Comparison of computed tomography response criteria after chemoembolization of hepatic carcinoma in dogs

Title:

Comparison of CT Response Criteria Following Chemoembolization of Hepatic Carcinoma in Dogs

Short Title:

CT Response Post-Chemoembolization

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Abstract:

The objective of this study was to evaluate unidimensional (mm), bidimensional (mm^2) or tridimensional (mL) CT tumor measurements for ability to discriminate changes in lesion size and predict survival in dogs with nonresectable hepatic carcinoma (HC) treated with drug-eluting bead transarterial-chemoembolization (DEB-TACE) and to compare CT response via RECIST 1.1 (mm), WHO (mm^2), ellipsoid and spherical volume (mL), and percent necrosis, for their ability to differentiate treatment responders. This was a prospective, single-arm clinical trial. DEB-TACE was performed to varying levels of blood flow stasis in 16 client-owned dogs with

nonresectable HC. CT imaging responses were assessed and compared to MST. Results revealed that initial, follow-up, or changes in unidimensional, bidimensional, or tridimensional tumor measurements were not associated with survival. Larger bidimensional and tridimensional tumor measurements/body weight on initial and follow-up CT were significantly associated with a shorter MST (Bidimensional [p=0.04, 0.016] and tridimensional [p=0.025, 0.015], respectively). A higher percent necrosis on initial CT was significantly associated with shorter MST (p=0.038). Ellipsoid volumetric criteria detected treatment response most frequently, however response classification was not associated with MST. CT bidimensional and tridimensional tumor measurements/body weight prior to and following DEB-TACE may help to predict MST for dogs undergoing DEB-TACE for HC.

Keywords:

Embolotherapy, hepatocellular, liver, RECIST

Abbreviations:

hepatic carcinoma, HC; hepatocellular carcinoma, HCC; drug-eluting bead transarterial chemoembolization, DEB-TACE; median survival time, MST; transarterial embolization, TAE; transarterial chemoembolization, TACE; computed tomography, CT; computed tomography angiography, CTA; Response Evaluation Criteria in Solid Tumors, RECIST; Modified Response Evaluation Criteria in Solid Tumors, mRECIST; World Health Organization, WHO; European Association for the Study of the Liver, EASL; Quantitative European Association for the Study of the liver (qEASL)

Drug-eluting bead transarterial chemoembolization (DEB-TACE) shows promise as a palliative option for dogs with nonresectable hepatic carcinoma (HC). [1–5] A recent study of 16 dogs with nonresectable HC undergoing DEB-TACE reported a MST of 337 days (range, 22-1061) with few complications. [3] Validation of predictive radiological tumor response criteria and identification of prognostic imaging features are critical to guide clinical recommendations.[6] Currently, no standardized CT response criteria have been compared regarding correlation with tumor response or median survival time (MST) for dogs undergoing DEB-TACE or other embolotherapies for HC, complicating assessment of treatment response.

Traditionally, imaging response to oncologic treatment was measured by change in solid tumor size and number, and treatment response classified via WHO and RECIST tumor response criteria. [7–11] These criteria correlated percent change in tumor dimensions with objective response classifications (complete response, partial response, stable disease, progressive disease) to predict treatment effect.[7–9] WHO criteria use bidimensional tumor measurements- the longest diameter multiplied by greatest orthogonal diameter on axial CT imaging. [7,8,12] RECIST versions 1.0 and 1.1 include only a unidimensional measurement of a tumor's longest diameter in the CT axial plane. [9,10] However, both RECIST and WHO criteria rely on linear measurements which are subject to significant intra- and inter-observer variation. [10,13–16] They were designed for systemic therapy response and fall short in evaluating responses to embolotherapy.[13,14,16] The Veterinary Cooperative Oncology Group published a consensus statement establishing a canine RECIST (cRECIST v1.0) based on RECIST 1.1.[17] However this was not validated for predicting response to embolotherapy. In human medicine, RECIST 1.1 lacks accuracy in predicting response post-embolotherapy.[9,15–19]

Recent advances in CT and MRI software allow for novel manual or semi-automated methods of tumor assessment.[6,14,20] These methods, including computer-assisted volumetric assessment, account for 3D tumor asymmetry and quantify smaller changes in size than with unidimensional or bidimensional measurements. [6,14,15] Changes in tumor volumes following treatment can then be classified to show treatment response based on changes in size (Figure 1). [6,15,21] Changes in tumor volumes can be classified based on spherical or ellipsoid response criteria. [6,15,21] In human medicine, ellipsoid volumetric response criteria classify a higher number of patients as responders than RECIST and may better predict survival. [6,15,21]

Our group investigated outcomes for 16 dogs receiving DEB-TACE for HC in a prospective single-arm clinical trial.[3] Classification of stable disease or partial response via elliptical tumor volume response criteria (mL) in 85% of dogs was reported. [3] However, a comparison of elliptical tumor volume response criteria to RECIST 1.1 (mm), WHO (mm^2), ellipsoid and spherical volume (mL), with and without body weight calculations with regard to their ability to identify treatment response was not reported.

The aim of this prospective, single-arm clinical trial of 16 client-owned dogs with nonresectable HC treated with 100-300µm doxorubicin DEB-TACE was to evaluate unidimensional (mm), bidimensional (mm^2) or tridimensional (mL) CT tumor measurements for their ability to discriminate changes in lesion size and predict survival. An additional aim was to compare CT response classification via RECIST 1.1 (mm), WHO (mm^2), ellipsoid and spherical volume (mL), with and without body weight calculations, and percent necrosis, for their ability to

differentiate treatment responders and correlate with survival. The authors hypothesized that tridimensional CT measurements would more frequently identify changes in lesion size and better predict survival and that CT response criteria via ellipsoid volume (mL) with and without body weight calculations would provide greater differentiation among treatment responders and would best correlate with survival.

Materials and Methods:

Case Selection:

Dogs diagnosed with nonresectable HC at XXXXX from April 2010 to July 2015 were prospectively enrolled in the clinical trial and treated with DEB-TACE after informed owner written consent. Study design, procedure protocol, and informed owner consent were approved by Institutional Animal Care and Use Committee.[3]

Dogs were included if a cytologic or histologic diagnosis of HC was obtained and if the mass was determined by a surgeon to be nonresectable via curative intent surgery without substantial risk. Dogs were excluded if they were treated with chemotherapy, radiation therapy, or surgical intervention within 3 months of therapy.[3]

Dogs were staged with standard techniques including three-view thoracic radiography or thoracic CT scan, abdominal CTA, complete blood cell count, and serum biochemistry profile. The first treatment was performed within 30 days of staging.[3]

Medical Records Review:

Medical records review was performed, and data recorded included signalment, weight, diagnostic imaging findings and tumor measurements, DEB-TACE procedural dates, number of treatments performed, and survival times.[3]

Treatment Protocol:

The DEB-TACE procedure was performed as described; dogs were to receive two DEB-TACE procedures 6 weeks apart. [1–3,5] The goal of the first DEB-TACE was drug-delivery only in order to permit persistent tumor blood flow and allow subsequent vessel access for the second treatment performed to blood flow stasis. Following superselective hepatic arterial branch access to the main arterial supply of the mass, 100-300 micron DEBs (Biocompatibles UK Limited, Farnham, UK) loaded with 30 mg/m^2 of doxorubicin (or 1mg/kg if under 10kg) (Pfizer Inc, Andover, MA) was administered.[3] Post-DEB-TACE angiography was performed to determine whether vascular stasis had been achieved. Stasis was achieved if there was no evidence of tumor blush or no continued hepatic arterial flow to the tumor after embolization. [22]

Immediately after DEB-TACE, non-contrast abdominal CT was performed to document treatment and evidence of non-target embolization. [3] Hospital discharge was anticipated the next day.[3,5]

Tumor Response Evaluation:

Dogs had baseline multiphase (arterial with multiple venous phase) abdominal CT angiography (CTA) performed within 1 day prior to initial DEB-TACE.[3] Approximately six weeks later, a

second DEB-TACE treatment was performed immediately followed by a non-contrast abdominal CT. [3]A final multiphase CTA was performed ~12 weeks after the first treatment in conjunction with intravenous doxorubicin (Pfizer Inc, Andover, MA) administration.[3] Dogs completing the entire study would receive four separate CT imaging sessions (CTA before treatment, 2 non-contrast CT's immediately after DEB-TACE, and 1 final CTA ~12 weeks after treatment initiation).[3] Some dogs either did not have a second DEB-TACE treatment performed or only had a second CTA performed after the first DEB-TACE.[3] Since these CTA's were still able to assess response to treatment, they were included in the analysis.[3]

CTA image series were reviewed by a board-certified radiologist (XX) who was aware of the diagnosis and procedures performed. Images were reviewed using a dedicated workstation (Siemens AG, Erlangen, Germany) and oncological imaging software (Siemens AG, Erlangen, Germany). CTA's before and after treatment were compared for the same individual (Table 1). Subjective assessment was performed for hepatic lesion description (number of lesions and lobes involved), portal vein thrombosis, and for degree of lesion necrosis (1: 0-25%, 2: 26-50%, 3: 51-75%, 4: >75% of total mass) (Table 1) based on portal phase CTA images (Figure 2).[3] Manual correction of hepatic lesion borders was performed after automatic delineation by software (Figure 2). Lesion assessment was then generated by the system and included unidimensional measurement (RECIST 1.1 in mm),[9] maximum orthogonal tumor diameter (in mm), bidimensional measurement (WHO in mm^2),[8] and tridimensional measurement (tumor volume in mL)[6] (Figure 1, 2, 3). Tumor response classification via RECIST 1.1, WHO, ellipsoid tumor volume, and spherical tumor volume was performed as previously described **(**Figure 1, Table 2). [6–9,15,21] Significance for survival and ability to detect changes in lesion size was assessed.

Assessment via mRECIST using tumor arterial perfusion could not be performed because not all cases had an arterial phase CTA series of sufficient quality.[11]

Statistical Analysis

Survival time (ST) was defined as duration from date of DEB-TACE treatment to time of death. Descriptive measures were presented as median and range or quantitative variables and frequency (percentage) for qualitative variables. Independent groups were compared using Fisher for qualitative variables, and t-test, Mann-Whitney or Brunner-Munzel test for quantitative variables based on the assumption of normality and equality of variances. Homoscedasticity was tested using Levene test, and normality was tested using Shapiro-Francia test. Survival curves were presented using Kaplan-Meier estimator, and simple proportional hazard Cox models were fitted to estimate hazard ratios with 95% confidence intervals. Marginal homogeneity was tested using McNemar test. Agreement was classified based on Kappa statistic based on 0-0.2 no agreement, 0.21-0.40 slight agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, 0.81-1 almost perfect agreement.[23] All hypotheses were two-sided at 5% significance level. Calculations were performed using R-package, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria)

Results:

Population:

Sixteen dogs diagnosed with nonresectable HC satisfied study inclusion criteria and treated with DEB-TACE at XXXX. [3]

Signalment:

There were 8 male castrated dogs, 7 female spayed dogs, and one intact male dog. The median age at the time of first treatment was 11.1 years (range, 5.8-13.2 years). The median weight was 14.7 kg (range, 6.3-30.8 kg). Breeds represented included Shih Tzu (3), Labrador retriever (1), German wirehaired pointer (1), Schnauzer (1), Beagle (1), Australian Shepherd (1), Pekingese (1) and mixed (7).[3]

Preliminary CTA analysis

All dogs had an abdominal CTA performed 1 day prior to treatment (Table 1). On initial CTA the distribution of hepatic masses was as follows: 7 out of 16 (44%) dogs had a single right-sided mass, 2 dogs (2/16; 13%) had a single left-sided mass, and 2 dogs (2/16; 13%) had a single mass extending from the right side to the caudate lobe. 12/16 (75%) had masses solely or including the right side of the liver while 2/16 (12.5%) were solely left and 2/16 (12.5%) were centrally located masses.[3]

DEB-TACE and Chemotherapy Treatments

Treatments performed and survival are previously reported.[3] MST for all of the dogs from the first DEB-TACE treatment to date of death was 337 days (range, 22-1061).[3]

CT Tumor Response

Nine dogs had a CT scan following two DEB-TACE treatments, 4 dogs had a follow-up CT scan following a single DEB-TACE treatment, and 3 dogs lacked a CT scan following DEB-TACE.[3]

Tables 1 and 2 report CT tumor size measurements and CT tumor response criteria before and after DEB-TACE.[3,6,8,9,15,21]

On pre-treatment CT imaging, greater percent tumor necrosis (p=0.038), increased tumor size as assessed by bidimensional measurements/body weight (mm^2/kg) (p=0.04), and larger tumor size as assessed by tridimensional measurements/ body weight (mL/kg) (p=0.025) were all significantly associated with shorter survival times. There were no significant associations between pre-treatment tumor size as assessed via unidimensional measurement (mm) (p=0.085), bidimensional measurement without body weight adjustment (mm^2) (p=0.129), tridimensional measurement without body weight adjustment (mL) (p=0.199), or via unidimensional measurement/body weight (p=0.386) and survival (Table 1).

On post-treatment CT imaging, increased tumor size as assessed by bidimensional measurements/body weight (mm^2/kg) (p=0.016) and increased tridimensional measurements/body weight (mL/kg) (p=0.015) were both significantly associated with shorter survival times. There were no significant associations between tumor size as assessed via unidimensional measurement with without out body weight adjustment (mm) (p=0.083, p=0.089), bidimensional measurement without body weight adjustment (mm^2) (p=0.12), tridimensional measurement without body weight adjustment (mL) (p=0.15), or percent tumor necrosis (p=0.051) and survival times. Stated differently, there was no association between survival and any of the post-treatment CT parameters which did not account for body weight. Only when variation in body weight was accounted for did bidimensional and tridimensional measurements correlate with survival on pre- and post-treatment imaging (Table 1).

Percent change in tumor size following treatment using any of the CT size measurements were not significantly associated with survival, even when correcting for body weight (Table 1). Percent change in tumor necrosis was not significantly associated with survival (Table 1).

There were no significant associations between survival times of the dogs and classification of tumor response as partial, stable, or progressive via ellipsoid tumor volume response criteria ($p=0.11$), spherical tumor volume response criteria ($p=0.165$) or WHO tumor response criteria($p=0.165$) (Table 2). Associations between tumor response classification and survival could not be calculated for RECIST 1.1 because all of the dogs demonstrated stable disease via this criteria (Table 2). Ellipsoid volumetric tumor response criteria detected a wider distribution of treatment responses classification than RECIST 1.1, WHO, or spherical volumetric response criteria (Table 2). However tumor response classification as PR, SD, or PD was not associated with survival with any of the response criteria. Additionally, there was no association between survival and increase/decrease in tumor size based on any of the CT response criteria, including unidimensional ($p=0.577$), bidimensional ($p=0.977$), and tridimensional ($p=0.121$) measurements. Tridimensional measurements detected changes in tumor size (decreased vs unchanged vs increased) more frequently than percent tumor necrosis, unidimensional or bidimensional measurements. However, change in size (increased versus unchanged versus decreased) did not predict survival.

Discussion

In this study, larger tumor size as assessed by bidimensional measurements/ body weight and larger tumor size as assessed by tridimensional measurements/body weight on CTA prior to and following DEB-TACE were able to predict shorter MST for dogs undergoing DEB-TACE for HC.[3] A larger percent tumor necrosis prior to DEB-TACE was also significantly associated with shorter survival. Tridimensional assessments were better able to detect changes in tumor size than uni- or bidimensional assessments. Ellipsoid volumetric tumor response criteria identified a higher treatment response rate than RECIST 1.1, WHO, or spherical volumetric tumor response criteria. Ellipsoid volumetric tumor response criteria classified more dogs with progressive disease or partial response than the other response criteria but classification for all response criteria failed to show an association with survival. Pre-treatment to post-treatment changes in size via uni-, bi-, or tridimensional assessment with or without body weight adjustment did not correlate with survival times.

These findings regarding identification of a wider distribution of treatment responses with the ellipsoid criteria versus other response criteria are in line with human studies reporting ellipsoid volume tumor response criteria showing a higher sensitivity for detecting tumor response [6,15,20]. The irregular outline of tumors in both humans and dogs is thought to more closely resemble an ellipse than a perfect sphere, supporting these findings. [14–16]

Traditionally, response to treatment was measured according to the WHO and RECIST criteria, which presume that tumors grow symmetrically and spherically. However, they measure lesion size without accounting for cellular makeup or viability.[11,16] For a positive WHO or RECIST response post-embolization therapy, the necrosis occurring from embolization must be

298 successfully replaced with local parenchymal regeneration to result in a shorter maximum
299 diameter of the lesion; this assumes both that regional tissues are sufficiently healthy for growth
300 and that sufficient time has elapsed between the intervention and follow-up imaging to capture
301 this phenomenon.[24,25] In humans, studies comparing post-TACE CT with pathology results for
302 hepatocellular carcinoma (HCC) show that the maximum CT response time via WHO or
303 RECIST is approximately 4-6 months post-embolization.[24,25] If the biological behavior of canine
304 HC parallels that of humans, the imaging time frame used in this study may not have allowed for
305 maximal tumor regression.
306
307 The EASL criteria uses contrast-enhanced imaging and bi-dimensional tumor measurement; the
308 EASL identified HCC embolotherapy response approximately 1 month following treatment,
309 which is earlier than the 4-6 months required to assess maximum WHO or RECIST 1.1
310 response.[11,25,26] The mRECIST considers both tumor viability defined as uptake of contrast agent
311 in the arterial phase of CT or MRI and a more simplified response classification compared to the
312 EASL, using only a single tumor diameter.[11,27]
313
314 The assessment of volumetric CT tumor measurements, expedited and standardized by advances
315 in computer software, allows for multi-slice semi-automated tumor contouring, providing a more
316 accurate calculation of tumor burden compared to one and two-dimensional measurements.
317 [6,15,20,28,29] In comparison to linear measurements, volumetric measurements better assess irregular
318 tumor margins and are able to detect changes in tumor size with less intra-observer and inter-
319 observer variability.[6,15,18,20,28–31] In humans, histopathologic tumor responses better correlate with
320 volumetric than linear measurements [6,15,32–34] and volumetric evaluation is more

reproducible.[6,14,15,35,36] The results of our study found increased tridimensional tumor size/body weight prior to and following DEB-TACE to be a negative prognostic indicator. Based on the results in this study, decreased WHO/body weight prior to and following treatment might be used to help predict survival where volumetric software is limited when considering DEB-TACE in certain dogs. However, in human medicine, there is reported to be a lack of standardization of volumetric software being used in clinical research; this is an area of future possible research in veterinary medicine as well.[6]

Tumor size and change in tumor size post-procedurally are prognostic for survival in people with hepatic carcinomas.[16,37,38] In this study, unidimensional, bidimensional, or tridimensional tumor size on CTA before or after DEB-TACE were not predictors of survival. However, tumor size assessments were designed for human adults who have comparatively less variation in hepatic size versus canine breeds. Tridimensional tumor size and bidimensional tumor size before and after treatment did become significantly associated with MST when divided by body weight in this study of dogs with HC. However, the difference in these variables, essentially capturing whether a specific dog's tumor burden grew or shrank did not predict survival, possibly due to the lack of criteria taking tumor necrosis and tumor enhancement into account.

Limitations of this study included variability in treatment protocols, small sample size, use of a single radiologist in assessing the images, and the absence of mRECIST, EASL or qEASL to assess CT data. The timing of post-DEB-TACE imaging varied in this study and some dogs did not have follow-up imaging performed. Post-mortem comparisons of CT measurements to gross lesions size were not performed. A negative control group could have included dogs maintained

on medical management. Larger studies are indicated to both validate these findings and identify differences that this study may have lacked the power to reveal.

In this study, larger tumor burden as assessed by increased bidimensional tumor size/body weight and increased tridimensional tumor size/body weight on CT prior to and following DEB-TACE were identified as predictors for shorter MST for dogs undergoing DEB-TACE for HC. Increased percent tumor necrosis prior to DEB-TACE was also a negative prognostic indicator for survival. This study challenges the implementation of RECIST 1.1, WHO, ellipsoid volumetric measurement, spherical volumetric measurements, RECIST 1.1/body weight, WHO/body weight, or volumetric measurement/body weight criteria for predicting survival following DEB-TACE.

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477 Tables:
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480 **Table 1: CT Response Criteria before and after DEB-TACE for Dogs with HC as Risk Factors for Survival**

Size Measurement	Median (Range)	P-Value	Median (Range)	P-Value	Median (Range)	P-Value	Counts of Change in Size Following DEB-TACE (n=13)		
	Before DEB-TACE (n=16)		After DEB-TACE (n=13)		Percent Change Following DEB-TACE (n=13)		Decreased	No Change	Increased
Unidimensional (mm)	113 (67.7 to 176)	0.085	99.1 (61.4 to 163.3)	0.089	-1 (-25 to 15)	0.95	7 (54%)	1 (7%)	5 (38%)
Bidimensional (mm^2)	7320 (2660 to 19300)	0.13	6410 (1910 to 18800)	0.12	-1 (-46 to 40)	0.75	7 (54%)	2 (15%)	4 (31%)
Tridimensional (mL)	281 (48.7 to 1580)	0.2	258 (45.0 to 1301)	0.15	-26.4 (-267 to 419)	0.39	10 (77%)	0 (0%)	3 (23%)
Unidimensional/ body weight (mm/kg)	7.45 (3.60 to 18.7)	0.386	6.31 (4.39 to 20.1)	0.083	-0.15 (-2.23 to 1.55)	0.71	7 (54%)	1 (7%)	5 (38%)
Bidimensional/body weight (mm^2/kg)	597 (202 to 1900)	0.040*	573 (190 to 2080	0.016*	-13 (-56 to 77)	0.75	7 (54%)	2 (15%)	4 (31%)
Tridimensional/body weight (mL/kg)	30 (5.7 to 87.3)	0.025*	25.7 (3.9 to 117)	0.015*	-13 (-56 to 77)	0.39	10 (77%)	0 (0%)	3 (23%)
Percent Tumor Necrosis	2 (1- 4)	0.038*	2 (1- 4)	0.051	0 (0- 1)	0.35	0 (0%)	9 (70%)	4 (31%)

481 * P-value <0.05; significant p-value suggests larger tumors were associated with shorter survival

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486 **Table 2: CT Tumor Response Classification following DEB-TACE for 13 Dogs with HC**

CT Tumor Response Criteria	Tumor Response Classification			
	Complete Response	Partial Response	Stable Disease	Progressive Disease

RECIST 1.1	0 (0%)	0 (0%)	13 (100%)	0 (0%)
WHO	0 (0%)	0 (0%)	12 (92%)	1 (7%)
Volume (Spherical)	0 (0%)	0 (0%)	12 (92%)	1 (7%)
Volume (Ellipsoid)	0 (0%)	3 (23%)	8 (62%)	2 (15%)

Figure 1: Different size-based criteria with relative geometrically derived-cut-offs for partial response (PR) and progressive disease (PD). Corresponding geometrical shapes are shown at the left side of the figure. Stable disease (SD) corresponds to intermediate changes between PR and PD. Both volumetric imaging response criteria are based on the same CT tumor volume which is then assessed with differing criteria.

Abbreviations: r, r_i (i = 1,2,3), radius; RECIST, Response Evaluation Criteria in Solid Tumors; S, size. Symbols: *appearance of a new lesion.

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Figure 2: Portal venous phase CT images of the liver of a 6-year-old female spayed mixed breed dog with hepatocellular carcinoma in the right liver lobes. The outlined area of contrast enhancement in the portal phase is used to assess tumor volume. Image (A) and Image (B) are in transverse plane; image right is patient left, image top is patient dorsal. Image (C) and Image (D) are in frontal plane; image right is patient left; image top is patient cranial. Image (A) and Image

(C) are prior to DEB-TACE (tumor volume = 591.0 mL). Image (B) and Image (D) are following DEB-TACE (tumor volume = 323.7 mL) showing a 45% decrease in tumor volume.

Figure 3. Automated software generated measurements of a hepatic carcinoma in the liver of a 12-year-old male neutered Pekingese dog following DEB-TACE. Image (A) shows a 3D volume of the liver first generated by the software. Image (B) shows a transverse CT image generated from the previous 3D volume. Generated measurements including the maximal area, length and orthogonal length of a target lesion in a transverse plane CT image, and the lesion volume measured from the dataset, are obtained, and compared for lesion progression. Image right is patient left; image top is patient dorsal.