Use of combined maximum and minimum intensity projections to determine internal target volume in 4-dimensional CT scans for hepatic malignancies

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Abstract

Background: To evaluate the accuracy of the combined maximum and minimum intensity projection-based internal target volume (ITV) delineation in 4-dimensional (4D) CT scans for liver malignancies.

Methods: 4D CT with synchronized IV contrast data were acquired from 15 liver cancer patients (4 hepatocellular carcinomas; 11 hepatic metastases). We used five approaches to determine ITVs: (1) ITVAllPhases: contouring gross tumor volume (GTV) on each of 10 respiratory phases of 4D CT data set and combining these GTVs; (2) ITV2Phase: contouring GTV on CT of the peak inhale phase (0% phase) and the peak exhale phase (50%) and then combining the two; (3) ITVMIP: contouring GTV on MIP with modifications based on physician’s visual verification of contours in each respiratory phase; (4). ITVMinIP: contouring GTV on MinIP with modification by physician; (5). ITV2M: combining ITVMIP and ITVMinIP. ITVAllPhases was taken as the reference ITV, and the metrics used for comparison were: matching index (MI), under- and over-estimated volume (Vunder and Vover).

Results: 4D CT images were successfully acquired from 15 patients and tumor margins were clearly discernable in all patients. There were 9 cases of low density and 6, mixed on CT images. After comparisons of metrics, the tool of ITV2M was the most appropriate to contour ITV for liver malignancies with the highest MI of 0.93 ± 0.04 and the lowest proportion of Vunder (0.07 ± 0.04). Moreover, tumor volume, target motion three-dimensionally and ratio of tumor vertical diameter over tumor motion magnitude in cranio-caudal direction did not significantly influence the values of MI and proportion of Vunder.

Conclusion: The tool of ITV2M is recommended as a reliable method for generating ITVs from 4D CT data sets in liver cancer.

Keywords: liver malignancy, radiotherapy, internal target volume, 4-dimensional CT, maximum intensity projection, minimum intensity projection

Introduction

Primary and metastatic hepatic malignancies are commonly treated by surgery, but radiation therapy is also one of options as non-surgical modalities. It has been demonstrated that radiation therapy is feasible and the outcomes are promising [1,2]. However, due to respiration liver motion up to 3 cm [3] is one of obstacles to accurately localize the target. Moreover, respiratory-induced tumor motion is known to be anisotropic, thus individual determination of internal margin around gross tumor volume (GTV) is crucial to form an internal target volume (ITV), which can avoid both inadequate tumor coverage and unnecessary liver parenchymal irradiation for individual patient. Four-dimensional computed tomography (4D CT) is one of appropriate approaches to estimate and determine ITV for tumor with respiratory motion [4,5].

4D CT has been widely used in lung cancer to determine ITV [6,7]. Ideally, ITV should be delineated by...
manually contouring GTV in all 10 breath phases of a 4D scan image sets to form ITV, which is the most accurate tool to determine ITV, but it is a time-consuming and labor-intensive task. To reduce the workload of contouring multiple GTVs, one solution is to contour only two extreme phases at end-inhalation and end-exhalation and then to sum of the two becoming ITV [8,9]; and the other is to use the post-processing tools of maximum intensity projection (MIP) and minimum intensity projection (MinIP) from 4D CT data sets to generate ITV. MIP-based ITV delineation is performed on a single 3-D CT data set, where each pixel in this set represents the brightest object encountered by corresponding voxels in all volumetric 4D CT data sets, for instance, MIP-based ITV delineation for lung cancer, which was recommended as a reliable tool and a good first estimation [10-12]. Conversely, MinIP-based ITV is on the CT set, where each pixel represents the lowest data value in the volumetric data [10].

MIP and MinIP methods seem not suitable for liver cancer because most tumors in the liver have similar attenuation to the normal liver parenchyma and therefore are not easily discernable. Contrast-enhanced CT scan has been routinely used for radiation oncologists to differentiate the tumor from normal tissues. It should be noted that regardless of with contrast enhancement or not, most liver tumors present inhomogeneous density, either because of the inherent nature of the tumor, such as the routes of blood supply, vascular volume and permeability, or because of areas of fluid, hemorrhage, and necrosis within tumors, or because of secondary change due to treatments, for example, iodine deposition as a result of transcatheter arterial chemoembolization (TACE). Recently, Beddar et al described a simple method for 4D CT acquisition by using synchronized intravenous contrast injection to improve the accuracy of liver tumor delineation. By this way most liver metastases and cholangiocarcinomas can be identified on image of portal venous phase, while HCC, most visible in the delayed phase [13].

In theory, for tumors with homogeneous hyperdensity or hypodensity comparing to the surrounding normal liver, MIP or MinIP projections should accordingly reflect the tumor trajectory across all time-resolved data sets. Visualization of tumor with mixed-density means the tumor border should be discernable; regardless which part of it is more hyperdense or hypodense than the adjacent liver parenchyma. Using MIP technique or MinIP technique only definitely misses the spatial information of the moving liver tumor. Therefore, our hypothesis is to combine MIP and MinIP, which may fit for the situation of mixed tumor density. Thus, the purpose of this study is to evaluate the feasibility and accuracy of the MIP and/or MinIP-based ITV delineation in 4DCT scans for liver tumors.

Methods
Patient selection
Patients who met the following criteria were qualified to this study: (1). Patient suffered from hepatic malignancies, primary or metastatic, and were planned to receive irradiation; (2). The margins of hepatic lesion were clear on intravenous contrast enhanced CT; (3). Patient’s breath was regular after a training session; (4). Patient did not have the history of allege to contrast; and (5). Informed consent was obtained.

4D CT image acquisition
In order to enhance the visibility of tumors on 4D CT, 100 mL of contrast at a concentration of 300 mg I/mL was injected synchronously with 4D CT image acquisition. All patients were imaged during the portal venous phase. A time delay was programmed within 4D CT image acquisition protocol so that the start of contrast injection is initiated simultaneously with the start of the scanner’s timer countdown. For those with liver metastases, the liver was scanned with a 45 s time delay, while for hepatocellular carcinoma (HCC) patients the time delay was 65 s. This CT scan protocol was proposed by Beddar et al [13].

All patients were immobilized using customized vacuum lock in supine position with arms placed on their forehead. A16-slice Brilliance Big Bore CT scanner (Philips Co.) was used for 4D CT image acquisition. The patient respiration was tracked using Real-Time Position Management (RPM) System (Varian Medical Systems, Palo Alto, CA). The region of interest usually comprises the area from 2 to 3 cm above diaphragm to iliac crest. A 4D CT scan is performed in cine mode with at least one complete breath cycle for each couch position. After scanning 4-dimensional images were binned based on the respiratory traces to become a complete image set, which covered each of 10 breathing phases. MIP and minimum intensity projections (MinIP) were then generated from the raw data set of 4D CT scans.

ITV determination
All reconstructed CT series were transferred to MIM software (Version 5.1, MIMvista Corp., Cleveland, OH). Window/level was adjusted to optimize the visual contrast between the tumor and normal parenchyma regions. All the contours were drawn by a single radiation oncologist (JL) and verified by a senior radiation oncologist (JDZ). We used 5 approaches to determine ITV, which were: (1). ITVAllPhases: contouring GTV on each of 10 respiratory phases of 4D CT data set and
combining these GTVs; (2). ITV\textsubscript{2Phase}: contouring GTV on CT of the peak inhale phase (0% phase) and the peak exhale phases (50%) and then combining the two; (3). ITV\textsubscript{MIP}: contouring GTV on MIP with modifications based on physician’s visual verification of contours in each respiratory phase; (4). ITV\textsubscript{MinIP}: contouring GTV on MinIP with modification by physician; (5). ITV\textsubscript{2M}: combining ITV\textsubscript{MIP} and ITV\textsubscript{MinIP}. Figure 1 illustrates different approaches in the determination of ITV for patient 13.

**Evaluation of target motion**
We used MIM software (version 5.1) to measure cranio-caudal, left-right and anterior-posterior movement of the tumor. Tumor motion was also expressed as a 3D vector, which is the quadratic mean of the motions in 3 orthogonal directions.

**Data analysis and statistics**
ITV\textsubscript{2Phase}, ITV\textsubscript{MIP}, ITV\textsubscript{MinIP} and ITV\textsubscript{2M} as the tested ITVs, would be compared with the reference of ITV\textsubscript{All-Phases} respectively. The metrics used for comparison were: (1) Matching index (MI), which was the percentage of overlapped volume in 3-dimensions between 2 ITVs. When 2 ITVs were totally overlapped, MI was 1.00, whereas when 2 ITVs were totally separate, MI was 0; and (2) under- and over-estimated volume (V\textsubscript{under} and V\textsubscript{over}). A tested ITV (V\textsubscript{test}) was compared to the standard volume, ITV\textsubscript{All-Phases}. The formulas were: $V_{\text{under}} = V_{\text{All-Phases}} \setminus V_{\text{test}}$ and $V_{\text{over}} = V_{\text{test}} \setminus V_{\text{All-Phases}}$.

$$V_{\text{Under}} = \int (A_{\text{all-phase}} \setminus A_{\text{test}})\,dz$$

$$V_{\text{Over}} = \int (A_{\text{test}} \setminus A_{\text{all-phase}})\,dz$$

The definitions and calculations of those metrics were referred to Ezhil [12].

Paired sample $t$-test and Independent-Samples $T$ test (SPSS v.13, SPSS Inc., Chicago, IL) were applied to compare the differences with $p$ value of < 0.05 considered significant.  

**Results**
**Patients**
From August 2010 to February 2011, 15 eligible patients with liver cancer were enrolled in this study and underwent 4D CT simulation for irradiation treatment planning in our institution. Of these patients 11 had metastatic liver cancers and 4, HCC with mean lesion volume of 152 cm$^3$ (range, 2 cm$^3$ - 932 cm$^3$). 4D CT images were successfully obtained from 15 patients and tumor margins were clearly discernable in all patients. There were 9 cases of low density and 6, mixed on CT images (Table 1).

**Target motion**
The cranio-caudal motion of the target was predominant with a mean distance of 8.0 mm ± 3.3 mm, while the left-right and anterior-posterior motions were much
less with mean values of 1.6 mm ± 0.9 mm and 3.2 mm ± 2.2 mm, respectively (Table 2).

Comparison of ITVs countered by different approaches

1. **ITVs volume**

   Table 3 shows all volumes of ITV. The mean volume of ITV$_{2M}$ was closest to that of ITV$_{AllPhases}$ and then followed by ITV$_{2Phase}$. The volume difference between ITV$_{2M}$ and ITV$_{2Phase}$ was statistically significant with a p value of 0.04. Taking ITV$_{AllPhases}$ as the reference, the mean ratios of the tested ITVs to ITV$_{AllPhases}$ were 88.9% ± 5.7%, 82.7% ± 12.6%, 82.5% ± 10.8% and 94.0% ± 3.6%, respectively for ITV$_{2phase}$, ITV$_{MinIP}$, ITV$_{MIP}$ and ITV$_{2M}$.

2. **MI**

   As shown in Table 4, ITV$_{2M}$ was closest matched with ITV$_{AllPhases}$ with mean MI of 0.93 ± 0.04, and mean MIs were 0.89 ± 0.06, 0.82 ± 0.12 and 0.82 ± 0.10, respectively for ITV$_{2Phase}$, ITV$_{MinIP}$ and ITV$_{MIP}$. The differences of MI were statistically significant between ITV$_{2M}$ and ITV$_{2Phase}$ (p = 0.004), between ITV$_{2M}$ and ITV$_{MinIP}$ (p = 0.003), and between ITV$_{2M}$ and ITV$_{MIP}$ (p = 0.000). All the other comparisons between ITVs were not significant.

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### Table 1 Tumor Characteristics

| Patient | Tumor | Tumor size* (mm) | GTV (cm$^3$) | Location | Tumor density |
|---------|-------|-----------------|-------------|----------|---------------|
| 1       | HCC   | 51 x 42 x 23    | 34          | Right upper lobe; adjacent to right lung. | Mixed          |
| 2       | LM from lung cancer | 33 x 49 x 33 | 30         | Left lobe; intrahepatic                 | Low            |
| 3       | LM from gastric carcinoma | 42 x 78 x 52 | 77         | Caudate and left lobe; intrahepatic     | Low            |
| 4       | LM from pancreatic carcinoma | 42 x 51 x 48 | 66         | Right lower lobe; intrahepatic          | Mixed          |
| 5       | LM from nasopharyngeal carcinoma | 12 x 15 x 15 | 2          | Right upper lobe; intrahepatic          | Low            |
| 6       | LM from rectal carcinoma | 10 x 12 x 11 | 2          | Right upper lobe; intrahepatic          | Low            |
| 7       | HCC   | 35 x 39 x 48    | 59         | Right upper lobe; adjacent to right lung | Mixed          |
| 8       | LM from gallbladder carcinoma | 9 x 18 x 18 | 3          | Right lower lobe; intrahepatic          | Low            |
| 9       | LM from gastric carcinoma | 51 x 99 x 58 | 213        | Left lobe; adjacent to stomach         | Low            |
| 10      | HCC   | 78 x 96 x 99    | 384        | Right lobe, adjacent to right lung and kidney | Mixed          |
| 11      | LM from lung cancer | 50 x 59 x 45 | 80         | Left lobe; adjacent to stomach         | Low            |
| 12      | LM from gallbladder carcinoma | 33 x 38 x 42 | 28         | Right lobe; intrahepatic                 | Low            |
| 13      | LM from rectal carcinoma | 54 x 56 x 54 | 91         | Right upper lobe; adjacent to right lung | Mixed          |
| 14      | HCC   | 108 x 126 x 145 | 932    | Right upper lobe; adjacent to right lung | Mixed          |
| 15      | LM from esophageal carcinoma | 60 x 91 x 88 | 284        | Right lobe; adjacent to right lung and kidney | Low            |

Abbreviations: GTV: gross tumor volume; HCC: hepatocellular carcinoma; LM: liver metastasis.

* Tumor size was expressed as multiplying diameters in cranio-caudal, in left-right and in anterior-posterior directions.

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### Table 2 Motion magnitudes of GTV centroid measured by 4D CT in 15 patients (mm)

| Patient | Cranio-caudal | Left-right | Anterior-posterior | 3D vector |
|---------|---------------|------------|-------------------|-----------|
| 1       | 8.8           | 2.9        | 2.3               | 9.6       |
| 2       | 11.9          | 1.1        | 1.4               | 12.0      |
| 3       | 6.9           | 1.0        | 2.8               | 7.5       |
| 4       | 8.8           | 1.3        | 3.0               | 9.4       |
| 5       | 8.7           | 1.7        | 2.2               | 9.1       |
| 6       | 10.0          | 1.1        | 3.9               | 10.8      |
| 7       | 15.2          | 2.5        | 8.1               | 17.4      |
| 8       | 7.6           | 3.6        | 4.3               | 9.5       |
| 9       | 8.0           | 1.1        | 1.4               | 8.2       |
| 10      | 5.3           | 2.7        | 8.2               | 10.1      |
| 11      | 3.4           | 1.0        | 3.2               | 4.8       |
| 12      | 3.0           | 1.0        | 2.1               | 3.8       |
| 13      | 11.5          | 1.7        | 2.3               | 11.9      |
| 14      | 3.9           | 0.9        | 0.7               | 4.1       |
| 15      | 7.4           | 1.0        | 1.7               | 7.7       |
| Mean    | 8.0           | 1.6        | 3.2               | 9.1       |
| SD      | 3.3           | 0.9        | 2.2               | 3.4       |

### Table 3 Volumes of ITV$_{AllPhases}$, ITV$_{2M}$, ITV$_{2Phase}$, ITV$_{MinIP}$ and ITV$_{MIP}$ (cm$^3$)

| Patient | ITV$_{AllPhases}$ | ITV$_{2M}$ | ITV$_{2Phase}$ | ITV$_{MinIP}$ | ITV$_{MIP}$ |
|---------|------------------|------------|---------------|---------------|-------------|
| 1       | 52.8             | 44.2       | 43.2          | 32.5          | 41.5        |
| 2       | 50.9             | 48.8       | 47.1          | 43.7          | 43.6        |
| 3       | 112.6            | 101.4      | 102.4         | 97.5          | 80.9        |
| 4       | 100.1            | 94.8       | 91.2          | 70.9          | 94.5        |
| 5       | 5.7              | 5.1        | 4.3           | 5.0           | 4.1         |
| 6       | 5.0              | 4.7        | 4.1           | 4.6           | 2.9         |
| 7       | 96.1             | 91.4       | 85.3          | 56.0          | 90.0        |
| 8       | 6.8              | 6.5        | 5.9           | 6.5           | 5.0         |
| 9       | 294.8            | 283.0      | 280.6         | 233.3         | 275.2       |
| 10      | 569.3            | 549.6      | 514.6         | 390.3         | 528.7       |
| 11      | 99.5             | 95.7       | 88.9          | 93.8          | 86.2        |
| 12      | 40.3             | 38.9       | 37.2          | 38.8          | 30.1        |
| 13      | 123.2            | 116.8      | 110.0         | 98.9          | 104.9       |
| 14      | 1082.7           | 1041.1     | 1040.3        | 963.8         | 1013.6      |
| 15      | 372.0            | 357.6      | 347.3         | 355.7         | 312.5       |

Mean 200.8 192.0 186.8 166.1 180.9

SD 290.4 280.0 277.0 252.0 272.0
We further analyze the tumor characteristics, which would impact MI.

1). MI and tumor volume: As lesion of > 5 cm is not a candidate for stereotactic body radiation therapy in our practice, the patients were split into two groups: ≤ 65.4 cm³ (equivalent to the volume of a sphere with 5 cm in diameter) vs. > 65.4 cm³. MIs of ITV2M were 0.94 ± 0.02 for the former and 0.92 ± 0.04 for the latter (p = 0.260). Nevertheless, there was significant difference between tumor size and MIs of ITV2Phase, MI being 0.92 ± 0.03 for tumor of ≤ 65.4 cm³ and 0.85 ± 0.06 for tumor of > 65.4 cm³ (p = 0.015). For ITV2M as tumor volume increased MI did not change much with no correlation between them (R = 0.364, p = 0.182). However, for ITV2Phase, when tumor volume increased MI was significantly enhanced with positive correlation (R = 0.527, p = 0.044) (Figure 2).

2). MI and target motion three-dimensionally: It is recommended that for tumor motion of > 10 mm, we need to reduce the movement by breath control devices, such as Active Breathing Coordinator or RPM gating system. The patients were divided into two groups: 3D vector of ≤ 10 mm vs. > 10 mm. Mean MIs of ITV2M were 0.94 ± 0.01 and 0.92 ± 0.04 (p = 0.542), and mean of MIs of ITV2Phase 0.88 ± 0.04 and 0.89 ± 0.06 (p = 0.756), respectively for the former and the latter. There was no significant correlation between the magnitude of target motion and MI.

3). MI and ratio of tumor vertical diameter over tumor motion magnitude in cranio-caudal direction: As shown in Figure 3, for ITV2M when vertical diameter over tumor motion magnitude in cranio-caudal direction increased MI was increased slightly, but with no significant correlation (R = 0.352, p = 0.198). However, for ITV2Phase there was a positive correlation between them (R = 0.535, p = 0.040).

Table 4 MI values for four ITVs based on ITV2M, ITV2Phase, ITVMinIP and ITVMIP relative to the reference ITVAllPhases

| Patient | ITV2M | ITV2Phase | ITVMIP | ITVMINIP |
|---------|-------|-----------|--------|----------|
| 1       | 0.83  | 0.82      | 0.61   | 0.78     |
| 2       | 0.94  | 0.92      | 0.86   | 0.83     |
| 3       | 0.89  | 0.91      | 0.86   | 0.72     |
| 4       | 0.93  | 0.91      | 0.71   | 0.93     |
| 5       | 0.89  | 0.75      | 0.87   | 0.73     |
| 6       | 0.91  | 0.81      | 0.91   | 0.58     |
| 7       | 0.94  | 0.89      | 0.58   | 0.93     |
| 8       | 0.95  | 0.87      | 0.95   | 0.72     |
| 9       | 0.94  | 0.95      | 0.79   | 0.92     |
| 10      | 0.95  | 0.90      | 0.68   | 0.92     |
| 11      | 0.95  | 0.89      | 0.94   | 0.86     |
| 12      | 0.95  | 0.92      | 0.95   | 0.75     |
| 13      | 0.93  | 0.89      | 0.80   | 0.84     |
| 14      | 0.96  | 0.96      | 0.89   | 0.93     |
| 15      | 0.96  | 0.94      | 0.95   | 0.84     |
| Mean    | 0.93  | 0.89      | 0.82   | 0.82     |
| SD      | 0.04  | 0.06      | 0.12   | 0.10     |
For the tumor of low density or mixed density, there was no significant difference in MIs between them for both ITV数据分析2M and ITV数据分析2Phase, MIs of ITV数据分析2M being 0.93 ± 0.02 and 0.92 ± 0.05 (p = 0.676), and MIs of ITV数据分析2Phase. 088 ± 0.07 and 0.90 ± 0.05 (p = 0.702), respectively for low density tumor and the mixed. However, for low density tumor MI of ITV数据分析MinIP was better than that for mixed density tumor with MI of 0.90 ± 0.05 and 0.71 ± 0.11 (p = 0.001), respectively.

We also noticed that for low density tumors, which located within liver parenchyma and were not closed to adjacent organs, such as 5th, 6th, 8th and 12th patient (Table 1), when using ITV数据分析MinIP mean MI was 0.92 ± 0.04, while using ITV数据分析2M it was 0.93 ± 0.03 with no significant difference between ITV数据分析MinIP and ITV数据分析2M (p = 0.114).

### (3). Proportion of V数据分析under

Figure 4 illustrates the proportions of V数据分析under in 15 patients. Compared to ITV数据分析AllPhases, the proportional V数据分析under of ITV数据分析2M was the lowest (0.07 ± 0.04) with the maximum of 0.17 among ITV数据分析2Phase, ITV数据分析MinIP, ITV数据分析MIP and ITV数据分析2M. While proportional V数据分析under of ITV数据分析2Phase was 0.11 ± 0.06 with the maximum of 0.26. The mean proportion of V数据分析under for ITV数据分析2M were significantly less than that for ITV数据分析2Phase (p = 0.001). However, ITV数据分析MinIP and ITV数据分析MIP underestimated larger volumes, the proportions of V数据分析under being 0.18 ± 0.12 and 0.18 ± 0.11, respectively.

The analyses of tumor characteristics, which would impact proportion of V数据分析under were as follows.

#### 1). Proportion of V数据分析under and tumor volume:

There were no correlations between the diameter of GTV and the proportion of V数据分析under for ITV数据分析2M, no matter the diameter over than or less than 5 cm. The proportions of V数据分析under were respectively 0.06 ± 0.02 and 0.08 ± 0.05 (p = 0.244). However, there was significant difference in proportion of V数据分析under between tumor size of ≤ 5 cm and > 5 cm with proportions of ITV数据分析2Phase being 0.08 ± 0.03 and 0.15 ± 0.07 (p = 0.018), respectively. For ITV数据分析2M as tumor size increased the proportions of V数据分析under did not change significantly with no correlations between them (R = -0.340, p = 0.215). In contrast, for ITV数据分析2Phase there was negative correlation between GTV volume and the proportion of V数据分析under (R = -0.528, p = 0.043) (Figure 5).

#### 2). Proportion of V数据分析under and target motion three-dimensionally:

There was no strong correlation between 3 victor tumor motion of ≤ 10 mm and > 10 mm, and the proportions of V数据分析under were 0.06 ± 0.01 and 0.07 ± 0.04 (p = 0.480) for ITV数据分析2M, and 0.12 ± 0.04 and 0.10 ± 0.07 (p = 0.758) for ITV数据分析2Phase.

#### 3). Proportion of V数据分析under and ratio of tumor vertical diameter over tumor motion:

For ITV数据分析2M there was no strong correlation between them (R = -0.344, p = 0.210). However, for ITV数据分析2Phase as ratio of tumor vertical diameter over tumor motion increased the proportions of V数据分析under decreased significantly (R = -0.523, p = 0.040) (Figure 6).

#### 4). Proportion of V数据分析under and tumor density:

For both low density and mixed density tumors there was no significant difference in the underestimations, regardless ITV数据分析2M or ITV数据分析2Phase. For ITV数据分析2M the proportions of V数据分析under were 0.06 ± 0.03 and 0.07 ± 0.05 (p = 0.723),

![Figure 4](https://example.com/f4.png)

**Figure 4** The proportional volumetric underestimations of each ITV (ITV数据分析2M, ITV数据分析2Phase, ITV数据分析MinIP and ITV数据分析MIP) relative to the reference ITV数据分析AllPhases in the 15 individual patients.

![Figure 5](https://example.com/f5.png)

**Figure 5** Relationship between gross tumor volume and proportional volumetric underestimations of ITV数据分析2M and ITV数据分析2Phase.
respectively for low density tumor and the mixed, and for ITV2Phase they were 0.12 ± 0.07 and 0.11 ± 0.05 (p = 0.680). However, when using ITV_MinIP the underestimated proportion was 0.10 ± 0.06 for 9 low density tumors, but it was 0.29 ± 0.11 for 6 mixed density tumors (p = 0.001).

As for MI in 5th, 6th, 8th and 12th patient, when ITV_MinIP was used the mean proportion of V_under was 0.08 ± 0.04, while it was 0.07 ± 0.03 when ITV2M was used (p = 0.094).

(4). V_over

Compared to ITVAllPhases, the percentages of V_over were all less than 1% for ITV2Phase, ITV_MinIP, ITV_MIP and ITV2M.

Discussion
MIP method as an image post-processing is based on more complex algorithms and can be used for generating three-dimensional vascular reconstructions [14,15]. In lung cancer, MIPs are believed to be a reliable tool to generate ITVs from 4D CT data sets [10], however, it is mandatory to modify each individual MIP to improve ITV delineation for tumors adjacent to the thoracic wall, mediastinum, heart, or diaphragm [11,12]. In the current study, we also had to verify ITVs contoured on MIP and MinIP CT by overlaying it on a movie loop displaying 4D CT data and then editing it, especially for those closed to adjacent organs. Mancosu had recently proposed a semiautomatic technique, which allowed for inclusion of the residual part of ITV covered by liver and spleen cupula when using MIP algorithm. It was validated on phantom and selected patients, which revealed this possibility when lesion located near liver and spleen cupula by performing only the contours on MIP series [16]. Thus, the dedicated software needs to be developed to exclude diaphragm and chest wall in some breathing phases using 4D CT for better tumor MIP/MinIP images.

Theoretically, for tumors with homogeneous hyper-density or hypodensity compared to the surrounding normal liver, MIP or MinIP projections should accordingly reflect the tumor trajectory across all time-resolved data sets. In patients when the lesions were homogeneous low CT density, located intrahepatic, not adjacent to perihepatic organs and also small size (5th, 6th, 8th and 12th patient), using MinIP was also an appropriate tool with good MI of 0.92 ± 0.04 and low proportion of V_under of 0.08 ± 0.04. Thus, ITV_MinIP method can be used for fast contouring of liver tumor with homogeneous low CT density including respiratory motion.

However, a number of liver cancers present inhomogeneous density, results from this study showed combined MIP and MinIP fit excellently in this situation. In current study we compared MIs and proportions of V_under resulting from ITV2Phase, ITV_MinIP, ITV_MIP and ITV2M contoured by 4 approaches, and found that the closest to ITVAllPhases was the combined one (ITV2M) of ITV_MinIP and ITV_MIP, which were contoured on MinIP and MIP series of 4D CT set because it resulted in the highest MI and lowest proportion of V_under. Moreover, the size of tumor and the ratio of tumor vertical diameter over cranio-caudal movement did not have influence on MI or proportion of V_under when using ITV2M.

In other words, no matter how big the tumor was, and the tumor vertical diameter over cranio-caudal movement was small or big, the tool of ITV2M could always result in the best outcome.

For moving target it was also a practice to sum 2 GTVs to generate ITV, one contoured on CT image set acquired after end-inhale and holding breath and the other contoured on CT acquired after end-exhale and holding breath when 4D CT was not available. The similar method was also used for 4D CT, i.e., to contour only two extreme phases at end-inhalation and end-exhalation. However, possible hysteresis effects would be neglected as occurred in lung cancer [17,18]. Seppenwoolde and colleagues [18] reported that when the tumor was small and had a large range of motion, the separation between the positions of the images of inspiration and expiration phases was relatively obvious and the information of the intermediate breathing might not be comprehensive. Besides, the combined images of
the two time phases might omit the lag of the tumor. The phenomenon was caused by the time difference among the document recorded by the computer, the transition of respiratory cycle and the transition between inspiration and expiration in a respiratory cycle. Xi [9] reported the feasibility of using limited 4D CT images for treatment planning for liver radiotherapy. As recognized by the authors, deriving ITV by two extreme phases was reasonably safe only for low and medium tumor motion amplitude (< 1.6 cm). The tumor motion in cranio-caudal direction between Xi’s study and ours’ were comparable, but the tumor size of our data (152.20 cm$^3$ ± 242.85 cm$^3$) was more diverse than Xi’s (70.36 cm$^3$ ± 66.23 cm$^3$). Xi did not investigate the influence of tumor size on ITV determination using 4D CT data. Our study did find a smaller volume of ITV$_{2M}$Phase (186.8 cm$^3$) than that of ITV$_{AllPhases}$ (208.0 cm$^3$) with significant difference ($p = 0.004$). And also we found that MI and proportion of V$_{under}$ were influenced by the tumor volume and the ratio of tumor size over tumor motion magnitude significantly. Whereas, ITV$_{2M}$ was the closest to ITV$_{AllPhases}$ and MI and proportion of V$_{under}$ were not influenced by tumor volume and the ratio of tumor size over tumor motion magnitude when using tool of ITV$_{2M}$.

Conclusion
To reduce the workload of contouring multiple GTVs in 4D CT data sets, contouring only two extreme phases is appropriate only when tumor volume is big and tumor motion magnitude is relatively small. For hepatic malignancies with inhomogeneous density we found that the method of using ITV$_{2M}$ was a more reliable and appropriate tool for generating ITVs from 4D CT data sets, compared to the others.

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Authors’ contributions
ZJD and XJL designed the study. LJ, WJZ and ZJD did the study and wrote the manuscript. XJL was responsible for manuscript revision and submission. WJZ and XZY were involved in 4D CT simulation and data analysis. All authors read and approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

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