CT-pathologic correlation in primary hepatocellular carcinoma: an implication for target delineation

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The purpose of this investigation was to analyze the correlation between CT size and gross pathologic size for subjects with primary hepatocellular carcinoma (HCC). This analysis included 174 patients with HCC who underwent surgery. Enhanced computed tomography (CT) was performed up to 30 days before surgery. After resection, the size of the tumor on gross pathologic examination was recorded. The maximal measurement in one dimension on imaging and pathologic examination was extracted for statistical analysis. The clinical and pathologic sizes were compared using a percent size difference (%Δsize) as an end point. A regression analysis was applied to study the association between pathologic and radiographic size. The median radiographic and pathologic size were 70.58 ± 38.9 mm and 68.59 ± 40.56 mm, respectively. The radiographic size was larger than or equal to the pathologic size in 110/174 tumors (63.2%), and smaller in 64/174 (36.8%) tumors. Overall, the radiographic and pathologic sizes were positively correlated (r = 0.983, P = 0.000). CT seemed to overestimate the tumor size by 2.16 mm compared to final pathology (P = 0.024). The median %Δsize was 3.3%. Pathologic tumor size was significantly underestimated in patients with a tumor size 3–5 cm (P = 0.011), Grade I HCC (P = 0.023), with clear boundary (P = 0.013). We concluded that CT size and pathologic size were positively correlated, but differences did exist. Utilizing the radiographic tumor when planning radiation would have covered 63.2% of gross tumors. For a radiographic tumor size < 50 mm, utilizing a 3-mm margin around the radiographic tumor would have covered 90% of gross lesions, while a margin of 5 mm would have covered 95%, and a margin of 15 mm would have covered 100%.

Keywords: hepatocellular carcinoma; CT-pathologic relation; target delineation; radiation

INTRODUCTION

Primary hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the third most common cause of cancer-related death [1]. For patients who are not surgical candidates, radiotherapy, transarterial chemembolization (TACE), and percutaneous ablation may be available. The developments in imaging, radiation planning, motion management, and image guidance at the time of radiation delivery make safe delivery of ablative doses of radiation therapy to focal liver tumors possible, and have led to a body of evidence that now supports the careful use of radiotherapy for unresectable HCC [2]. Three-dimensional conformal radiation treatment planning relies on imaging, primarily computed tomography (CT) plus fusion with diagnostic magnetic resonance imaging (MRI) in selected cases, to accurately target the full extent of the tumor [3]. Radiographic–pathologic correlation studies are needed to ensure that imaging before radiotherapy accurately delineates the true extent of disease. The purpose of our analysis was to understand the correlation between CT and true gross pathologic size for subjects with HCC.

MATERIALS AND METHODS

Between June 2009 and October 2012, 254 patients underwent a preoperative hepatic enhanced CT leading to partial
hepatectomy or orthotopic liver transplant for HCC, all without presurgery antitumor treatment. Of these, 64 were excluded because of diffuse lesions which could not be measured exactly, or absence of an intact record of pathologic diameter. Another 16 were excluded because of the CT–operation interval being >30 days. A total of 174 cases were analyzed. Patient characteristics are listed in Table 1.

All preoperative scans were performed using a 64-multidetector CT scanner (GE Healthcare, Discovery 750HD) during breathhold. After a simple scan, 100 ml urografin was injected intravenously (IV), then the liver was rescanned at the arterial phase (30 s delay after injection), and again at the venous phase (60 s–80 s delay); the late delayed phase images were obtained at 120 s after injection. The data were reconstructed at 1.25-mm slice thickness at 1.25-mm intervals and were three-dimensionally reconstructed. Only patients who underwent preoperative CT at our institution within 4 weeks of surgery were included. All examinations were reviewed by a single attending radiologic doctor, with subspecialty expertise in hepatic imaging. In each patient, tumor diameter was initially measured in various axes (including the anterior–posterior and left–right diameter in the cross section, and the diameter in the caudal–cephalic direction in reformed coronal and sagittal images) via CT images, and the largest diameter was recorded as the radiographic tumor size (RTS).

At our institution, the largest diameter of tumor mass measured before formalin fixation of gross surgical specimen was recorded in the pathologic report and was designated as pathologic tumor size (PTS) for our study. With regard to patients with multifocal hepatic tumors, the largest tumor was included in the analysis. Tumor dimensions are determined by direct visual inspection and measurement using a metric ruler with millimeter demarcations. The largest recorded tumor dimension from the surgical pathology report was used for statistical analysis.

The SPSS software package version 19.0 was used for statistical analysis. The Wilcoxon signed-ranked test was used to analyze the difference between the RTS and the PTS. The radiographic and pathologic sizes were compared using a percent size difference (%Δsize) as an end point for each patient using the following formula:

\[
\%\Delta\text{size} = \frac{\text{radiographic size} - \text{pathologic size}}{\text{radiographic size}}
\]

Correlation between continuous variables was assessed via the Spearman correlation coefficient. All categorical variables were analyzed by nonparametric tests. Simple linear regression analysis was also applied in assessing the effect of various clinical factors on the observed difference between radiographic and pathologic tumor size. \(P < 0.05\) indicated statistical significance.

**RESULTS**

**Normal conditions**

The mean and median age were 53.9 (range, 23–77) and 54 years. Of the 174 patients, 155 were male and 19 were female. Chronic hepatitis B infection was present in 147 patients, and 127 had cirrhosis. Hepatectomy was performed on 132 patients, and 42 received an orthotopic liver transplantation. The mean and median time from preoperative imaging to surgical resection was 7 and 4 days (range, 1–30 days), and 78% of cases were <10 days.

**Radiographic–pathologic tumor size features**

The mean RTS and PTS were 70.58 ± 38.9 mm (17–195 mm) and 68.59 ± 40.56 mm (8–220 mm). The radiographic size was larger than pathologic size in 98/174 tumors (56.3%), smaller in 64/174 tumors (36.8%), and equal in 12/174 tumors (6.9%). Radiographic size correlated well with pathology, \(r = 0.95\), \(P = 0.000\); but difference did exist in the Wilcoxon signed-ranked test, \(P = 0.024\). Tumors were overestimated by 2.16 mm (37–41.30 mm) on CT compared to pathology, \(\%\Delta\text{size} = 3.3\%\) (46.7–57.9%). For all patients, a margin of ‘radiographic tumor × 120%’ would have covered 90% of gross lesions, a margin of ‘radiographic tumor × 128%’ would have covered 95% of gross lesions. Utilizing a 15-mm margin around the radiographic tumor would have covered 90% of pathologic gross lesions, while a margin of 21 mm would have covered 95% of gross lesions. For lesions <50 mm, a margin of ‘radiographic tumor × 114%’ would have covered 90% of gross lesions, and a margin of ‘radiographic tumor × 120%’ would have covered 95% of gross lesions. Utilizing a 3-mm margin around the radiographic tumor would have covered 90% of pathologic gross lesions, while a margin of 5 mm would have covered 95% of gross lesions, and a margin of 15 mm would have covered 100% of gross lesions.

**Radiographic–pathologic discrepancy analysis**

The radiographic tumor sizes were categorized to <3 cm, 3–5 cm, 5–10 cm and >10 cm. The corresponding radiographic and pathologic sizes for each group were 24.30 mm and 24.14 mm, 39.8 mm and 7.49 mm, 70.73 mm and 69.01 mm, and 132.26 mm and 129.1 mm respectively, with \(P\) values of 0.968, 0.011, 0.247 and 0.334, respectively. Tumors with RTS 3–5 cm were overestimated on CT by a median of 3.0 mm \(P = 0.011\), \%Δsize was 5.7%. But mean radiographic tumor size was greater than pathologic tumor size in other ranges of tumor size.

Tumors with clear borders were overestimated on CT by a median of 4.0 mm compared to pathology \(P = 0.017\), while tumors with vague borders were not \(P = 0.415\). When compared according to pathologic subtypes of...
tumors, a significant difference between radiographic and pathologic tumor size was observed among those with Grade I HCC ($P = 0.023$), with an overestimation of 26.6 mm. In patients with other grades of tumors, no significant differences were observed. In our study, various factors such as AFP value, and presence or absence of cirrhosis, were observed to have no significant impact on the differences observed between radiographic and pathologic tumor size (details in Table 1).

### Regression analysis
No significant correlation was observed between %Δsize and patient AFP, radiographic tumor size, tumor boundary, cirrhosis, pathologic grading, interval of CT-surgery in univariate analysis, nonparametric tests (Kruskal-Wallis H test), or linear regression (details in Table 2).

### DISCUSSION
Radiotherapy has not played a significant role in the treatment of HCC historically. Without multiphase contrast CT scans or MRI, tumor volume delineation has been a challenge, and radiation volume usually included a significant portion of the normal liver. Because the whole liver has a low tolerance to radiation, patients were at risk for liver toxicity, and did not derive much benefit from low-dose radiotherapy. Development in imaging (CT scans, MRI, PET-CT and so on), radiation planning, motion management, and image guidance at the time of radiation delivery, make safe delivery of ablative doses of radiation therapy to focal liver tumors possible [3–7].

In a series of prospective studies at the University of Michigan [8], which included 35 patients with HCC, doses well above the whole-liver tolerance dose have been delivered safely to focal lesions. The prescribed dose ranged from 40–90 Gy (median 60.75 Gy) in 1.5 Gy twice-daily fractions delivered with concurrent hepatic arterial fluorodeoxyuridine. The 1-year overall survival was 81% in patients with HCC. In a prospective Phase II trial from France [9], 27 patients of Child-Pugh Class A or B with a single tumor of 5 cm, or two tumors of 3 cm, were treated with 66 Gy in 2-Gy fractions. In 25 assessable patients, tumor response was very high at 92% (80% complete response and 12% partial response). Intensity-modulated

### Table 1. Radiographic and pathologic tumor size of 174 primary hepatocellular carcinomas

|            | Case | RTS ± SD mm | PTS ± SD mm | $P$ value | %Δsize ± SD |
|------------|------|-------------|-------------|-----------|-------------|
| ALL        | 174  | 70.58 ± 38.9| 68.59 ± 40.58| 0.024     | 3.39 ± 28.9 |
| AFP normal | 66   | 62.72 ± 40.38| 60.53 ± 38.86| 0.107     | 3.1 ± 17.4  |
| 10–200     | 33   | 67.75 ± 37.49| 65.67 ± 41.31| 0.354     | 4.08 ± 19.85|
| 200–1000   | 17   | 55.07 ± 32.42| 49.17 ± 31.32| 0.121     | 8.69 ± 23.95|
| >1000      | 58   | 85.68 ± 35.62| 85.1 ± 39.76 | 0.479     | 1.7 ± 17.27 |
| Cirrhosis yes | 127  | 67.17 ± 35.9 | 65.28 ± 37.45| 0.070     | 3.18 ± 18.91|
| no         | 47   | 79.85 ± 45.12| 77.51 ± 47.44| 0.202     | 3.95 ± 17.55|
| Border clear | 76   | 71.22 ± 40.42| 67.59 ± 38.51| 0.013     | 3.8 ± 16.91 |
| vague      | 107  | 70.08 ± 37.89| 69.36 ± 42.36| 0.415     | 3.04 ± 19.73|
| Pathology Grade I | 28   | 47.41 ± 25.09| 44.74 ± 25.65| 0.023     | 6.8 ± 15.1  |
| Grade II   | 90   | 66.67 ± 36.72| 64.13 ± 38.35| 0.163     | 3.8 ± 21.3  |
| Grade III  | 56   | 88.45 ± 40.55| 87.66 ± 42.35| 0.361     | 1.0 ± 14.85 |
| RTS <3 cm  | 21   | 24.3 ± 4.08  | 24.14 ± 7.6  | 0.968     | 1.1 ± 24.3  |
| 3–5 cm     | 43   | 39.8 ± 6.42  | 37.49 ± 8.2  | 0.011     | 5.7 ± 16.0  |
| 5–10 cm    | 73   | 70.73 ± 14.23| 69.01 ± 22.17| 0.247     | 3.3 ± 19.1  |
| >10 cm     | 37   | 132.26 ± 22.83| 129.10 ± 27.57| 0.334     | 2.1 ± 14.51 |

RTS = radiographic tumor size, PTS = pathologic tumor size.

### Table 2. Kruskal-Wallis H and linear regression analysis of %Δsize

|                | Kruskal-Wallis H | Linear regression |
|----------------|-----------------|------------------|
|                | $P$ value       | $P$ value        |
| AFP            | 0.716           | 0.953            |
| Cirrhosis      | 0.791           | 0.873            |
| Boundary       | 0.561           | 0.991            |
| Patholo Gy     | 0.466           | 0.222            |
| RTS            | 0.373           | 0.776            |
| Time interval  | 0.129           | 0.496            |

RTS = radiographic tumor size.
radiotherapy has allowed the delivery of higher doses of radiation, with the caveat that the volume of liver receiving even low doses of radiation must be limited, as discussed later. Series from Asian studies also show that survival benefit can be achieved from optimal radiotherapy [10–11].

Stereotactic body radiotherapy (SBRT) has also been applied to selected patients with HCC. The first prospective trial of SBRT came from Mendez-Romero et al. [12], who treated 25 patients with liver tumors, 8 of whom had HCC. The 1-year local control rate was 75%, with all failures in the 25-Gy group, and the 1-year survival rate was 48%. Other prospective studies from Dawsons et al. [13], and Cardenes et al. [14] also supported SBRT as being a good choice for some patients with HCC.

No matter which techniques are used, increasing the radiation dose to the tumor lesions, and simultaneously decreasing the dose to normal liver tissue is the primary purpose. Accurate delineation of tumor volume is the prerequisite of tumor control. The more precise the radiation technique is, the more precise delineation of the tumor is required. This depends on radiographic images to target the tumor extent. Visualization of the tumor and the tumor boundaries within normal tissues is critical for high-precision treatment planning. Use of IV contrast has been shown to be critical for the identification of most tumors in liver images using CT, but the relationship between the RTS and the PTS is not well understood. In a retrospective analysis from Kelsey et al. [15], 18 people with 27 hepatic tumors were analyzed. They showed that radiographic tumor size was larger or equal to pathologic size in 22/27 cases, and smaller in 5/27, with a %Δsize of −20–144%. The imaging in their study included simple CT scan, dual-phase CT scan and MRI. The use of too many imaging techniques may have influenced their results.

The 174 patients in our study all received tri-phase enhanced CT. The radiographic size was larger than the pathologic size in 56.3% of patients, smaller in 36.8%, and equal in 6.9%. Radiographic size correlated well with pathologic size, but differences did exist, and the amount by which CT overestimated tumor size varied greatly between patients. Tumors were overestimated by 2.16 mm (−37–41.30 mm) on CT, %Δsize was 3.3% (−46.7–57.9%). Being able to predict when CT will significantly overestimate tumor size allows expansion of margins in patients most likely to benefit. In univariate analysis, we found that in cases of radiographic size of 3–5 cm and pathologic Grade I with clear boundaries, overestimation of tumor size by CT was predicted. But when it came to multivariate analysis, none of the variables such as radiographic tumor size, pathologic grading, tumor boundary or cirrhosis were found to be predictive of larger discrepancy. Since radiotherapy is mainly used for hepatic lesions <50 mm, expanding the sample size in this subgroup in further prospective study maybe helpful.

CT tumor size was larger or equal to pathologic size in 63.2% of patients. This means that when planning radiation according to enhanced CT, it would have covered 63.2% of pathologic gross lesions, and 36.8% may have some lesions out of the target. Utilizing the radiographic tumor when planning radiation would have covered 63.2% of pathologic gross lesions, while a margin of ‘radiographic tumor × 120%’ would have covered 90% of gross lesions, and a margin of ‘radiographic tumor × 128%’ would have covered 95% of gross lesions. The study from Kelsey et al. [15] found that utilizing a 5-mm margin around the radiographic tumor would have covered 93% of pathologic gross lesions, while a margin of 10 mm would have covered 100% of gross lesions. The mean pathologic tumor size was 25 mm (10–48 mm) in their study, compared to 68.59 mm (8–220 mm) in our study. Considering that radiotherapy is mainly used for hepatic lesions <50 mm, we analyzed the radiographic–pathologic discrepancy for this tumor size, and found that a margin of ‘radiographic tumor × 114%’ would have covered 90% of gross lesions, and a margin of ‘radiographic tumor × 120%’ would have covered 95% of gross lesions. Utilizing a 3-mm margin around the radiographic tumor would have covered 90% of pathologic gross lesions, while a margin of 5 mm would have covered 95% of gross lesions, and a margin of 15 mm would have covered 100% of gross lesions. But for the whole group, a margin of ‘radiographic tumor × 120%’ would have covered 90% of gross lesions, and a margin of ‘radiographic tumor × 128%’ would have covered 95% of gross lesions.

The purpose of the present analysis was to compare the pathologic size of HCC with size on enhanced CT to guide clinicians in choosing appropriate margins for radiotherapy. But, as with most retrospective studies, it has several inherent limitations. First, it would be optimal to perform imaging immediately before surgical resection. The median interval was 4 days in our study. While the growth pattern of HCC varies significantly, the median doubling time has been estimated at 0–170 days [16]. But an interval between CT-surgery >7 days did not predict larger %Δsize in our study. Second, microscopic extension was not evaluated and is likely to be an important factor when deciding on optimal margins. Data from Zeng et al. [17] illustrated that there was 0.5–4 mm microscopic extension beyond the gross tumor; and Li [18] also recommended that a margin of 2 mm, 4.5 mm and 8.0 mm should be added to gross tumor volume to cover microscopic extension for Grade I, II and III HCCs, respectively. Third, the maximal gross size was obtained retrospectively by reviewing pathology reports, as opposed to prospective careful analysis of pathologic specimens. Pathologic observations were made by a number of individuals, and there is no reason to suspect a systematic bias because of the method of measurement.

According to our study, radiographic size of HCC on triphase hepatic CT correlated well with pathologic size, but
differences did exist. Utilizing the radiographic tumor when planning radiation would have covered 63.2% of pathologic gross lesions. For a radiographic tumor size <50 mm, utilizing a 3-mm margin around the radiographic tumor would have covered 90% of pathologic gross lesions, while a margin of 5 mm would have covered 95% of gross lesions, and a margin of 15 mm would have covered 100%.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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