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Assessing splenic enlargement on CT by unidimensional measurement changes in patients with colorectal liver metastases

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Abstract

Purpose—The aim of this study was to assess splenic volume and to correlate unidimensional measurements with reference volumetric changes in chemotherapy-treated patients with colorectal cancer (CRC) liver metastases.

Methods—Forty consecutive patients were selected from the cohort of a previously reported study of chemotherapy-related morbidity following major hepatectomy for CRC liver metastases. Patients were treated for 6 months prior to resection, with imaging performed at baseline and after 6 months of chemotherapy. Three unidimensional spleen measurements were recorded—width, thickness, and height (*W*, *T*, and *H*). Reference splenic volume was measured at baseline and after chemotherapy. The best unidimensional splenic measurement was determined by regression analysis. The 95% CI for the predicted values and R^2 values was calculated for each regression. The percentage of volume increase at 6 months was calculated.

Results—*W* and *H* showed the highest correlation with splenic volume prior to and following chemotherapy ($R^2 = 0.65$ – 0.74 , $p < 0.001$), while *T* showed a low correlation ($R^2 = 0.11$ and 0.18 , $p < 0.05$). The mean reference splenic volume increased after 6 months of chemotherapy compared to baseline (326 vs. 278 mL). Splenic volume changes showed the highest correlation with changes in *W* ($R^2 = 0.56$, $p < 0.001$), then *H* ($R^2 = 0.40$, $p < 0.001$), but were not significantly correlated with changes in *T* ($R^2 = 0.01$, $p = 0.055$).

Conclusions—Our results show the potential utility of measuring changes in splenic width to predict clinically significant changes in splenic volume in chemotherapy-treated patients with CRC liver metastases.

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Conflict of interest. The authors declare that they have no conflict of interest.

Keywords

Splenic volume; Splenomegaly; Colorectal cancer liver metastases; Hepatectomy; CT imaging; Chemotherapy

Increase in splenic volume has been observed in colorectal cancer (CRC) patients undergoing oxaliplatin-based chemotherapy [1–4]. However, identification of splenic enlargement, or splenomegaly, can be subjective even when performed via imaging [5]. Radiological assessment is often used to confirm splenomegaly, as 16% of clinically palpable spleens were found to be normal after radiological evaluation [6]. Computed tomography (CT) enables accurate, non-invasive estimation of splenic volume, but consensus about the definition of splenomegaly is lacking [7, 8]. One can estimate spleen size simply using craniocaudal length or maximum longitudinal dimension from cross-sectional imaging methods, however, due to normal anatomic variation of the organ's shape, a common definition of splenomegaly based on these measures is problematic [7, 9]. Splenic index, calculated by the product of anteroposterior width (W), transverse thickness (T), and craniocaudal height (H), may offer a better measure of splenic volume than unidimensional measurements. More accurate but time-consuming methods, such as the summation of the cross-sectional areas taking into account the slice thickness, or use of the prolate ellipsoid formula, $W \times T \times H \times 0.52$, also provide estimates of splenic volumes [1, 3, 8, 10, 11]. Both of these methods assume an upper limit of 314.5 mL for normal splenic volume [7, 8, 11, 12].

A method to assess splenic enlargement that is both accurate and practical would be helpful for patients with CRC liver metastases as those who develop splenomegaly as a result of chemotherapy are at risk for complications [13]. Although the radiological studies cited above have emphasized accuracy of splenic volumetry to evaluate for splenomegaly, the existing methods are cumbersome in clinical practice [7, 8, 11, 12]. Our hypothesis is that a unidimensional change can accurately reflect a splenic volumetric change following chemotherapy. To this end, the purpose of this study was to assess splenic volumes in CRC patients with liver metastases undergoing chemotherapy and to correlate unidimensional measurements with reference volumetric changes.

Methods and materials

Patient selection

Our hospital's Institutional Review Board approved this study via a waiver of the Health Insurance Portability and Accountability Act. In this retrospective study, 40 consecutive patients were selected from a cohort of 384 patients included in a previously reported study of chemotherapy-related morbidity following major hepatectomy for CRC liver metastases [14]. The 40 patients were treated with chemotherapy for 6 months prior to resection, with imaging performed at baseline (before chemotherapy) and after 6 months of chemotherapy (before resection). Chemotherapy regimens consisted of either FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) [15]. Splenic measurements were performed at baseline (0 months) and 6 months. Patient age,

gender, and weight were collected prospectively and reviewed retrospectively. The median age of the study population was 61 years (range 28–83 years) and 67% of patients were male. Both the chemotherapy and surgical management have been described previously [16].

Image analysis

Contrast-enhanced CT images acquired during the portal venous phase were reviewed by a medical student, under supervision by an attending radiologist, on a PACS workstation (picture archiving and communication system, Centricity PACS 2.0, GE Healthcare, Milwaukee, WI, USA), and with a GE Advantage Workstation available for multiplanar reconstruction. Three unidimensional measurements of the spleen were undertaken—width (W), thickness at the hilum (T), and height (H) (Fig. 1). Splenic W was defined as the maximum length measured on transverse images, regardless of obliquity. Splenic T was defined as the maximum perpendicular length on the transverse section at the splenic hilum where splenic vessels enter and leave the spleen. Splenic H was measured as the maximal craniocaudal dimension by one of two methods. If the slice positions were available for the transverse images on PACS, the difference between the first and last slice position was used to calculate H ; alternatively, if unavailable, the difference between the first and last slice number (the total number of slices covered by the spleen) was multiplied by the slice thickness (which ranged from 0.8 to 7.5 cm). Splenic index (SI) was calculated with the following formula: $SI = W \times T \times H$. Splenic ellipsoid volume (EV) was calculated with the following prolate ellipsoid formula: $EV = SI \times 0.52$ [17]. An attending radiologist measured the same three unidimensional spleen lengths (W , T , H) 6 months later.

Reference splenic volume was measured using Scout™ Liver (Pathfinder Technologies, Nashville, TN), commercial software for preoperative liver planning. Scout Liver generates a three-dimensional model using contours derived from the organ. While the software is intended for three-dimensional reconstruction of the liver, the spleen is easily segmented due to its obvious contour and the presence of neighboring fat (Fig. 2).

We used two strategies to define splenic enlargement based on the reference splenic volume provided by the Scout software. First, an upper limit of 314.5 mL for splenic volume was defined as normal [7, 8, 11]. Second, an increase of >39% from baseline measure was determined to be associated with major complications and, therefore, clinically relevant [13].

Statistics

Clinicopathological factors were expressed as mean ($\pm$ standard deviation) or median (range), as appropriate. Reference splenic volume and unidimensional measurements (W , T , and H) were expressed as mean (range). All statistical analyses were performed with SPSS version 21 (IBM Corporation). To determine which unidimensional measurement is the best indicator of splenic volume, regression lines were generated separately between splenic volume and predictors. The 95% confidence interval for the predicted values and R^2 values (Pearson's correlation coefficient) were calculated for each regression. The percentage of spleen volume increase was calculated at the 6-month time point. Intra-class correlations

were calculated between splenic unidimensional measurements performed by the two readers.

Results

Splenic volumes

The mean ($\pm$ standard deviation) of the reference splenic volume for the study group was 278 ($\pm$ 148.2) mL and 326 ($\pm$ 147.5) mL at the baseline and 6-month time points, respectively. At baseline, 12 patients were determined to have splenic enlargement, which was defined as greater than 314.5 mL (Fig. 3). At 6 months, 18 patients had splenic volumes >314.5 mL. Of these 18 patients with enlarged spleens, 7 had newly developed splenomegaly from baseline, whereas 11 patients had splenomegaly diagnosed at baseline. Of note, 1 of the 12 patients with splenomegaly at baseline subsequently showed a reduction in volume to below 314.5 mL.

Comparison of unidimensional measurements and ellipsoid volumes with splenic reference volumes

We calculated intra-class correlations between the two sets of splenic unidimensional measurements performed by the two readers. This demonstrated near perfect agreement of the measurements at baseline and 6-month follow-up, for W , ICC = 0.994 (95% CI 0.989–0.997) and 0.990 (0.982–0.995) and for H , ICC = 0.996 (0.992–0.998) and 0.994 (0.989–0.997). For T , substantial to near perfect agreement was found, with ICC = 0.887 (0.785–0.941) and 0.759 (0.554–0.873) at baseline and 6-month CTs. We then compared reference splenic volumes at baseline and after 6 months of chemotherapy with unidimensional measurements (W , T , and H) of the spleen performed by one of the two readers (Table 1; Fig. 4). At baseline, both H ($R^2 = 0.70$, $p < 0.001$) and W ($R^2 = 0.65$, $p < 0.001$) were better correlated than T ($R^2 = 0.11$, $p < 0.05$). Similar results were also found at 6 months (Fig. 5). Ellipsoid volumes were similarly correlated with reference splenic volumes at baseline ($R^2 = 0.84$, $p < 0.001$) and 6 months ($R^2 = 0.86$, $p < 0.001$) after chemotherapy (Figs. 4, 5; Table 1).

Changes in volumes after treatment

We next correlated changes in unidimensional measurements (W , T , H) and reference splenic volumes (Table 2; Fig. 6). A change in splenic volume occurring between 0 and 6 months was correlated with W ($R^2 = 0.56$, $p < 0.001$) and H ($R^2 = 0.40$, $p < 0.001$). Changes in splenic volume showed higher correlation with W than with EV ($R^2 = 0.50$, $p < 0.001$), whereas splenic volume changes were not significantly correlated with T ($R^2 = 0.01$, $p = 0.055$) (Fig. 6). The linear regression equations for W and H are as follows:

$$\Delta W = 0.021 (\% \text{ volume change}) + 0.045 \quad (1)$$

$$\Delta H = 0.027 (\% \text{ volume change}) - 0.156 \quad (2)$$

When patient weight was factored into the model, the results improved modestly for W ($R^2 = 0.62, p < 0.001$) and H ($R^2 = 0.46, p < 0.001$). The multiple linear regression equations for W and H with weight factored in are as follows:

$$\Delta W = 0.022 (\% \text{ volume change}) + 0.011 (\text{weight}) - 0.832 \quad (3)$$

$$\Delta H = 0.028 (\% \text{ volume change}) + 0.015 (\text{weight}) - 1.415 \quad (4)$$

Comparison of changes in unidimensional measurements with changes in reference spleen volumes

Equations (1–4) were used to predict changes greater than 39% in reference splenic volume. Subbing into Eqs. (1) and (2), unidimensional changes for splenic width and height were 0.9 and 0.9 cm, respectively. Using the average weight of the cohort for Eqs. (3) and (4), unidimensional changes for splenic width and height were 0.9 and 0.9 cm, respectively. Most of the variation in W and H is explained by volume change as evidenced by modest improvement in R^2 when weight is factored into the regression. These linear equations show that a change of >0.9 cm in width or height predicts a splenic volumetric enlargement of approximately 39%, which has been associated with major complications [13].

Discussion

In patients with CRC liver metastases, splenic enlargement can often develop following chemotherapy, with potential clinical complications [1–4]. Because CT imaging is routinely used to monitor the response of liver metastases, it provides an opportunity for the detection of splenomegaly in this patient population. Unfortunately, with a wide range of definitions for the upper limits of normal splenic volume on CT imaging, a single size cutoff for splenomegaly may not be useful for individual patients [7, 8, 12]. In addition, while individual unidimensional measurements of the spleen such as width (W), thickness (T), or height (H) have been used to define splenomegaly, studies report that splenic volumetry is more accurate. However, splenic volume estimate by ellipsoid formula or three-dimensional measurements with software may not be practical in daily clinical practice. In this retrospective study, we investigated the relationship between changes in unidimensional measurements to changes in reference splenic volume, in patients with CRC liver metastases after six months of chemotherapy.

The results of our study showed that W and H correlated well with splenic volume before and after chemotherapy ($R^2 = 0.65$ – $0.74, p < 0.001$). This result is concordant with that by Lamb et al. [10], who observed a similar relationship between craniocaudal height and splenic volume ($R^2 = 0.83, p < 0.001$). Other studies have shown that height correlates well with splenic volume, although estimates of splenic volumes based on the product of all 3 dimensions show the most significant correlation [8], as was seen in our study ($R^2 = 0.84$ – $0.86, p < 0.001$) (Table 1; Figs. 4, 5). In contrast to our results, Prassopoulos et al. found that splenic T correlated best with normal splenic volume in children [18], whereas we found the lowest correlation between T and splenic volumes in our adult CRC patient population ($R^2 =$

0.11–0.18, $p < 0.05$) (Table 1; Figs. 4, 5). We often noticed a lobulated contour of the spleen at the splenic hilum, which may account for the less reliable use of T for splenic volumes in our patient population. Furthermore, the interobserver agreement was slightly smaller for T than it was for H and W measurements.

We also found statistically significant correlation between reference volumetric changes and changes in unidimensional measurements for W ($R^2 = 0.56$, $p < 0.001$) and H ($R^2 = 0.40$, $p < 0.001$), following 6 months of chemotherapy, but not for T ($R^2 = 0.01$, $p = 0.055$).

Interestingly, changes in the calculated splenic ellipsoid volume ($R^2 = 0.50$, $p < 0.001$) did not correlate better than changes in W ($R^2 = 0.56$, $p < 0.001$), possibly because the ellipsoid volume formula also depends on T (Table 2). Our results suggest that a change in splenic W or H can be used in clinical practice to estimate volumetric changes.

A range of upper limits of craniocaudal height have been proposed, from 9.76 to 13.9 cm [8, 19–23]. For most radiologists, $H > 13$ cm is considered a specific indicator of splenomegaly [19]. Our results show that of the three unidimensional measurements H was best correlated with reference splenic volume (Table 1). However, in the assessment of splenic enlargement, changes in W showed a somewhat better correlation than H and EV , and changes in W can therefore be used for clinical purposes. Based on linear regression analyses, a >0.9 cm increase in either width or height is a predictor of clinically relevant splenic enlargement in our population.

This retrospective study has several limitations. Our sample size was small, with only 40 subjects, limited by the number of patients who underwent chemotherapy for 6 consecutive months. Splenic volumes were determined from images archived on PACS, and the slice thickness was not consistent for all patients (and sometimes as large as 0.75 cm), thus reducing the accuracy for our measurements of H . Coronal reformats from thin-slice source images would have been preferable had this study been done prospectively. A few of our patients had prior systemic chemotherapy before their treatment at our institution, the details of which were not consistently available from their electronic medical record. Nevertheless, we limited our study to patients who had 6 months of chemotherapy at our institution, with new baseline and 6-month CT scans. We did not attempt to compare the differences between FOLFOX and FOLFIRI chemotherapy regimens with respect to splenic enlargement as we would need a greater number of patients in each category to make meaningful conclusions. Finally, our results are limited to the specific population of patients with CRC liver metastases, and may not be applicable to patients with other conditions, such as cirrhosis from portal hypertension.

In summary, our results show the utility of measuring changes in splenic width on transverse CT images to predict clinically significant changes in splenic volume in patients with CRC liver metastases treated with chemotherapy. This approach may circumvent the limitation inherent in using a single size cutoff to determine splenomegaly, as normal splenic size is known to vary with patient height and body surface area.

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Fig. 1.

Three unidimensional measurements were performed for each spleen: maximal width or *W* (*dashed line*) and perpendicular thickness or *T* (*dotted line*) at the splenic hilum on transaxial CT images (**A**, **B**); and height or *H* (*dashed line*) defined as the difference between the first and last axial slice position of the spleen, equivalent to the maximal vertical craniocaudal extent (**C**).

Fig. 2.
Example of changes in spleen volume after 6 months of chemotherapy. Splenic volume + percentage increase displayed beneath three-dimensional rendering and corresponding CT.

Fig. 3. Comparison of baseline and 6-month post treatment splenic volumes in 40 patients. Baseline volumes (*gray bars*) are ordered from smallest to largest. Six-month post treatment volumes (*white bars*) are also shown for each patient.

Fig. 4. Scatterplot of the regression analysis of unidimensional measurements and ellipsoid volume correlated with reference splenic volumes in 40 patients at baseline with the 95% confidence interval (dashed lines).

Fig. 5.

Scatterplot of the regression analysis of unidimensional measurements and ellipsoid volume correlated with reference splenic volumes in 40 patients at 6 months with the 95% confidence interval (*dashed lines*).

Fig. 6.

Scatterplot of the regression analysis of changes in unidimensional measurements and ellipsoid volume with percentage changes in splenic reference volumes after a 6-month period with the 95% confidence interval (*dashed lines*).

Table 1

Correlation between unidimensional measurements and reference spleen volumes

Months	Dimension	R^2	p
0	W	0.65	<0.001
	T	0.11	<0.05
	H	0.70	<0.001
	EV	0.84	<0.001
6	W	0.67	<0.001
	T	0.18	<0.01
	H	0.74	<0.001
	EV	0.86	<0.001

W , width on transaxial images; T , thickness at the hilum on transaxial images; H , craniocaudal height; EV, calculated ellipsoid volume; R^2 , Pearson's correlation coefficient

Table 2

Correlation between changes in unidimensional measurements and changes in reference spleen volumes

Comparison dates	Dimension	R^2	p
0, 6 months	W	0.56	<0.001
	T	0.01	0.055
	H	0.40	< 0.001
	EV	0.50	< 0.001

W , change in width on transaxial images; T , change in thickness at the hilum on transaxial images; H , change in craniocaudal height; EV , change in calculated ellipsoid volume; R^2 , Pearson's correlation coefficient