

## RESEARCH ARTICLE

## Retrospective Evaluation of Discrepancies between Radiological and Pathological Size of Hepatocellular Carcinoma Masses

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### Abstract

**Background:** The size of a hepatic neoplasm is critical for staging, prognosis and selection of appropriate treatment. Our study aimed to compare the radiological size of solid hepatocellular carcinoma (HCC) masses on magnetic resonance imaging (MRI) with the pathological size in a Chinese population, and to elucidate discrepancies. **Materials and Methods:** A total of 178 consecutive patients diagnosed with HCC who underwent curative hepatic resection after enhanced MRI between July 2010 and October 2013 were retrospectively identified and analyzed. Pathological data of the whole removed tumors were assessed and differences between radiological and pathological tumor size were identified. All patients were restaged using a modified Tumor-Node-Metastasis (TNM) staging system postoperatively according to the maximum diameter alteration. The lesions were classified as hypo-staged, iso-staged or hyper-staged for qualitative assessment. In the quantitative analysis, the relative pre and postoperative tumor size contrast ratio ( $\% \Delta$ size) was also computed according to size intervals. In addition, the relationship between radiological and pathological tumor diameter variation and histologic grade was analyzed. **Results:** Pathological examination showed 85 (47.8%) patients were overestimated, 82 (46.1%) patients underestimated, while accurate measurement by MRI was found in 11 (6.2%) patients. Among the total subjects, 14 (7.9%) patients were hypo-staged and 15 (8.4%) were hyper-staged post-operatively. Accuracy of MRI for calculation and characterized staging was related to the lesion size, ranging from 83.1% to 87.4% (<2cm to  $\geq$ 5cm,  $p=0.328$ ) and from 62.5% to 89.1% (cT1 to cT4,  $p=0.006$ ), respectively. Overall, MRI misjudged pathological size by 6.0 mm ( $p=0.588$ ), and the greatest difference was observed in tumors <2cm (3.6 mm,  $\% \Delta$ size=16.9%,  $p=0.028$ ). No statistically significant difference was observed for moderately differentiated HCC (5.5mm,  $p=0.781$ ). However, for well differentiated and poorly differentiated cases, radiographic tumor maximum diameter was significantly larger than the pathological maximum diameter by 3.15 mm and underestimated by 4.51 mm, respectively ( $p=0.034$  and  $0.020$ ). **Conclusions:** A preoperative HCC tumor size measurement using MRI can provide relatively acceptable accuracy but may give rise to discrepancy in tumors in a certain size range or histologic grade. In pathological well differentiated subjects, the pathological tumor size was significantly overestimated, but underestimated in poorly differentiated HCC. The difference between radiological and pathological tumor size was greatest for tumors <2 cm. For some HCC patients, the size difference may have implications for the decision of resection, transplantation, ablation, or arterially directed therapy, and should be considered in staging or selecting the appropriate treatment tactics.

**Keywords:** Hepatocellular carcinoma - discrepancy - radiological and pathological size

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### Introduction

Tumor size of hepatocellular carcinoma (HCC) is an important indicator for prognostic assessment and the choice of treatment, and also be a critical variable in staging systems. Although the prognosis of HCC is extremely complicated and depends not only on the stage of the tumor, but also on the residual liver function and serum  $\alpha$ -fetoprotein (AFP) levels (Xu et al., 2012),

the tumor size is still an independent pivotal factor for clinical reference. The 2013 American Joint Committee on Cancer (AJCC) TNM staging system for HCC stratifies tumor mass at 5cm criterion for multiple tumors (multiple tumors none more than 5 cm belong to T2; multiple tumors more than 5 cm belong to T3a). In the Japanese TNM system, a tumor size of 2 cm is used as a staging criterion, in combination with microvascular invasion and nodule multiplicity. In addition, several previous studies

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(Kikuchi et al., 2009; Nathan et al., 2009) have reported that the selection of 2 cm for the size criterion was based on that a tumor size greater than 2 cm is an independent prognostic factor after resection for HCC.

Recently, a modified TNM classification of HCC have been proposed (Yen et al., 2009), which classified the tumor size at a more detailed stratification criterion, and may be a better model than other systems for staging and predicting the outcome, especially in cases where early detection and treatment of HCC are possible. Other available combined-staging systems such as the Barcelona Clinic Liver Cancer (BCLC) and the Japan Integrated Staging (JIS) score also incorporate tumor size as a vital staging parameter.

The treatment of patients with HCC also necessitates the consideration of tumor size, as different therapies are applicable for different targets. Partial hepatectomy is a potentially curative therapy for patients with early-stage HCC (solitary tumor  $\leq 5$  cm in size, or  $\leq 3$  tumors each  $\leq 3$  cm in size and no evidence of gross vascular invasion) who are eligible to undergo the procedure (Truty et al., 2010). In a landmark study published in 1996, Mazzaferro et al. (Mazzaferro et al., 1996) proposed the Milan criteria (single tumors  $\leq 5$  cm in diameter or no more than three nodules  $\leq 3$  cm in diameter in patients with multiple tumors) for patients with unresectable HCC and cirrhosis to resort to liver transplantation. Several studies (Livraghi et al., 2008; Peng et al., 2012) support radiofrequency ablation as the first-line treatment in patients with HCC tumors that are 2 cm or less in diameter, as ablation alone may be curative in treating tumors  $\leq 3$  cm. Arterially directed treatment or systemic therapy should be recommended for unresectable lesions  $>5$  cm (Wang et al., 2013).

Nowadays, clinicians often rely on pathological tumor size rather than radiological estimates to guide patient concerning prognosis evaluation and treatment consideration. A recent report (Freeman et al., 2006) from the United Network of Organ Sharing (UNOS) database showed that preoperative radiological staging based on CT (computed tomography) underestimates tumor extent in 25% of cases, and overestimates tumor extent in 28% of cases when compared with the pathological stage. These data suggest that a discrepancy between radiological size and pathological size, may give rise to intervention in clinical decision-making. To our knowledge, magnetic resonance imaging (MRI) is widely used for HCC treatment planning and can play a key role in preoperative staging. Several previous studies have evaluated the accuracy of MRI for preoperative staging and tumor size measurement, using pathologic analysis as the reference standard, and reported that accuracies varied from 82% to 94.7% (Libbrecht et al., 2002; Hanna et al., 2008; Han et al., 2014), which were significantly higher than CT and ultrasonography. Until now, there has been no such study reported and the aim of this study was to compare the radiological size of HCC on MRI with the pathological size, to define the histopathological correlation with size difference, and hence assess the accuracy of the most widely used MRI technology for the preoperative measurement of HCC mass in a specific Chinese population.

## Materials and Methods

### Patients

Between July 2010 and April 2014, a total of 326 consecutive patients underwent preoperative MRI evaluation and curative hepatic resection for HCC confirmed by postoperative histologic examination at our institution. The clinical and radiological characteristics were retrospectively analyzed by reviewing their medical records. Patients were excluded from the study if MRI was not performed within 15 days before surgery, transarterial chemoembolization and radiofrequency ablation or any other preoperative treatment was done before surgery, or combined with intrahepatic cholangiocarcinoma nodules.

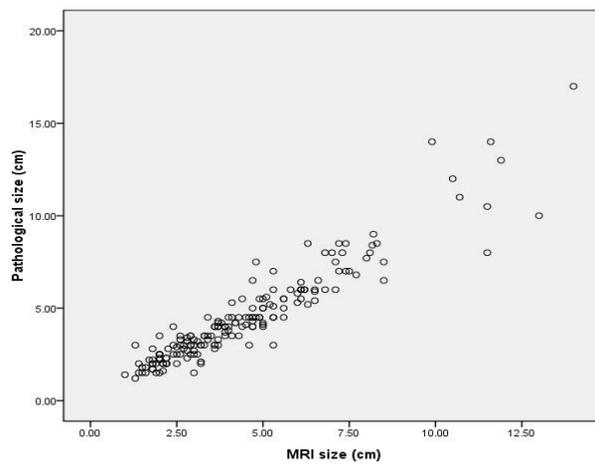
### Image analysis

All patients underwent an intravenous contrast enhanced abdominal MRI examination before surgery. Contrast-enhanced multiphase MRI scans were obtained using a 3.0-T MR system (Signa Excite HD 3.0T, General Electric Company, USA). Images of arterial, portal venous and delayed phases were obtained 5 s to the time of peak aortic enhancement, 60 s and 180 s after contrast injection, respectively. Scanning parameters were as follows: (TR/TE, 4/1.5 ms; Flip angle, 10°; FOV, 370×240mm<sup>2</sup>; section thickness, 3.6 mm; matrix, 320×168; parallel factor, 2). Contrast material was administered with gadoteric acid (Primovist; Bayer Schering Pharma AG, Berlin, Germany).

Tumor size was measured in the arterial phase in which the tumor margins were most obvious and the size of was measured in three axes: superior to inferior (coronal), anterior to posterior (sagittal), and left to right (transversal). The largest diameter in one of three axial planes was defined as the radiological tumor size. Some adjacent structures such as major branches of Glissonian pedicles or main liver fissures were labeled as landmarks to identify the correct stereo-relationship for postoperative pathological measurement. For the quantitative analysis, the tumor size was analyzed as a continuously scaled variable and was stratified by 2 cm, 3 cm, and 5 cm. In patients with multiple unilateral tumors of the same histologic grade, the largest tumor was included. The resulted data were calculated by a single experienced abdominal imaging radiologist to avoid interobserver and intraobserver variability. In this study, we used a modified Tumor-Node-Metastasis (TNM) staging system (Yen et al., 2009) to classify all cases based on imaging data.

### Pathological evaluation

After extraction of the specimen, the tumor was oriented and transected in the axial plane corresponding to the section on the MRI scan from which the radiographic size was measured and the pathological tumor size was defined as the largest diameter of the tumor examined just without formalin fixation. Three surgeons were invited to investigate the transection plane to make sure the cut surface is exactly corresponded with the radiological plane. Another single experienced pathologist interpreted all the data measured by the caliber. Only HCC masses confirmed by histologic and immunohistochemical tests



**Figure 1. Scatter Plot of Pathological Tumor Size Against Radiological Tumor Size**

were taken from the original pathological reports. The HCC tumor grades were classified according to the Edmondson-Steiner nuclear grading system (Edmondson et al., 1954). When different tumor grades were found within the same tumor, the predominant grade was used as the tumor grade. Patients were categorized into four groups as well differentiated, moderately differentiated, poorly differentiated and undifferentiated. All patients were restaged according to pathological data using the same staging system. Only the staging difference due to the maximum diameter alteration was recorded and discrepancy due to other variables was excluded, which included organ invasion, vascular invasion, lymph node or distant metastasis. The primary investigator compared the radiological and pathological tumor sizes to identify all cases of post-operative hypo-staging, iso-staging, or hyper-staging. Fibrosis scoring system using a 0-6 scale as defined by Ishak (Ishak et al., 1995) was taken into account and appraised as F0 (none to moderate fibrosis) or F1 (severe fibrosis to cirrhosis). The amount of estimated blood loss was derived from the operation reports and as well taken into assessment. The relationship between tumor diameter variation and some clinical or pathological features were also analyzed.

#### Statistical analysis

Clinical data of the patients and characteristics of the tumors were expressed as mean $\pm$ SE. The absolute size difference ( $\Delta$ size) was computed as | (clinical size) - (pathologic size) |, and the relative size difference (% $\Delta$ size) was calculated by the following formula as: % $\Delta$ size = | (clinical size) - (pathologic size) | / (pathologic size)  $\times$  100. Comparison between radiological and pathological tumor diameter was done by using the Student's t test for continuous variables and the Chi-square test for categorical variables. Kruskal Wallis test was also used to examine associations between size stratification, histologic grade and % $\Delta$ size. The predictive accuracy of the enhanced MRI was also calculated using ROC curve analysis, differences in predictive accuracy between subgroups were compared. All analyses were performed using statistical software SPSS17.0. A P-value of less than 0.05 was considered significant.

**Table 1. Patients' Characteristics**

Variables		Median or n (%)
No. of total subjects		178
Age (years)		55.0 (range 27-84)
Gender		
	Male	155 (87.1%)
	Female	23 (12.9%)
Type of surgery		
	Half hepatectomy	15 (8.4%)
	Partial hepatectomy	163 (91.6%)
Pathological stage		
	T1	22 (12.3%)
	T2	86 (48.3%)
	T3	14 (7.8%)
	T4	56 (31.4%)
	hyper-staged	15 (8.4%)
	hypo-staged	14 (7.8%)
Edmondson-Steiner grade		
	G1	23(12.9%)
	G2	119(66.8%)
	G3	36(20.2%)
	G4	0(0.0%)
Intrahepatic location		
	Left	36(20.2%)
	Middle	35(19.6%)
	Right	107(60.1%)
Estimated blood loss		
	$\leq$ 400	156(87.6%)
	> 400	22(12.3%)
Pathological Findings		
	fibrosis score F0	101(56.7%)
	fibrosis score F1	77(43.3%)
	hemorrhage or necrosis	26(14.6%)
	hemangioma	9(5.1%)
	multiple cysts	37(20.7%)
	adjacent to a cystic lesion	10(5.6%)
	adjacent to the pedicle system	35(19.6%)
	adjacent to hepatic vein system	41(23.0%)

## Results

Ultimately, a total of 178 HCC patients were identified, including 155 (87.1%) males and 23 (12.9%) females (Table 1). Median age at diagnosis was 55 years (range, 27-84 years) and the mean interval between MRI and surgery was 11.7 days. Of the total subjects, there were 36 (20.2%) cases identified by poorly differentiated, 23 (12.9%) by well differentiated and 119 (66.9%) by moderately differentiated but no undifferentiated cases. Also, 163 (91.6%) subjects received partial hepatectomy, and 15 (8.4%) underwent half hepatectomy or enlarged half hepatectomy. Among the total subjects, mean radiographic tumor size and pathologic tumor size were 4.48 $\pm$ 2.45 cm and 4.51 $\pm$ 2.59 cm respectively. The mean change in size ( $\Delta$ size) for all tumors examined was 6.0 $\pm$ 6.6 mm, but demonstrating no significant difference ( $p=0.588$ ). Figure 1 shows the scatter plot describing the relationship of pathological tumor size against radiological tumor size.

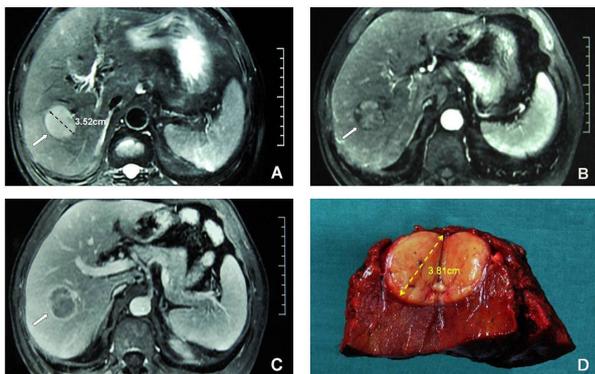
Over all, pathological examination showed that MRI overestimated tumor size in 85 (47.8%) patients, underestimated in 82 (46.1%) patients and equaled pathological size in 11 (6.1%) patients. Table 2 lists the mean radiological and pathological sizes of the tumors, which were divided by 2 cm, 3 cm, 5cm ranges according to radiological size. In tumors less than 2 cm, there was a statistically significant underestimation by MRI scan, where the mean pathological size was found to be 0.27 cm larger in size than the mean radiological size (1.60 $\pm$ 0.25 vs 1.87 $\pm$ 0.46 cm,  $\Delta$ size=0.36 cm,  $p=0.028$ ). However, in the 2 to <3 cm and 3 to <5 cm size category, patients were found to have an underestimation in radiographic size versus pathologic size of 2.43 mm and overestimation

**Table 2. Differences in Radiological and Pathological Tumor Size According to Radiological Size Range**

Radiological size range (cm)	No. of patients	Radiological tumor size (cm, Mean±SD)	Pathological tumor size (cm, Mean±SD)	Difference (cm, Mean±SD)	Δsize (cm, Mean±SD)	% Δsize	P-value
<2	18	1.60±0.25	1.87±0.46	0.27±0.47	0.36±0.41	16.9	0.028
2.0-2.9	36	2.41±0.32	2.65±0.59	0.24±0.49	0.40±0.35	14.8	0.005
3.0-4.9	63	3.89±0.61	3.84±1.01	0.05±0.69	0.49±0.48	14.3	0.519
≥ 5	61	7.15±2.16	7.10±2.66	0.05±1.26	0.89±0.88	12.6	0.719
Total	178	4.48±2.45	4.51±2.59	0.03±0.89	0.60±0.66	14.1	0.588

**Table 3. Mean Radiological and Pathological Tumor Size by Histologic Grade**

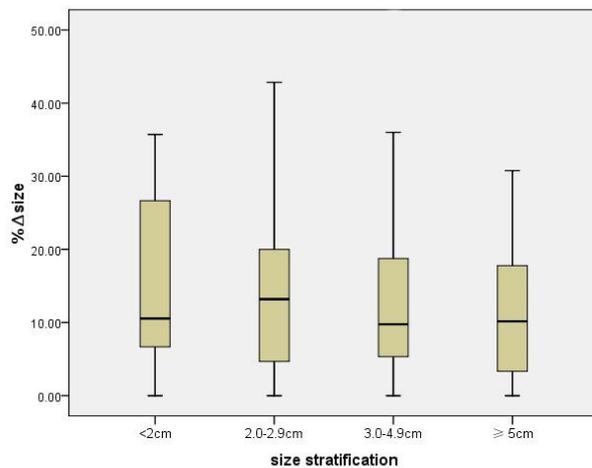
Histologic type (Differentiated grade)	No. of patients	Radiological tumor size (cm, Mean±SD)	Pathological tumor size (cm, Mean±SD)	Difference (cm, Mean±SD)	Δsize (cm, Mean±SD)	% Δsize	P-value
well (G1)	23	4.61±1.57	4.30±1.51	0.31±0.66	0.54±0.48	16.1	0.034
moderately (G2)	119	4.28±2.42	4.25±2.35	0.02±0.82	0.55±0.57	13.5	0.781
poorly (G3)	36	5.06±2.94	5.51±3.56	0.45±1.10	0.76±0.91	15.1	0.02



**Figure 2. Images Obtained from A 62-Year-old Man who Underwent Curative Partial Hepatic Resection.** (A) T2-weighted image reveals a hyperintense nodule, measuring at 3.52 cm in diameter, in segment VIII of the liver. On gadolinium-enhanced MRI, this nodule shows contrast enhancement on arterial phase; (B) and sharp washout on delayed phase; (C, arrow); (D) This nodule was postoperatively measured at 3.81 cm in largest diameter and pathologically confirmed as moderately differentiated HCC with microvascular invasion

of 0.57 mm respectively. (Δsize=4.0 mm and 4.9 mm,  $p=0.005$ , 0.519). In particular, in tumors larger than 5 cm, the largest absolute size difference in radiographic size versus pathological size was found, with Δsize at 8.9 mm. Nevertheless, the relative size difference was not significant (% Δsize=12.6%,  $p=0.719$ ).

Table 1 shows the proportional distribution of tumors divided into pT1, pT2, pT3 and pT4 groups. Among all the 178 HCC patients, 14 (7.8%) patients were hypo-staged post-operatively and 15 (8.4%) were hyper-staged. When compared according to histologic grades, for 23 well differentiated cases, radiographic tumor maximum diameter was larger than the pathological maximum diameter by 3.15 mm (Δsize=5.4mm,  $p=0.034$ ). For the 36 subjects with poorly differentiated grading, pathological tumor size was underestimated by an average of 4.51 mm (Δsize=7.6mm,  $p=0.020$ ) measured on MRI whereas it was overestimated by a mean of 0.21 mm among the 119 moderately differentiated cases (Δsize=5.5mm,  $p=0.781$ , Table 3, Figure 2). We also observed that high-grade disease (Edmondson-Steiner G3) was more common in larger tumors. The prevalence of poorly differentiated

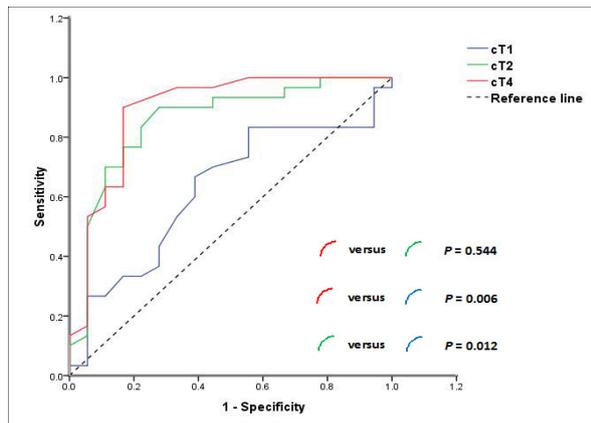


**Figure 3. Boxplot Charts Show that with the Tumor Size Increased, the % ΔSize Decreased Consecutively from 16.9% (<2cm) to 12.6% (≥5cm), however, no Significant difference had been Analyzed ( $p=0.328$ )**

disease was 16.7%, 19.4%, 20.6% and 21.3% for tumors <2 cm, ≥2 cm but <3 cm, ≥3 cm but <5 cm, ≥5 cm respectively, however, the difference was not significant ( $p=0.961$ ).

In 29 of the 178 patients, the absolute size difference was more than 1 cm and with the tumor size increased, the mean % Δsize decreased from 16.9% (<2cm) to 12.6% (≥5cm) (Figure 3). Nevertheless, the analysis of these variables showed that neither size stratification nor histologic grading had significant influence on the % Δsize ( $p=0.328$ , 0.950 respectively) (Table 2 and 3).

The predictive accuracy of the enhanced MRI for clinical T stage (cTx) was calculated using receiver operating characteristic (ROC) curve analysis, and when the clinical stage increased, the predictive accuracy continued to increase. For patients with cT1 (≤2 cm) tumors, the accuracy of MRI alone in measuring size, as measured by area under the ROC curve, was 62.5% (Figure 4). When tumor size was added to cT2 (2 to ≤5 cm), its predictive accuracy increased to 85.5%. This increase in predictive accuracy, based solely on the addition of tumor size, was statistically significant ( $p=0.012$ ). Predictive accuracy of the cT4 tumors (>5 cm) that not included 5 cm variable was 89.1%, which was significantly higher than the cT1 subgroup (89.1% versus 62.5%;  $p=0.006$ ;



**Figure 4. The Predictive Accuracy of the Enhanced MRI for cT Stage Calculated using ROC curve analysis is shown.** cT4 (red) was significantly higher at 89.1%, compared to 62.5% for cT1 (blue). (cT3 not shown)

Figure 4), but no conspicuous difference with the other two groups (cT2=85.5%, cT3=87.5%;  $p=0.544$  and 1.000).

Some clinical and pathologic features such as combined with cystic mass or hemangioma, the amount of estimated blood loss, fibrosis scale, evidence of hemorrhage and necrosis, localization of tumor adjacent to the pedicle system, invasion of a major branch of the hepatic vein system, and cysts adjacent to the tumor were also analyzed. Of our series of 178 patients, no special above features that might be responsible for the measurement discrepancy were identified.

## Discussion

HCC is the fifth most common malignancy with an estimated annual death incidence of approximately 600,000 worldwide (Bosch et al., 1999). Although it is common in Asia-Pacific area, the incidence of HCC has increased rapidly in the USA (El-Serag et al., 1999; Can et al., 2014; Norsal'adah et al., 2014; Somboon et al., 2014). Tumor size is an independent prognostic feature and an important indicator for treatment strategy in patients with HCC and it is incorporated into the TNM staging system. The latest AJCC TNM staging system established 5 cm as the cutoff between stage T2 and T3a for tumors with multiple nodules. Combined staging systems using tumor and residual liver function factors such as the BCLC staging system established 2 cm as the demarcation point between very early stage and early stage for tumors with single mass. The TNM staging system according to the Liver Cancer Study Group of Japan criteria have advocated that tumor size boundary should be set at 2 cm. Yen et al. (2009) further proposed a modified TNM staging system based the Japan criteria, which further divided tumor size at  $\leq 2$ cm,  $>2$ cm and  $\leq 5$ cm, and  $> 5$ cm. Instead of a subclassification of T stage by 5cm size, the newly devised system suggested that the cutoff between stage T1 and T2 should be brought down to 2 cm, which was based on a series of survival analysis of patients stratified for different pathological tumor size. Chen et al. (2011) found that the overall prognosis is well reflected by tumor size when performing hepatectomy for HCCs  $<5$  cm,

and that the 5-year overall survival rate and disease free survival rate are best predicted by 3 cm criterion. Zhou et al. (2012) had reported that patients who had tumors that measured  $\leq 3$  cm had a significantly better prognosis compared with patients who had tumors that measured 3-5 cm and  $>5$ cm. Ko et al. (2011) had also reported that for small HCCs including tumors up to 5 cm in size, an increase in tumor size has been shown to directly correlate with an increased risk of vascular invasion.

In addition, tumor size assessed by imaging techniques is critical in determining the management strategy for solid liver tumors. The increased usage of advanced imaging techniques has led to an increase in detection of incidental tumors, and the size of incidental tumors tends to be smaller. With this increase in incidental localized HCC and variation in tumor size, the treatment modality of HCC changed correspondingly. To a single HCC lesion  $<2$  cm, resection and radiofrequency ablation (RFA) likely offer similar 5-year survival rates (Livraghi et al., 2008; Peng et al., 2012). The patients with a solitary HCC or up to 3 nodules, each  $\leq 3$  cm in size can be effectively treated by resection, liver transplantation, or ablation with the possibility of long-term cure (Poon et al., 2007; Truty et al., 2010; Ruzzenente et al., 2012). The currently recommended tumor burden criteria for transplantation for HCC as established by the United Network for Organ Sharing (UNOS) are 1 lesion  $\leq 5$  cm or maximum 3 lesions  $<3$  cm in diameter (Martin et al., 2007). Expanded selection criteria (a single lesion of  $\leq 6.5$  cm or up to 3 lesions, none of which are larger than 4.5 cm, with a maximum combined tumor bulk of  $\leq 8.0$  cm), have also been proposed by Yao et al. (2001) at the University of California in San Francisco. Although the choice of therapy depends on the tumor location, degree of portal hypertension, severity of the liver function and presence of medical comorbidities, tumor size was still shown to be an indispensable reference factor. However, there is limited information in the contemporary literature concerning the relationship between radiological and pathological tumor size variation. It is well known that the pathological size is used in staging and prognosis assessment, however, it is the radiographic size that is used when determining the appropriate treatment strategy when the postoperative histologic examination has not been performed. Several studies (Irani et al., 2001; Lee et al., 2010; Choi et al., 2010; Jeffery et al., 2011) have examined the relationship between the radiographic and pathological tumor size for renal tumors, yet no findings were available concerning liver tumors.

This retrospective study of a continuous 178 patients demonstrated that enhanced MRI misjudged pathological tumor size by a mean 6.0 mm, which was not a small amount but had reached no statistical significance. For renal tumors, a series of literature had been reported comparing the relationship between the radiographic and pathological tumor size. Jeffery et al. (2011) studied a cohort of Australian patients and found that mean radiological tumor size was larger than mean pathological tumor size by 3.1 mm. Similarly, Lee et al. (2010) retrospectively investigated 467 patients treated with radical or partial nephrectomy and found that CT

overestimated pathological tumor size overall by 0.7 mm. Choi et al. (2010) evaluated a total of 175 patients with pT1 or pT2 renal cell carcinomas underwent radical or partial nephrectomy, and reported that the mean radiological tumor size was larger than the pathological size by 4.3 mm, but not significantly so. However, when analyzed by stratification respectively, in tumors less than 6 cm, mean radiological tumor size was significantly larger than mean pathological size, and the difference ( $0.63 \pm 1.19$  cm) was largest in the range of 3 to 4 cm. In a multiple regression analysis, Irani and coworkers (Irani et al., 2001) retrospectively reviewed 100 patients with renal tumors and found that the smaller the tumor, the more the pathological size was overestimated. To our knowledge, extremely limited studies had been performed evaluating the discrepancy between radiological and pathological size of hepatic tumor masses. An et al. (2012) devised a preoperative MRI staging system for HCC and collaterally found that mean histologic tumor size was  $3.9 \pm 2.4$  cm, and the mean tumor size measured by MRI was  $4.1 \pm 2.6$  cm. In their prospectively conducted study, the mean difference was only 2 mm, and they concluded that MRI could provide an accurate method with which to estimate and stage HCC tumor size.

Compared with aforementioned reports, the observed difference between radiographic and pathological size of HCC tumors in our study can be considered moderate. Although the average radiological and pathological size for all 178 tumors was not significantly different, significant differences were noted in the classified size ranges. And as contrary to the results mentioned by Choi et al. (2010), larger tumors ( $>5$  cm) showed a trend of having slighter degree of shrinkage on average following surgery compared with smaller (3 to 5 cm) tumors in our study. However, in tumors less than 2 cm, there was a statistically significant underestimation by MRI scan, where the mean pathological size was found to be 0.27 cm larger in size than the mean radiological size ( $p=0.028$ ), and the relative size difference had also reached the greatest among all size intervals ( $\% \Delta \text{size}=16.9\%$ ). For renal tumors, the typical reduction in tumor size on pathological evaluation relative to the radiological measurement has previously been attributed to the loss of blood flow within the tumor issue after excision (Herr et al., 2001). Yaycioglu et al. (2002) retrospectively reviewed 291 patients with renal cell carcinoma and found that tumors tend to reduce their size in cases estimated blood loss during surgery was  $\leq 700$  ml. In terms of blood loss volume variation, no conspicuous influence has been observed in our study.

We segregated the degree of size variation by the histologic grade of HCC. Due to extremely limited published reports concerning comparison between radiological and pathological tumor size for HCC, no available results could be referred to, so we must rely upon some renal tumor data to guide consultation. Analysis of renal tumors grouped according to Fuhrman grade by Jeffery et al. (2011) had shown a positive correlation between Fuhrman grade and tumor size, with a higher prevalence of high-grade disease in the larger size groups. Our study has made similar observations, but it is distinct in that in this study, the higher Edmondson-Steiner grade

(G3) is not only related to the absolute size value but also the size variation ( $\Delta \text{size}$ ). We demonstrated that 23 well differentiated and 119 moderately differentiated cases tended to contract after surgical removal. However, the amount of shrinkage for moderately differentiated cases was not enough to reach a significant difference ( $0.02 \pm 0.82$  cm,  $p=0.781$ ). Our finding that histologic characteristics were correlated with tumor size variation is also consistent with findings from other studies concerning renal tumor research. Kanofsky et al. (2006) demonstrated that 59% of clear renal cell carcinomas, 34% of papillary renal cell carcinomas, and 38% of chromophobe renal cell carcinomas regressed after excision. The amount of shrinkage in 79 chromophobe renal cell carcinomas had resulted in a downstage by the TNM system in 13 (16%) patients. Of them, seven cases were identified from radiographic stage T1b to pathologic stage T1a and six cases from stage T2 to T1b. They attributed this phenomenon to interval growth that occurred between the imaging study and surgical excision or a lack of uniform methods in radiological assessment. For example, the largest radiological and pathological diameters were not necessarily measured in the same geometric dimensions. However, this kind of circumstance was tactically avoided in our study. The tumor was oriented and transected by its transaxial diameter corresponding to the plane from which the radiographic size was measured just prior to formalin fixation. Therefore, the largest radiological and pathological diameters were measured in the same geometric dimensions. We believe this regression effect except poorly differentiated patients may contribute, in part, to the tumor blood drainage after excision, to the constriction effect of necrosis tissue, or to the surface hypothermia. This effect is probably more salient for well differentiated carcinomas because they typically have a fewer number of necrosis nodules than other histologic grading subtypes. Nevertheless, for the 36 poorly differentiated specimens, pathological tumor size was to the opposite underestimated by a mean of 4.51 mm, and the absolute size difference ( $\Delta \text{size}$ ) had further more reached 7.6 mm. This suggests that tumors propagate at the fastest pace may often end up swelling due to the surface tension relief after excision on pathological examination. We conclude that well differentiated and moderately differentiated masses are more indolent tumors compared with the more aggressive poorly differentiated tumors, which can support the aforementioned phenomenon. As the swelling effect offset the constriction effect caused by necrosis, the increased tumor volume was presented at the measuring apparatus.

As we know, the 7<sup>th</sup> AJCC staging system is generally accepted and widely used. However, it has many limits because it is mainly assessed by postsurgical pathological data, such as microvascular invasion which can not be evaluated objectively preoperatively. Therefore, we selected a modified TNM classification (Yen et al., 2009) of HCC depended more on the radiological data for this study, which we thought was more suitable for clinical staging and consisted of comprehensive stratification abilities. In this study, the discrepancy between clinical and pathological tumor size has resulted in a discordance

between clinical and pathological stage in 29 (16.2%) patients, with 14 (7.8%) patients hypo-staged post-operatively and 15 (8.4%) hyper-staged. Jeffery et al. (2011) compared the renal tumor size as assessed on CT for 122 patients with pT1 or pT2 tumors, and found a discrepancy between clinical and pathological staging in 35 (29%) patients. Of these, 21 (17%) patients were down-staged post-operatively and 14 (11.5%) were up-staged. They concluded that as prognosis counseling and treatment strategy were based on pathological staging but mainly assessed by radiological detection for patients without surgical treatment, the only 3.1 mm shrinkage may still take a conspicuous impact upon clinical management. Kanofsky et al. (2006) and his coworkers had also reported 13 cases stage change for 79 chromophobe renal cell carcinomas as discussed above. Similar with Kanofsky's findings, our observation gave a stage discordance in 16.2% patients. Although the tumor size is not the solely appraisal criterion of T stage for HCC, difference between clinical and pathological maximum diameter still has a significant influence on the treatment management. As for tumors <3cm, radiofrequency ablative therapy can be used as a favorable substitute for patients not suitable for resection.

We used the ROC curve to analyze the predictive accuracy of the enhanced MRI for T stage. With increased tumor size, the predictive accuracy of MRI alone in measuring size, as measured by area under the ROC curve, had increased from 62.5% to 89.1%. Predictive accuracy of pT4 tumors (>5 cm) that not including base characteristics, irrespective of the tumor's histologic subtype, was significantly higher than the pT1 tumors ( $p=0.006$ ). Yacyioglu et al. (2002) and coworkers retrospectively reviewed the charts of 291 patients with malignant renal tumors, and demonstrated that no special features might be responsible for the estimation errors. Additionally, in approximately one half of these patients, features such as cystic masses, evidence of bleeding and hematoma, concomitant inflammatory diseases, localization of tumor adjacent to the collecting system, invasion of the collecting system, cysts adjacent to the tumor, and multiple cysts within the kidney might have influenced the accuracy of the clinical size. Contradicting with their findings, in the present study, we did not evidently identify any factors might cause deflection on the accuracy of MRI.

To our knowledge, this retrospective review was the first literature which systematically reported the size difference between radiological and pathological measurement for HCC tumors. However, some inherent limitations can be identified. We only measured patients with unitary HCC, taking no account of intrahepatic cholangiocarcinoma (ICC), which was subject to selection bias. Therefore, whether or not mixed ICC nodules within the HCC tumors might influence the accuracy of the clinical size can not be extrapolated from this study. The discrepancies between preoperative and postoperative tumor size might also have been caused by the lack of technical uniformity during measurement. Although after surgical excision the tumor was oriented and calculated in the axial plane corresponding to the radiographic section, the maximal dimensions might not

well be completely consistent, which therefore produced errors in comparison. In particular, interobserver and intraobserver variability cannot be ruled out. Furthermore, parameters such as concomitant hemorrhage or necrosis, hepatic hemangioma, tumor involving a major branch of the Glisson's system, invasion of the hepatic vein system, patients treated with half hepatectomy are in a small number, which were inadequately powered to detect a difference. Another weakness was that in this study we did not find any exact mechanism leading to the significant size discrepancy of tumors which were <2 cm or poorly differentiated.

Overall, despite these weaknesses, the overall predictive accuracy of radiological size by MRI and its correlation with the pathological size was acceptable. It is important to realize the discrepancy between radiological and pathological tumor size, as treatment decisions and prognosis evaluation may be made based on size parameters. Since our data was retrospectively reviewed, the results were subject to an observational variability. Additional prospective randomized cohort studies are needed to elucidate this relationship in further detail and clarify the mechanism with different contrast induction protocols.

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