus on HCC, and lastly carcinoma.<sup>8</sup> They are highly vascular tumors that receive their blood supply from the hepatic artery unlike most liver tissue which is supplied blood from the portal vein.<sup>9</sup> These tumors show aggressive growth, frequently metastasize and often recur after treatment.<sup>10</sup>

### **Risk Factors**

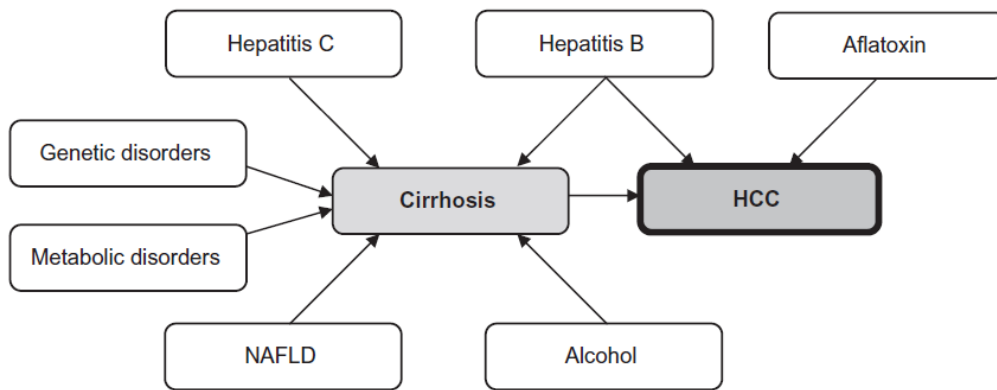
The precursors to cirrhosis are major risk factors for HCC as approximately 80% of cases develop in cirrhotic livers. In the USA and developed countries, cirrhosis of the liver is present in most patients with HCC.<sup>11</sup> In these countries; there has been a rise of

alcohol related cirrhosis due to an increase in chronic alcohol use. Hepatitis B (HBV) is the leading risk factor globally with more than half of the world's tumor burden attributed to this infection. The under-developed world (East-Asia and Sub-Saharan Africa) has a high incidence of HBV. Hepatitis C (HCV) also increases the risk of HCC although it takes approximately 20 years for cirrhosis to develop after contracting HCV, so the timing of the viral infection is important to take into consideration.<sup>11,13</sup> As the incidence of HCV has increased in the developed world, so has the incidence of HCC.<sup>1,5,10,12</sup> Risk is higher among males with HBV and/or HCV infections, especially if they are elderly.<sup>13</sup>

A risk factor that has a high prevalence in developed parts of the world, particularly the United States, is non-alcoholic fatty liver disease (NAFLD). NAFLD causes the development of non-alcoholic steatohepatitis (NASH) and cirrhosis, which can lead to HCC. NAFLD is being diagnosed more frequently in patients with obesity and type-2 diabetes. As a leading cause of chronic liver disease in these developed countries, NAFLD may become one of the leading causes of HCC as the incidence of obesity and type-2 diabetes continue to rise.<sup>11,13,14,15</sup>

There are a number of other risk factors that have been studied in association with HCC. As previously mentioned alcohol use is a cause of cirrhosis and may be a significant risk factor of HCC, especially in geographic areas where there is low HBV/HCV infection.<sup>14</sup> Additionally, dietary aflatoxin, a toxic metabolite created by certain fungi, is a carcinogen and there is a high incidence of HCC in areas where there is regular consumption of contaminated food, particularly in sub-Sahara Africa, South-East Asia, and China.<sup>1,14</sup> Genetic haemochromatosis is a metabolic disorder that causes iron-

overload, which may also be a risk factor of HCC, although the carcinogenicity of iron is still under debate.<sup>16</sup> Furthermore, any other cause of cirrhosis could be a risk factor to HCC and the combination of any cirrhosis risk factors could increase the risk of HCC (Fig.1).



**Figure 1: Risk factors for the development of hepatocellular carcinoma.<sup>15</sup>**

### **Current Treatments**

Classification of HCC can be challenging as it is a largely heterogeneous malignancy. In order to determine an appropriate treatment, factors such as tumor burden and underlying cirrhosis or hepatic dysfunction must be taken into consideration, especially because cirrhosis puts the patient at risk for new primary tumors even while the current tumor burden is being treated.<sup>17</sup>

Early stage HCC is the only solid tumor that can be treated by orthotopic liver transplantation (OLT) with the possibility of being cured, as this procedure requires

removing the subject's liver and replacing it with a donor liver. There are strict criteria used to decide if a subject is eligible for this treatment as donor organs are scarce. Surgical resection is also available for subjects without cirrhosis and this can potentially be curative, however only a small percentage of subjects are eligible for these treatments due to HCC multifocality on a background of chronic liver disease. For patients with intermediate stage HCC, there are a number of treatments available that are non-curative but they degrade the tumor while keeping the other liver tissue intact. For HCC with multifocal lesions without vascular invasion, transcatheter arterial chemoembolization (TACE), with or without drug eluting beads, or transarterial embolization (TAE) are appropriate options as they are minimally invasive procedures that can be used to directly cut off a tumors blood supply. Locoregional therapies such as percutaneous ethanol injection (PEI), cryotherapy, and radiofrequency ablation (RFA) are also available to treat early stage disease.<sup>6</sup>

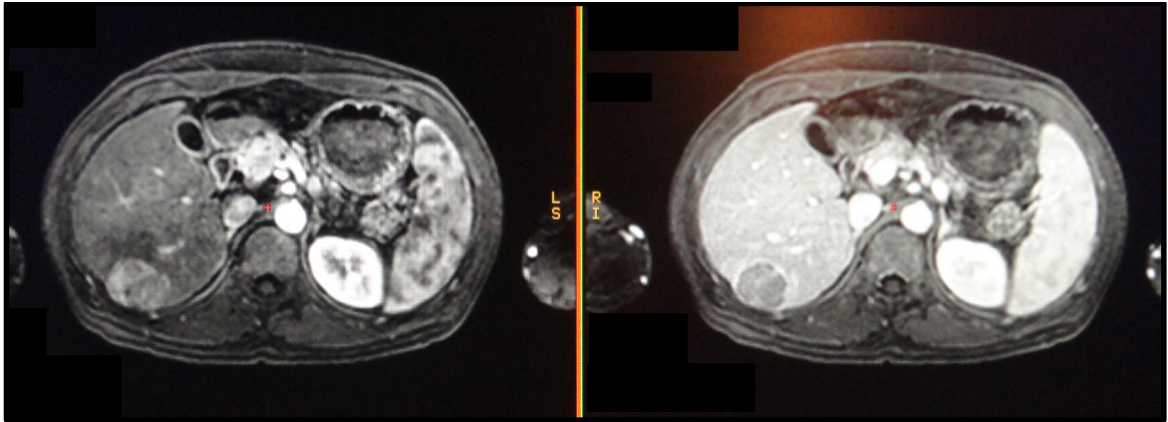
A number of drug treatments have been developed and have gone through clinical trials; however Sorafenib, approved by the FDA in 2007, is the first agent that has shown improved overall survival (OS) benefits in advanced HCC.<sup>12</sup> It targets two of the key pathways that play an important role in the pathogenesis of HCC.<sup>18</sup> Further study of this drug is needed as the clinical benefits have only been seen in certain patients. HCC tumors generally have a low response rate to chemotherapy as they have high resistance to drugs and there is difficulty getting the drug into the tumor. Previously there was no effective treatment available for the advanced stage of this disease or for subjects who progressed to the advanced stage after other treatments failed.<sup>18</sup> Sorafenib stabilizes the

tumor by delaying progression, however while it does improve OS, progressive disease eventually develops in most patients.<sup>17</sup>

### **Imaging and HCC**

Medical imaging is useful for HCC diagnosis, as patients typically do not present with symptoms until later stages of the disease. Ultrasound (US) is the first line diagnostic method for HCC, however, cirrhosis can complicate detection and lesions can be missed.<sup>19</sup> Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are the current preferred modalities for identifying HCC as they provide a clear and detailed picture of internal anatomy.

Arterial enhancement is considered an essential characteristic of HCC and is used as a main imaging characteristic for HCC diagnosis. During the arterial phase, most of the liver is not yet enhancing because 75% of the liver's blood supply will arrive later via that portal vein. HCC, however, shows pronounced enhancement during the arterial phase due to the source of the tumor tissue blood supply.<sup>7</sup> Enhancement tends to be heterogeneous in large lesions and more homogeneous in smaller ones. A mosaic pattern is created by confluent nodules separated by fibrosis septa and areas of necrosis.<sup>19</sup> The most common appearance of HCC is early arterial contrast enhancement with "washout" on delayed phases. On the portal venous phase there is also relative hypoenhancement compared to surrounding liver parenchyma with a delayed enhancing outer rim "capsule" (Fig. 2).<sup>15</sup>



**Figure 2: HCC lesion showing typical arterial contrast enhancement (left) and portal venous washout (right) on 3D-GRE MRI.**

CT with contrast can identify HCC lesions based on early arterial enhancement and late portal venous washout. MRI (with contrast) is sensitive for the detection of lesions measuring 2cm or larger but is less sensitive for the diagnosis of small HCC lesions.<sup>19</sup> Tumors are generally bright on T1-weighted sequences mainly attributed to the presence of intratumoral fat, copper deposition within the tumor and the degree of differentiation, presence of fibrosis, and intratumoral necrosis<sup>19,20</sup>. Also, intratumoral hemorrhage, coagulative necrosis and mucin production can make signal intensity mixed.<sup>21</sup> There is moderately high tumor signal intensity on T2-weighted sequences; however it can be difficult to detect lesions on T2 because of the heterogeneity of the cirrhotic liver.<sup>8</sup> MRI also provides structural information on unenhanced images.

3D-GRE is a MRI imaging technique with a fast acquisition time.<sup>22</sup> This volumetric MRI technique can image the entire volume of the tissue simultaneously, allowing for efficient imaging by acquiring thinner sections and covering the anatomy of interest in reduced time.<sup>7</sup> This imaging provides detailed anatomical information and

good spatial resolution with an acceptable acquisition time for assessment of tumor size; however, it does not show partial volume averaging artifacts which can make it difficult to assess disease due to blurring.<sup>23</sup>

### **Evaluation Criteria**

Evaluation of tumor response is critical for determining whether a particular treatment is effective in a patient, or whether an experimental agent is effective against a specific tumor type. Many cancer related deaths are actually due to delayed tumor evaluation.<sup>39</sup> The accurate and early prediction of response or progression, while important for treating patients, is critical to clinical trials. For example, HCC clinical trials often use Time to Progression (TTP) as a primary endpoint.<sup>40</sup> Early predictors, such as imaging biomarkers, could allow for earlier judgment of treatment effect, which may allow for faster approval of new drugs and reduced time to market. It may also help to limit the size of trials, requiring lower subject enrollment and lower cost.<sup>41</sup>

There are unmet needs with regards to evaluating treatment response of HCC in research protocols as well as in clinical practice, as management of patients is influenced by the response to treatment. Patients are typically without symptoms until the late stages of disease so the assessment of tumor burden via imaging is an important endpoint.<sup>24</sup> Currently the most commonly used imaging biomarker is the linear measurement of the tumor burden. The Response Evaluation Criteria in Solid Tumors (RECIST) is the most widely accepted criterion in clinical trials. It uses the sum of the largest diameters of each

lesion on the axial plane to calculate percent changes of the tumor burden. Response determinations are based on these percent changes.<sup>25</sup>

HCC lesions have unique imaging characteristics. A modified RECIST (mRECIST) criterion was developed to take these characteristics into account. mRECIST takes into account only viable tumors seen on contrast enhanced imaging. A viable tumor is defined as tumor tissue with arterial enhancement and portal venous washout. Linear measurements made on arterial phase axial images are used in this criterion to determine percent changes of tumor diameters between exams as the authors believe that the lesions are more accurately measured while enhanced.<sup>26</sup>

There has been, and continues to be, much discussion regarding linear measurements and their appropriateness for evaluating tumor burden and changes between timepoints.<sup>47</sup> In 1979, the first guidelines were proposed by the World Health Organization (WHO) using bi-dimensional measurements and assessing responses using the change in the sum of the products of the perpendicular diameters (SPPD).<sup>27</sup> In 2000 the RECIST criterion was published with the rationale that it would provide a quicker and simpler assessment of tumor response to treatment.<sup>25</sup> The simplicity of this criterion, developed almost 15 years ago, but still widely used today, differs with the increasing sophistication of imaging instruments. Volumetric imaging allows for precise 3D measurement of the entire tumor burden.

Quantification of tumor burden can be accurately performed using volumetric acquisitions.<sup>28</sup> Tumor volume change can provide insight into the actual effect of treatment rather than an estimate of action as shown by linear and bi-dimensional

measurements.<sup>42</sup> There are, however, no widely accepted criteria using the percent changes of volumes to determine response.

It was the aim of this study to answer the question: Are linear, bi-dimensional, and volumetric measurements of HCC lesions comparable for assessing change in tumor size?? The primary objective was to evaluate potential differences in the percent changes of the three different types of measurements. The secondary objective was to evaluate the potential differences in the measurements due to enhancement phase. The primary endpoint is the percent change of each measurement between the two scans. The hypothesis of this study was that there are significant differences in using linear, bi-dimensional and volumetric measurements for calculating percent change of HCC lesions on MRI.

## METHODS

### Subject selection

This study was a retrospective cohort study. The 25 subjects included in this study were identified using Centricity Electronic Medical Records (GE Healthcare, Little Chalfont, Buckinghamshire, UK) at Boston Medical Center (BMC). All of the subjects had at least one liver lesion with a longest diameter greater than 10mm that presented with the HCC characteristics of arterial phase enhancement and portal venous phase washout. These lesions had been previously identified by a BMC radiologist, per standard of care, and noted in the subject's medical record. 3D GRE scans, per standard of care, were available for each subject from two separate dates (Scan 1 and Scan 2), with both arterial and portal venous phases included (Table 1).

**Table 1. Days between Scan 1 and Scan 2**

	<b>Min</b>	<b>1st Q</b>	<b>Med</b>	<b>3rd Q</b>	<b>Max</b>	<b>Mean</b>
Days Between Scans	46	95	117	184	401	153

All scans were performed between 2008 and 2013 on a Philips MRI (Philips, Amsterdam, The Netherlands). The treatment that the subjects received between scans was identified from the medical records. 18 subjects had received no treatment, 4 subjects were treated with Nexavar, 1 subject was treated with chemoembolization, 1 subject had an

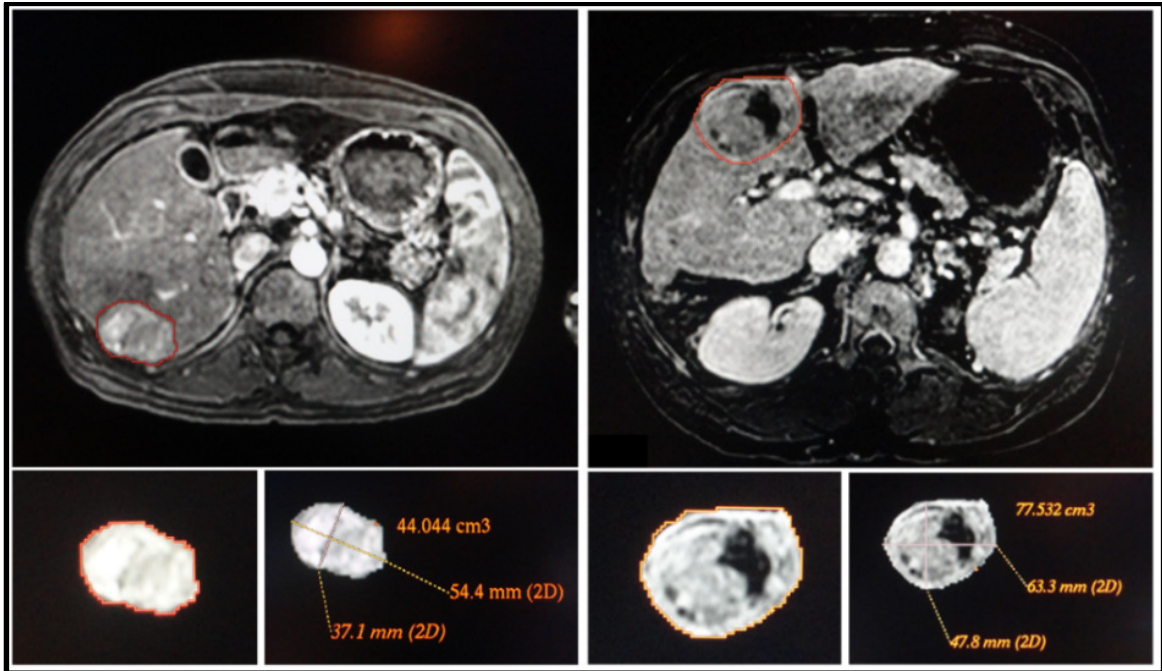
unsuccessful chemoembolization and intermittent Sorafenib, and 1 subject's treatment is Unknown (Table 2). All these treatments were per standard of care.

**Table 2. Treatments subjects received between Scan 1 and Scan 2**

Treatment	Number of Subjects	% of subjects
None	18	72%
Nexavar (Sorafenib)	4	16%
Chemoembolization	1	4%
Unsuccessful chemoembolization, intermittent Sorafenib	1	4%
Unknown	1	4%

### **Quantitative analysis: tumor size measurement**

All subject imaging was reviewed on a BMC GE AW Workstation (GE Healthcare, Little Chalfont, Buckinghamshire, UK ), which accessed the images from the picture archiving communication system (PACS). For the purpose of this study, a single reviewer, using AW VolumeShare 4 software, identified 27 lesions that were appropriate for linear, bi-dimensional, and volumetric measurements. Each lesion was measured on two 3D GRE scans, on both the arterial and portal venous phase for each (Fig. 3).



**Figure 3: Linear, bi-dimensional and volumetric measurements of lesion 2-1 on the arterial phase (right) and of lesion 6-1 on the portal venous phase (left).**

All measurements were made on the axial plane; however the sagittal and coronal planes were also available to view. The scans for each lesion were read in chronological order and were read without comparison to the other scan. The volume measurements were made by outlining the lesion on each axial slice and having the software calculate the volume in  $\text{cm}^3$ . Subsequently, the maximum diameter in millimeters (mm) was measured for each lesion where the lesion was the largest. After this measurement was completed, the longest perpendicular measurement was made in mm on the same slice. The longest diameter and the longest perpendicular diameter were multiplied to get the product of the perpendicular diameters (PPD) in  $\text{mm}^2$  (Tables 3a & 3b).

**Table 3a. Linear, bi-dimensional and volumetric lesion measurements on Scan 1 and Scan 2 in the arterial phase**

Subject Number	Scan	Lesion #	Arterial Longest Diameter (mm)	Arterial Perpendicular Diameter (mm)	Arterial Product of the Perpendicular Diameters (mm <sup>2</sup> )	Arterial Volume (cm <sup>3</sup> )
1	Scan 1	1-1	28.70	14.70	421.89	3.75
	Scan 2	1-1	23.80	16.20	385.56	1.37
2	Scan 1	2-1	54.40	37.10	2018.24	44.04
	Scan 2	2-1	72.40	59.50	4307.80	153.32
3	Scan 1	3-1	47.50	32.00	1520.00	23.40
	Scan 2	3-1	86.40	49.00	4233.60	83.97
4	Scan 1	4-1	33.50	26.70	894.45	8.15
	Scan 2	4-1	44.90	36.00	1616.40	17.54
5	Scan 1	5-1	31.20	20.30	633.36	5.46
	Scan 2	5-1	22.30	15.30	341.19	1.64
6	Scan 1	6-1	73.20	50.20	3674.64	73.23
	Scan 2	6-1	60.70	50.30	3053.21	65.66
7	Scan 1	7-1	61.30	50.10	3071.13	102.55
	Scan 2	7-1	55.20	49.80	2748.96	88.18
8	Scan 1	8-1	39.50	23.00	908.50	14.27
	Scan 2	8-1	38.90	28.40	1104.76	23.36
9	Scan 1	9-1	24.90	15.70	390.93	4.22
	Scan 2	9-1	25.50	17.50	446.25	7.65
10	Scan 1	10-1	50.10	44.80	2244.48	58.12
	Scan 2	10-1	66.30	44.30	2937.09	68.49
11	Scan 1	11-1	71.60	54.80	3923.68	79.49
	Scan 2	11-1	63.60	55.60	3536.16	104.99
12	Scan 1	12-1	37.10	29.20	1083.32	17.46
	Scan 2	12-1	128.10	109.20	13988.52	797.87
13	Scan 1	13-1	25.90	25.40	657.86	6.65
	Scan 2	13-1	28.60	26.40	755.04	10.19
14	Scan 1	14-1	21.40	20.00	428.00	4.33
	Scan 2	14-1	24.70	21.40	528.58	5.63
15	Scan 1	15-1	22.00	17.90	393.80	4.57
	Scan 2	15-1	20.20	17.10	345.42	3.50
15	Scan 1	15-2	26.50	15.80	418.70	6.19
	Scan 2	15-2	39.60	23.70	938.52	8.97
16	Scan 1	16-1	19.60	16.30	319.48	3.32
	Scan 2	16-1	22.60	15.60	352.56	4.67
17	Scan 1	17-1	33.90	16.20	549.18	9.98

	Scan 2	17-1	47.90	21.50	1029.85	32.37
18	Scan 1	18-1	56.10	49.40	2771.34	62.10
	Scan 2	18-1	52.70	50.70	2671.89	69.97
19	Scan 1	19-1	32.70	21.30	696.51	5.36
	Scan 2	19-1	68.00	41.40	2815.20	66.84
20	Scan 1	20-1	33.60	24.30	816.48	15.52
	Scan 2	20-1	41.30	34.30	1416.59	32.13
21	Scan 1	21-1	77.10	61.00	4703.10	136.68
	Scan 2	21-1	116.30	53.90	6268.57	239.65
22	Scan 1	22-1	37.60	28.60	1075.36	20.39
	Scan 2	22-1	62.90	29.00	1824.10	41.20
23	Scan 1	23-1	33.50	22.40	750.40	11.48
	Scan 2	23-1	22.40	8.10	181.44	3.42
24	Scan 1	24-1	20.90	15.70	328.13	2.66
	Scan 2	24-1	23.80	21.50	511.70	5.06
24	Scan 1	24-2	17.40	14.30	248.82	2.52
	Scan 2	24-2	32.00	30.10	963.20	11.24
25	Scan 1	25-1	20.60	18.20	374.92	3.89
	Scan 2	25-1	37.50	30.10	1128.75	17.24

**Table 3b. Linear, bi-dimensional and volumetric lesion measurements on Scan 1 and Scan 2 in the portal venous phase**

<b>Subject Number</b>	<b>Scan</b>	<b>Lesion #</b>	<b>Portal Venous Longest Diameter (mm)</b>	<b>Portal Venous Perpendicular Diameter (mm)</b>	<b>Portal Venous Product of the Perpendicular Diameters (mm<sup>2</sup>)</b>	<b>Portal Venous Volume (cm<sup>3</sup>)</b>
1	Scan 1	1-1	22.60	18.40	415.84	1.10
	Scan 2	1-1	31.00	18.30	567.30	5.46
2	Scan 1	2-1	46.70	37.30	1741.91	51.37
	Scan 2	2-1	70.30	57.00	4007.10	140.00
3	Scan 1	3-1	49.50	31.00	1534.50	15.23
	Scan 2	3-1	69.50	58.30	4051.85	70.48
4	Scan 1	4-1	33.10	28.70	949.97	10.12
	Scan 2	4-1	38.90	33.70	1310.93	16.66
5	Scan 1	5-1	39.10	25.00	977.50	6.90
	Scan 2	5-1	25.20	19.10	481.32	1.39
6	Scan 1	6-1	63.30	47.80	3025.74	77.53
	Scan 2	6-1	70.10	53.90	3778.39	69.43
7	Scan 1	7-1	59.40	48.20	2863.08	103.99
	Scan 2	7-1	58.60	49.80	2918.28	96.90
8	Scan 1	8-1	37.00	26.80	991.60	14.49
	Scan 2	8-1	50.30	38.10	1916.43	55.06
9	Scan 1	9-1	25.60	16.10	412.16	5.75
	Scan 2	9-1	26.40	26.40	696.96	11.42
10	Scan 1	10-1	59.10	47.30	2795.43	63.24
	Scan 2	10-1	57.10	48.80	2786.48	78.82
11	Scan 1	11-1	73.30	55.40	4060.82	123.97
	Scan 2	11-1	72.40	58.10	4206.44	129.14
12	Scan 1	12-1	40.50	31.80	1287.90	16.25
	Scan 2	12-1	123.10	85.00	10463.50	756.63
13	Scan 1	13-1	25.70	25.50	655.35	5.99
	Scan 2	13-1	28.50	27.00	769.50	9.13
14	Scan 1	14-1	23.50	16.50	387.75	4.96
	Scan 2	14-1	26.60	15.10	401.66	6.48
15	Scan 1	15-1	23.70	22.20	526.14	5.41
	Scan 2	15-1	17.40	10.90	189.66	1.21
15	Scan 1	15-2	29.30	21.80	638.74	4.78
	Scan 2	15-2	50.30	31.50	1584.45	13.16
16	Scan 1	16-1	23.00	20.20	464.60	5.03
	Scan 2	16-1	23.80	21.20	504.56	4.84

17	Scan 1	17-1	28.20	14.30	403.26	8.22
	Scan 2	17-1	47.20	29.40	1387.68	21.26
18	Scan 1	18-1	57.00	42.60	2428.20	66.68
	Scan 2	18-1	57.20	47.00	2688.40	72.63
19	Scan 1	19-1	42.10	30.50	1284.05	24.57
	Scan 2	19-1	46.20	35.50	1640.10	33.42
20	Scan 1	20-1	33.70	25.90	872.83	12.96
	Scan 2	20-1	48.90	37.70	1843.53	38.08
21	Scan 1	21-1	62.50	48.80	3050.00	111.09
	Scan 2	21-1	83.20	61.40	5108.48	202.53
22	Scan 1	22-1	30.10	26.20	788.62	16.37
	Scan 2	22-1	34.30	28.80	987.84	16.92
23	Scan 1	23-1	22.20	15.40	341.88	3.02
	Scan 2	23-1	18.90	12.70	240.03	0.93
24	Scan 1	24-1	17.50	13.80	241.50	1.56
	Scan 2	24-1	26.30	24.70	649.61	5.86
24	Scan 1	24-2	19.40	18.00	349.20	2.10
	Scan 2	24-2	32.60	26.60	867.16	11.83
25	Scan 1	25-1	22.20	16.50	366.30	2.81
	Scan 2	25-1	37.70	32.10	1210.17	15.56

**Table 3c. Summary of measurement data**

	<b>Variable</b>	<b>Min</b>	<b>1st Q</b>	<b>Med</b>	<b>3rd Q</b>	<b>Max</b>	<b>Mean</b>
<b>Both Scans</b>	Arterial Longest Diameter (mm)	17.40	25.05	37.30	55.88	128.10	43.71
	Arterial Perpendicular Diameter (mm <sup>2</sup> )	8.10	17.98	26.55	44.67	109.20	39.88
	Arterial Product of the Perpendicular Diameters (mm <sup>2</sup> )	181.40	432.60	950.90	2729.70	13988.50	1773.10
	Arterial Volume (mm <sup>3</sup> )	1.37	5.14	14.90	64.77	797.87	49.92
	PV Longest Diameter (mm)	17.40	25.85	37.35	57.08	123.10	42.25
	PV Perpendicular Diameter (mm <sup>2</sup> )	10.90	20.45	28.75	45.90	85.00	32.59
	PV Product of the Perpendicular Diameters (mm <sup>2</sup> )	189.70	510.00	989.70	2623.30	10463.50	1687.30
PV Arterial Volume (mm <sup>3</sup> )	0.93	5.53	14.86	65.82	756.63	49.09	
<b>Scan 1</b>	Arterial Longest Diameter (mm)	17.40	25.40	33.50	48.80	77.10	38.21
	Arterial Perpendicular Diameter (mm <sup>2</sup> )	14.30	17.10	23.00	34.55	61.00	28.35
	Arterial Product of the Perpendicular Diameters (mm <sup>2</sup> )	248.80	420.30	750.40	1769.10	4703.10	1308.00
	Arterial Volume (mm <sup>3</sup> )	2.52	4.45	9.98	33.72	136.68	27.03
	PV Longest Diameter (mm)	17.50	23.60	33.10	48.10	73.30	37.37
	PV Perpendicular Diameter (mm <sup>2</sup> )	13.80	18.20	25.90	34.55	55.40	28.59
	PV Product of the Perpendicular Diameters (mm <sup>2</sup> )	241.50	414.00	872.80	1638.20	4060.80	1253.90
PV Arterial Volume (mm <sup>3</sup> )	1.10	5.00	10.12	37.97	123.97	28.35	

<b>Scan 2</b>	Arterial Longest Diameter (mm)	20.20	25.10	41.30	63.25	128.10	49.21
	Arterial Perpendicular Diameter (mm <sup>2</sup> )	8.10	21.45	30.10	49.40	109.20	35.40
	Arterial Product of the Perpendicular Diameters (mm <sup>2</sup> )	181.40	520.10	1128.80	2876.10	13988.50	2238.20
	Arterial Volume (mm <sup>3</sup> )	1.37	6.64	23.36	69.23	797.87	72.82
	PV Longest Diameter (mm)	17.40	27.55	46.20	57.90	123.10	47.11
	PV Perpendicular Diameter (mm <sup>2</sup> )	10.90	25.55	32.10	49.30	85.00	36.60
	PV Product of the Perpendicular Diameters (mm <sup>2</sup> )	189.70	673.30	1387.70	2852.40	10463.50	2120.70
	PV Arterial Volume (mm <sup>3</sup> )	0.93	7.81	16.92	71.56	756.63	69.82

The size change (in percent) of each lesion was determined for each linear, bi-dimensional, and volumetric measurement in both the arterial and portal venous phases.

$$\frac{(\text{Scan 2 lesion size} - \text{Scan 1 lesion size}) \times 100}{\text{Scan 1 lesion size}} = \% \text{ change}$$

The percentage change of a lesion between the two scans was the data used for statistical analyses (Table 4).

**Table 4a. Percent changes of linear, bi-dimensional and volumetric measurements between Scan 1 and Scan 2 in the arterial and portal venous phases for each lesion**

Subject Number	Lesion Number	Phase	% Change Longest Diameter (mm)	% Change Product of the Perpendicular Diameters (mm <sup>2</sup> )	% Change Volume (mm <sup>3</sup> )
1	1-1	A	-1707.32%	-861.12%	-6352.47%
1	1-1	PV	3716.81%	3642.27%	39835.62%
2	2-1	A	3308.82%	11344.34%	24810.64%
2	2-1	PV	5053.53%	13004.06%	17251.67%
3	3-1	A	-3439.23%	-6471.52%	-8473.98%
3	3-1	PV	-2958.75%	-6170.55%	-8911.93%
4	4-1	A	3402.99%	8071.44%	11513.74%
4	4-1	PV	1752.27%	3799.70%	6452.63%
5	5-1	A	-2852.56%	-4613.02%	-6998.35%
5	5-1	PV	-3554.99%	-5076.01%	-7984.63%
6	6-1	A	-1707.65%	-2053.81%	-1034.11%
6	6-1	PV	1074.25%	2487.49%	-1044.99%
7	7-1	A	-995.11%	-1049.03%	-1401.71%
7	7-1	PV	-134.68%	192.80%	-681.43%
8	8-1	A	-151.90%	2160.26%	6371.86%
8	8-1	PV	3594.59%	9326.64%	28014.50%
9	9-1	A	240.96%	1415.09%	8120.41%
9	9-1	PV	312.50%	6909.94%	9850.46%
10	10-1	A	3233.53%	3085.84%	1784.16%
10	10-1	PV	-338.41%	-32.02%	2462.96%
11	11-1	A	-1117.32%	-987.64%	3208.12%
11	11-1	PV	-122.78%	358.60%	417.12%
12	12-1	A	24528.30%	119126.39%	447023.14%
12	12-1	PV	20395.06%	71244.66%	455533.75%
13	13-1	A	1042.47%	1477.21%	5318.70%
13	13-1	PV	1089.49%	1741.82%	5241.28%
14	14-1	A	1542.06%	2350.00%	3005.09%
14	14-1	PV	1319.15%	358.74%	3081.11%
15	15-1	A	-818.18%	-1228.54%	-2339.03%
15	15-1	PV	-2658.23%	-6395.26%	-7773.47%
15	15-2	A	4943.40%	12415.09%	4500.65%
15	15-2	PV	7167.24%	14805.87%	17548.16%
16	16-1	A	1530.61%	1035.43%	4065.70%
16	16-1	PV	347.83%	860.09%	-385.61%
17	17-1	A	4129.79%	8752.50%	22435.87%
17	17-1	PV	6737.59%	24411.55%	15865.17%
18	18-1	A	-606.06%	-358.85%	1266.59%
18	18-1	PV	35.09%	1071.58%	891.87%
19	19-1	A	10795.11%	30418.66%	114738.71%

19	19-1	PV	973.87%	2772.87%	3601.40%
20	20-1	A	2291.67%	7349.97%	10697.67%
20	20-1	PV	4510.39%	11121.30%	19381.22%
21	21-1	A	5084.31%	3328.59%	7533.86%
21	21-1	PV	3312.00%	6749.11%	8230.84%
22	22-1	A	6728.72%	6962.69%	10205.50%
22	22-1	PV	1395.35%	2526.18%	340.36%
23	23-1	A	-3313.43%	-7582.09%	-7017.94%
23	23-1	PV	-1486.49%	-2979.12%	-6932.50%
24	24-1	A	1387.56%	5594.43%	9021.82%
24	24-1	PV	5028.57%	16898.96%	27442.46%
24	24-2	A	8390.80%	28710.71%	34670.11%
24	24-2	PV	6804.12%	14832.76%	46455.15%
25	25-1	A	8203.88%	20106.42%	34342.68%
25	25-1	PV	6981.98%	23037.67%	45420.23%

**Table 4b. Summary of percent change data**

	Variable	Mean	Std. Dev	Min	Max
<b>Both Phases</b>	% Change Longest Diameter (mm)	26.75	51.87	35.55	245.28
	% Change Product of the Perpendicular Diameters (mm <sup>2</sup> )	85.19	197.71	-75.82	1191.26
	% Change Volume (mm <sup>3</sup> )	268.63	863.33	-89.12	4555.34
<b>Arterial Phase</b>	% Change Longest Diameter (mm)	27.44	57.22	-34.39	245.28
	% Change Product of the Perpendicular Diameters (mm <sup>2</sup> )	92.04	238.44	-75.82	1191.26
	% Change Volume (mm <sup>3</sup> )	270.75	871.80	-84.74	4470.23
<b>PV Phase</b>	% Change Longest Diameter (mm)	26.05	47.00	-35.55	203.95
	% Change Product of the Perpendicular Diameters (mm <sup>2</sup> )	78.33	150.77	-63.95	712.45
	% Change Volume (mm <sup>3</sup> )	266.52	871.40	-89.12	4555.34

## **Statistical analysis**

Comparisons were made of the percentage changes for the linear measurements versus the bi-dimensional measurements, the linear measurements versus the volumetric measurements, and the bi-dimensional measurements versus the volumetric measurements. Comparisons were also made between the arterial phase and the portal venous phase. The percent changes of the linear measurements in the arterial phase were compared to the percent changes of the linear measurements in the portal venous phase; the percent changes of the bi-dimensional measurements in the arterial phase were compared to the percent changes of the bi-dimensional measurements in the portal venous phase; and the percent changes of the volumetric measurements in the arterial phase were compared to the percent changes of the volumetric measurements in the portal venous phase. A Wilcoxon signed-rank test was used to compare differences in measurements due to the small sample size and the lack of normality in the data distribution. A simple correlation was run to compare the different measurement types within each phase, as well as to compare the same measurement types between phases. Additionally, a paired *t* test with a 95% confidence interval was performed on the measurements between phases. All statistical analyses were performed using statistical software (STATA version 11.2, StataCorp, College Station, TX, USA).

## RESULTS

### Comparison of linear, bi-dimensional and volumetric percent changes

Significant differences between the percent changes of the three measurement types were observed. For linear measurements versus bi-dimensional measurements, the Wilcoxon signed-rank test (Table 5) showed a  $p = 0.0001$  and the bi-dimensional percent changes on average 2.5 times (range, .02 - 29.54) greater, in either the positive or negative direction, than the linear percent changes. For bi-dimensional measurements versus the volumetric measurements,  $p = 0.0004$  and the volumetric percent changes were on average 5.2 times (range, .09 - 77.93) greater than the bi-dimensional percent changes. For linear measurements versus volumetric measurements,  $p = 0.0000$  and the volumetric percent changes were on average 5.8 times (range, .09 - 42.95) greater than the linear percent changes.

**Table 5. Wilcoxon signed-rank test results**

Percent Change Comparison	P - Value
Linear vs Bi-dimensional	0.0001
Linear vs Volumetric	0.0000
Bi-dimensional vs Volumetric	0.0004
Arterial Linear vs PV Linear	0.7916
Arterial Bi-dimensional vs PV Bi-dimensional	0.4004
Arterial Volumetric vs PV Volumetric	0.4711

The correlation assessment showed all positive correlations between the different measurement types (Table 6). The lowest correlations between two different

measurement types were linear versus volumetric in both phases with a correlation of 0.8679 in arterial phase and 0.8434 in portal venous phase.

**Table 6. Correlations**

<b>Percent Change Comparison</b>	<b>Correlation</b>
Arterial Linear vs Arterial Bi-dimensional	0.9333
Arterial Linear vs Arterial Volumetric	0.8679
Arterial Bi-dimensional vs Arterial Volumetric	0.9760
PV Linear vs PV Bi-dimensional	0.9675
PV Linear vs PV Volumetric	0.8434
PV Bi-dimensional vs PV Volumetric	0.9029
Arterial Linear vs PV Linear	0.8340
Arterial Bi-dimensional vs PV Bi-dimensional	0.9013
Arterial Volumetric vs PV Volumetric	0.9591

### **Comparison of arterial and portal venous percent changes**

The Wilcoxon signed-rank test did not show a significant difference between the percent changes of the same type of measurement in the arterial and portal venous phases (Table 5). The paired t test showed similar results with the two-tailed p-values. For the linear measurements the p-value = 0.8220, for the bi-dimensional measurements the p-value = 0.5631, and for the volumetric measurements the p-value = 0.9305.

All correlations between the arterial and portal venous phases were positive (Table 6). For the linear measurements the correlations was 0.8340, for the bi-dimensional measurements 0.9013 and for the volumetric measurements 0.9591.

## DISCUSSION

This study provides evidence that rejects the null hypothesis that there is no statistically significant difference in using linear, bi-dimensional and volumetric measurements for calculating percent change of HCC lesions on MRI.

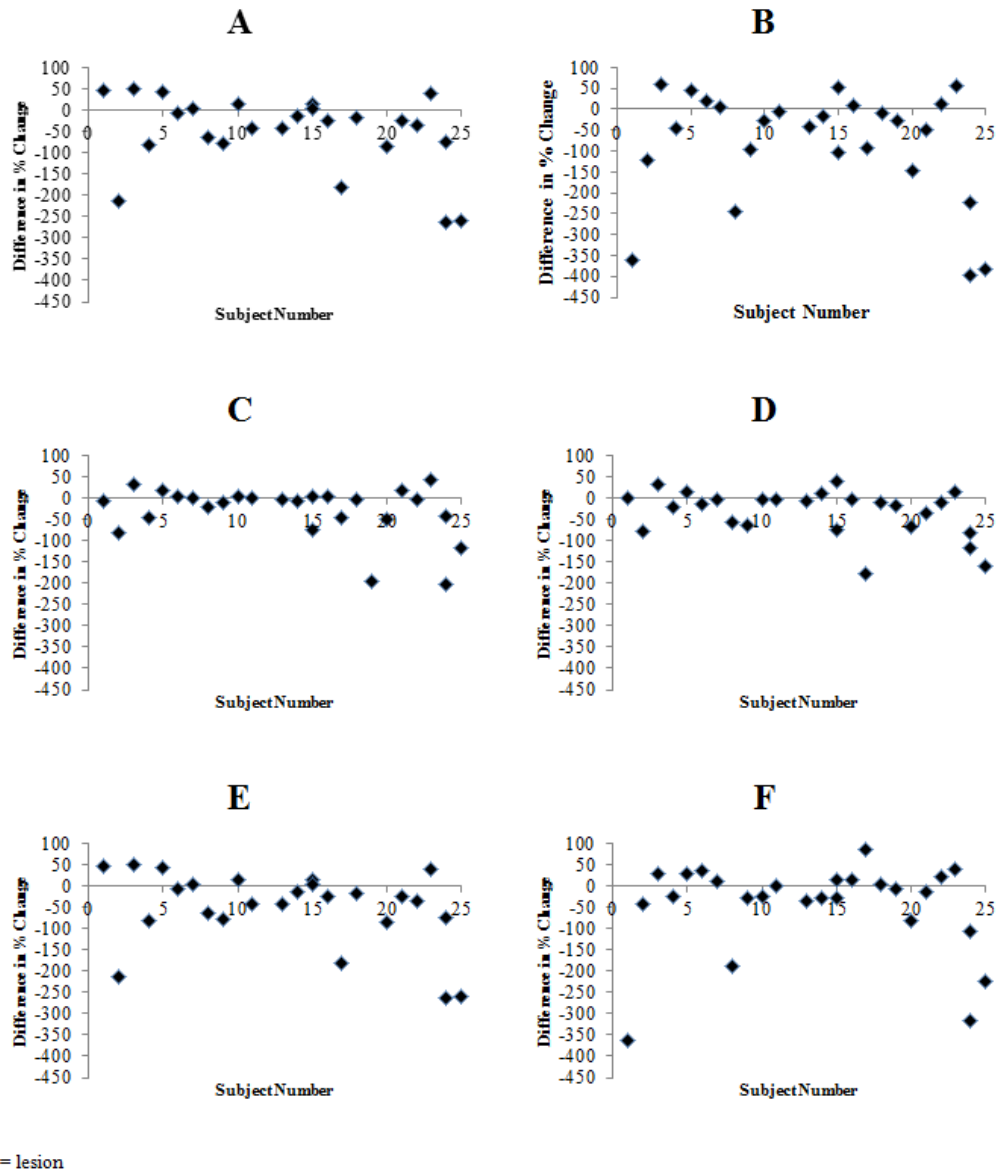
While most current criteria suggest using CT over MRI for tumor measurements, research indicates that MRI is more sensitive for visualizing lesions with a longest diameter of 2cm or larger. A number of studies have been performed comparing CT versus MRI, however, there have been inconclusive results with regards to whether or not CT is more sensitive than MRI for delineating lesions with a longest diameter less than 2cm.<sup>8</sup> A total of 4 lesions identified for this study had a longest diameter measurement of <2cm on Scan 1 in the arterial and/or the portal venous phase (lesion 24-2 measured <2cm on both phases). Visibility of the lesions was an inclusion requirement for this study: therefore, all lesions were able to be reviewed on both Scan 1 and Scan 2. Consequently, it was not a concern that the smaller lesion measurement was influenced by MRI sensitivity. The scans were also assessed for image quality issues, such as breathing artifacts, which can be an issue, particularly in subjects with ascites.<sup>8</sup> The 3D imaging series allowed for avoidance of partial volume artifacts. There were no image quality concerns on the scans that would affect the accuracy of lesion measurements.

A major advantage of measuring on the 3D-GRE series is that it provides detailed anatomical and pathological information.<sup>23</sup> This is important when delineating HCC lesions because it is often difficult to distinguish tumor tissue from the cirrhotic liver

tissue. The diffuse, infiltrative nature of the disease in the cirrhotic tissue and the pathology of the cirrhotic liver can affect the visibility of the tumor.<sup>9,29</sup> There are different types of HCC which have unique imaging characteristics, as well as, differences in clinical presentation and prognosis. A large majority of HCC cases have nodular lesions, with one or more focal well-circumscribed lesions that present with the arterial enhancement and portal venous washout. Conversely, infiltrative HCC (I-HCC) presents with large permeative areas of continuous tumor, an ill-defined growth pattern and a lack of reliability of arterial hypervascularity.<sup>30,31</sup> While the specific type of HCC was not listed in the available clinical information, all lesions selected for measurement appeared nodular and discrete on both scans and were easily distinguishable from the cirrhotic liver tissue. This study does not provide comparative data for infiltrative lesions or lesions that merge together when the liver disease becomes extensive.

The selected lesions were measured only once, by a single reader, on both the arterial phase and portal venous phase of each scan. An intra-reader variability analysis was not performed. Previous studies have validated the reproducibility of both linear and bi-dimensional measurements of tumors.<sup>25,27</sup> However, additional data studying the ability to repeat these measurements on HCC lesions would be beneficial. There is little data regarding the variability of volumetric measurements of HCC lesions. In future studies, a full inter- and intra-reader variability analysis should be performed for all measurement types for HCC.

All comparisons of measurement percent changes from Scan 1 to Scan 2 (linear versus volumetric, linear versus bi-dimensional, bi-dimensional versus volumetric) are significantly different for the data set as a whole which includes both the arterial phase measurements and the portal venous phase measurements.



◆ = lesion

**Figure 4:** As outliers, Subject 12 has been removed from all charts and Subject 19 has been removed from charts A and E. A) The difference in % changes of linear and volumetric measurements in the Arterial phase per lesion. B) The difference in % changes of linear and volumetric measurements in the Portal Venous phase per lesion. C) The difference in % changes of linear and bi-dimensional measurements in the Arterial phase per lesion. D) The difference in % changes of linear and bi-dimensional measurements in the Portal Venous phase per lesion. E) The difference in % changes of bi-dimensional and volumetric measurements in the Arterial phase per lesion. F) The difference in % changes of bi-dimensional and volumetric measurements in the Portal Venous phase per lesion.

When plotted (Fig. 4), the most distinct differences in percent changes are between the linear measurements and the volumetric measurements.

The majority of the differences in percent change from Scan 1 to Scan 2 are in the negative range, which shows that these volumetric percent changes were larger than the linear percent changes. In regards to positive changes, the volumetric measurements showed a larger tumor decrease than the linear measurements. When reviewing the findings of the full statistical analysis, they are in agreement with previous studies comparing all three measurement types for various indications.<sup>32,33,34</sup> The Wilcoxon signed rank test showed significant differences between all of the different measurement types, particularly with the linear versus the volumetric (Table 5). While not a significance test, the correlation assessment supports this finding with the lowest correlations being between the linear versus volumetric measurements in both phases (Table 6).

The percent decreases of the volumetric measurements between Scan 1 and Scan 2 are much larger than the percent decreases of the linear measurements. While this result is statistically significant, it will not be significant in determining tumor response until there is a consensus regarding volumetric criteria.<sup>35</sup> Per RECIST, a >30% decrease in tumor diameter from baseline is considered a partial response (PR). In one study comparing RECIST with volumetric algorithms, a threshold of 65% volumetric decrease was used when determining PR for the 3D measurements.<sup>36</sup> When this threshold is applied to the study data, three lesions measured in the portal venous phase and two

lesions measured in arterial phase can be considered PR volumetrically, while the change in longest diameter is considered stable disease (SD). These scenarios illustrate how volumetric measurements can capture an asymmetric decrease in tumor volume while the change in the one-dimensional longest diameter can appear stable. There is no agreement in regards to whether or not an observed difference like this in tumor response would lead to clinically relevant differences in classifying response.

The study mentioned previously also defined a threshold of 44% volumetric increase when determining progressive disease (PD) for 3D measurements.<sup>36</sup> When this threshold is applied to this study data, three lesions measured in the portal venous phase and three lesions measured in the arterial phase are considered PD volumetrically, while the change in longest diameter is considered SD. There was one case where the lesion measured in the portal venous phase would qualify for PD by RECIST (>20% increase in the longest diameter) but would only be considered SD volumetrically. The differences in the assessment of PD are important both clinically and in clinical trials.

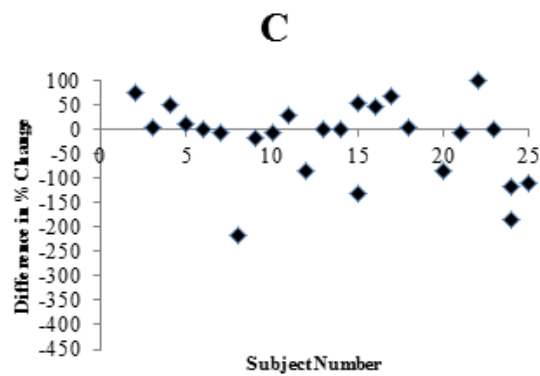
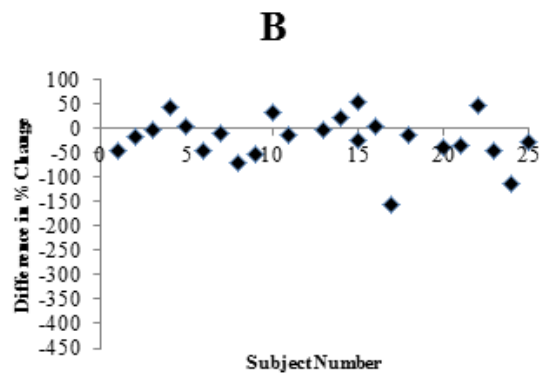
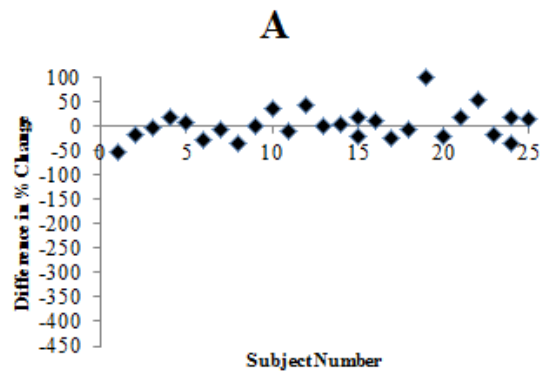
While linear and bi-dimensional tumor assessment criteria have become widely accepted, there are a number of limitations to consider that can be minimized by using volumetric measurements. A major limitation of a linear or bi-dimensional assessment is that measurements are only allowed on the axial plane in criteria such as RECIST. Some HCC lesions have complex morphology and show asymmetric growth that can be missed with the linear and bi-dimensional criteria. These criteria can only accurately assess tumor response when the lesions are spherical and grow in a spherical fashion.<sup>43,44</sup> Lesion

orientation or slice locations are not taken into consideration, nor are differences in machinery or imaging parameters, such as slice thickness, between visits.<sup>45</sup> Therefore, these measurements are estimating tumor change rather than illustrating true tumor volume change. This can make it especially difficult to account for small volume changes which could easily be accounted for by measuring the full lesion volume. Another limitation of linear and bi-dimensional criteria is measurement variability. A recent variability study comparing linear, bi-dimensional, and volumetric measurements showed that there was less measurement variability for volumetric measurements of lesions with complex shapes, which is consistent with a number of similar studies.<sup>46</sup> Volumetric measurements can provide more accurate and reproducible data.<sup>47</sup> More objective data can also be provided as the entire tumor is being measured rather than a slice of the tumor being subjectively chosen and measured by a reader.<sup>45,47</sup>

It is important to take note that this study is only analyzing percent changes of individual lesions rather than the whole tumor burden for the subject. For RECIST, the sum of diameters for all of the selected measureable lesions is used to calculate the percent change that can determine response or progression. This means that while one lesion is decreasing in size, another lesion may be increasing in size, thus, the net result of these tumor changes may then be SD. Further study is needed to compare the percent changes of the tumor burden for full volume versus the sum of diameters.

Another important consideration that is not included in this study is the heterogeneity of HCC lesions. In liver cancer, response to treatment may not only result

in reduction of tumor size, but also tumor necrosis, reduction in tumor vascularization, cavitation and colliquation of the tumor.<sup>37,38</sup> The tumor measurements included the tumor as a whole regardless of tissue viability. This could account for the lack of significance between the percent changes for the same lesion measured on the arterial phase versus the portal venous phase (Fig. 5).



◆ = lesion

**Figure 5: A) The difference in % changes of linear measurements on the Arterial and Portal Venous phases. B) The difference in % changes of bi-dimensional measurements on the Arterial and Portal Venous phases. Outlier subjects 12 and 19 removed. C) The difference in % changes of volumetric measurements on the Arterial and Portal Venous phases. Outlier subjects 1 and 19 removed.**

The arterial and portal venous phase measurements were compared in this study to evaluate if HCC's unique enhancement pattern has any effect on quantifying tumor change, as is suggested in the mRECIST criterion.<sup>26</sup> Even though the specific guidelines within the mRECIST criterion defining the type of tumor tissue that should be included in the measurements were followed, there was no significant difference seen between the arterial and portal venous phase percent changes. mRECIST results are currently not accepted as clinical trial results for HCC without RECIST data as well, so this finding does not affect current guidelines. It could, however, serve as an argument to eliminate an mRECIST evaluation. Additional research for volumetric measurements may still prove the arterial phase useful in analyzing tumor change. It would be necessary to define the types of tumor tissue that should be included in the volumetric measurements and then compare the viable volumetric tissue measurements in both the arterial and portal venous phases. This may prove difficult, as the assessment of viable tissue could be very subjective, therefore, a great deal of investigation will be required to determine if these hypothetical volumetric guidelines are reproducible.

In conclusion, the differences in the percent changes when comparing the measurement types is statistically significant, particularly when comparing linear and volumetric measurements, thus rejecting the null hypothesis. Further studies establishing volumetric review criteria and comparing those guidelines to accepted criteria, such as RECIST, are warranted. Establishing a reproducible volumetric criterion could lead to improvements in the implementation of clinical trials and the better handling of patient treatment.

## LIST OF JOURNAL ABBREVIATIONS

Acad Radiol	Academic Radiology
Am J Surg	The American Journal of Surgery
APJCP	Asian Pacific Journal of Cancer Prevention
Arch Intern Med	Archives of Internal Medicine
Clin Radiol	Clinical Radiology
Eur J Cancer	European Journal of Cancer
Eur J Radiol	European Journal of Radiology
Eur Radiol	European Radiology
Int. J. Cancer	International Journal of Cancer
J Clin Gastroenterol	Journal of Clinical Gastroenterology
J Clin Oncol	Journal of Clinical Oncology
J Eval Clin Pract	Journal of Evaluation in Clinical Practice
J Gastrointest Surg	Journal of Gastrointestinal Surgery
JGLD	Journal of Gastrointestinal and Liver Diseases
J Natl Cancer Inst	Journal of the National Cancer Institute
J Nucl Med	Journal of Nuclear Medicine
N Engl J Med	The New England Journal of Medicine
Radiol Med	Radiologia Medica
Semin Liver Dis	Seminars in Liver Disease
World J Gastroenterol	World Journal of Gastroenterology
World J Radiol	World Journal of Radiology

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## CURRICULUM VITAE

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### **Professional Experience**

#### **PAREXEL INFORMATICS, Medical Imaging**

##### **Billerica, MA**

*Principal Scientist, Scientific and Medical Services*

*November 2014 - present*

- Be accountable for the initiation and facilitation of the project specific Reviewer Training
- Own or be accountable for the development of project specific imaging parameters to ensure standardization of imaging techniques
- Be responsible for or accountable for providing scientific guidance for project specific imaging charter development
- Be responsible for or accountable for scientific guidance for development of project specific electronic case report forms (eCRFs) the customization of image analysis software tools
- Lead or consult on training of independent readers (i.e. radiologists, oncologists) on the use of imaging software, project specific eCRFs, and implementation of the review criteria
- Perform or support quality control and evaluation of the results of independent review and provide necessary guidance and feedback to independent readers
- Attend investigator meetings or support investigator meeting preparation, as necessary, to present and train sites and clients on assessment criteria and imaging parameters
- Provide scientific leadership to internal project teams
- Act as scientific liaison with client project teams
- Provide support for the preparation of clinical protocols, journal articles, and other documents for clients/sponsors
- Manage Scientific and Medical Services staff as required

*Senior Medical Research Scientist*

*May 2012 – November 2014*

- Continue to perform MRS tasks

- Manage the Medical Project Assistants (MPA)
- Update and maintain Standard Operating Procedures (SOP)
- Work with Production Service Group (PSG) and Business Development (BD) on capabilities and proposals
- Lead and provide work direction to junior members of the group
- Provide input from a scientific and medical perspective on charter development, user requirements, requirements specifications, requirement workshops, application demos, medical acceptance testing, reviewer manuals, image acquisition guidelines, criteria checklists, and medical Quality Control (QC)
- Work with the quality group to make sure imaging reviewer trainings and reviewer management are documented correctly

*Medical Research Scientist*

*February 2010 – May 2012*

- Hold independent imaging reviewer trainings and provide support to imaging reviewers throughout the trial
- Perform QC of both imaging reviewer test cases and production cases
- Provide feedback to imaging reviewers and re-train when necessary
- Develop training presentations for the Perceptive Academy (PA) training program
- Provide input during development of requirements for project specific analysis applications
- Hold Medical Acceptance Testing (MAT) for analysis applications to confirm functionality is based on requirements
- Train project teams on Image Acquisition Guidelines (IAG)
- Provide support to the Medical Owners (MO)
- Attend Investigator Meetings (IM) as a medical representative

*Imaging Research Associate*

*August 2008 – February 2010*

- Perform Initial QC and Final QC checks on images submitted for projects
- Answer investigator site imaging questions
- Provide trial information to clients, such as data reports and statistics
- Work with independent imaging reviewers reading on various projects
- Attend independent imaging reviewer trainings and assist with imaging criteria questions and analysis application questions
- Train new team members on project information

*Imaging Assistant*

*October 2007 – August 2008*

- Make initial contact with clinical trial investigator sites
- Support internal project teams

- Develop and coordinate study related activities in compliance with FDA Regulatory Requirements
- Use computer systems to convert medical image data to digital form
- Maintain a database of medical images and associated results

**Coldwell Banker Residential Brokerage Cares**

**Waltham, MA**

*Community Relations Coordinator*

*August 2005 – October 2007*

- Support the planning and management of all fundraising efforts including four major special events
- Support efforts to raise \$1,000,000 in annual revenue (2006)
- Provide PR support for the foundation
- Review funding requests and coordinate distribution of funds to over 150 non-profit organizations
- Identification and cultivation of relationships with primary non-profit grantees in four New England states
- Support volunteer opportunities for the company's 5,000 sales associates
- Create and maintain financial records and databases
- Communicate with and provide information to the members supporting the organization
- Provide administrative assistance to the Director of Corporate Giving and Community Relations

**Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University**

**Boston, MA**

*Research Technician in the Lipid Metabolism Lab*

*June 2004 – August 2005*

- Study of the effects of HRT on apolipoproteins

**Education**

**Stonehill College**

**Easton, MA**

*B.S. Biology – 2004*

**Suffolk University**

**Boston, MA**

*Non-Profit Financial Management – May 2007*

**Boston University School of Medicine Division of Graduate Medical Sciences**

**Boston, MA**

*Master of Science in Clinical Investigation – Expected Graduation January 2015*