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Physiological Imaging-Defined Response-Driven Subvolumes of a Tumor¹

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Summary

Dose painting of the physiological imaging-defined subvolumes of the tumors by intensity-modulated radiotherapy is hypothesized to lead to a better outcome than distributing a uniform dose within a target volume defined by anatomic imaging. We developed a general method to delineate the subvolumes of a tumor based upon multiple physiological imaging and tested their complementary roles for assessment of therapy response.

Purpose—To develop an image analysis framework to delineate the physiological imaging-defined subvolumes of a tumor in relating to treatment response and outcome.

Materials and Methods—Our proposed approach delineates the subvolumes of a tumor based upon its heterogeneous distributions of physiological imaging parameters. The method assigns each voxel a probabilistic membership function belonging to the physiological parameter classes defined in a sample of tumors, and then calculates the related subvolumes in each tumor. We applied our approach to regional cerebral blood volume (rCBV) and Gd-DTPA transfer constant (K^{trans}) images of patients who had brain metastases and were treated by whole brain radiotherapy (WBRT). Forty-five lesions were included in the analysis. Changes in the rCBV (or K^{trans})-defined subvolumes of the tumors from pre RT to 2 weeks (2W) after the start of WBRT were evaluated for differentiation of responsive, stable and progressive tumors using Mann-Whitney *U* test. Performance of the newly developed metrics for predicting tumor response to WBRT was evaluated by Receiver Operating Characteristic (ROC) analysis.

Results—The percentage decrease in the high-CBV defined subvolumes of the tumors from pre-RT to 2W was significantly greater in the group of responsive tumors than the group of stable and progressive ones ($p < 0.007$). The change in the high-CBV defined subvolumes of the tumors from

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pre-RT to 2W was a predictor for post-RT response significantly better than change in the gross tumor volume observed during the same time interval ($p=0.012$), suggesting the physiological change occurs prior to the volumetric change. Also, K^{trans} did not add significant discriminatory information for assessing response with respect to rCBV.

Conclusion—The physiological imaging-defined subvolumes of the tumors delineated by our method could be a candidate for boost target, for which further development and evaluation is warranted.

Introduction

The ability of intensity-modulated radiotherapy (IMRT) to deliver high-precision nonuniform dose patterns has brought up a question on how to paint doses in the radiation target volume to improve the therapeutic ratio and outcome (1). Conventional IMRT optimizes and delivers a treatment plan within a target volume primarily based upon anatomic images of computed tomography (CT) and/or magnetic resonance imaging (MRI). Geometrically conforming high doses within the target volume by IMRT can reduce dose-spread into normal tissue and organs at risk. However, target volume delineation based upon anatomic information is increasingly becoming a major limitation. Also, considering spatially-heterogeneous biological properties of a tumor, a uniform dose distribution within a target volume might not lead to an optimal treatment outcome. Hence, dose painting/sculpting based on the biological target has the potential to improve local control or even outcome (2).

The biological target can be defined by *in vivo* functional, metabolic and molecular imaging (1). It has been suggested that a tumor biological target volume could consist of multiple biological target subvolumes that are imaged by multiple functional imaging examinations, each having a prognostic or predictive value for radiation response and outcome. It has been hypothesized that dose painting of the biological target subvolumes defined this way could lead to a better outcome than distributing a uniform dose within a target volume (1-2). However, it lacks a robust methodology to delineate the subvolumes of a tumor based upon physiological imaging and to relate them to tumor response to radiotherapy.

In this study, our goal was to develop an image analysis framework to integrate the physiological and biological information from a variety of functional imaging sources, to delineate the imaging-defined “phenotype” subvolumes of a tumor and to relate them to treatment response and outcome. We applied the proposed strategy to delineate the tumor subvolumes from regional cerebral blood volume (rCBV) and Gd-DTPA transfer constant from blood plasma to tissue (K^{trans}) in patients who had brain metastases and received whole brain radiotherapy (WBRT). We then examined the association of a change in the subvolume of the tumor from pre to during RT with post-RT treatment response.

2. Materials and Method

2.1 Patients

Twenty patients (11 women and 9 men, ages 41-76 years) diagnosed with brain metastases were enrolled in an institutional review board (IRB)-approved prospective MRI study (Table 1). The histology included melanoma (11), non-small cell lung cancer (6), renal cell carcinoma (1), breast cancer (1), and head & neck squamous cell carcinoma (1). All patients received WBRT with a total dose of 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. Thirteen of the 20 patients received Bortezomib during WBRT as a radiation sensitizer as part of a separate IRB-approved study. If a patient had three brain metastases or fewer, all lesions were included in this analysis. If a patient had more than three lesions, only the three largest lesions were included. If a patient had more than three lesions larger than 1 cm³, the

lesions greater than 1 cm³ were also included. As a total, 45 lesions with a median volume of 1.65 cm³ and a range of 0.1-17.6 cm³ were analyzed.

2.2 Imaging and Data Acquisition

All patients had MRI scans on a Philips 3T scanner prior to RT (Pre-RT), 2 weeks after the start of RT (2W), and 1 month after the completion of treatment (1M Post-RT). MRI scans included pre and post Gd-DTPA volumetric T1-weighted images, multi-slice 2D T2-weighted images, and 3D volumetric dynamic contrast enhanced (DCE) T1-weighted images. The 40 image volumes of DCE-images were acquired using a 3D gradient echo sequence in the sagittal plane (a field-of-view of 240 × 240 × 160 (mm), a voxel size of 2 × 2 × 2 (mm³), a flip angle of 20°, TE/TR of 1.04/5.14 msec and a temporal resolution of 6 sec) with a 0.1 mM/kg Gd-DTPA in an injection rate of 2 s/cc.

2.3 Image Analysis

2.3.1 Pre-processing—Using an in-house software package, Functional Image Analysis Tool (FIAT) (3), anatomical and DCE-MR images were co-registered to have a voxel size of 0.9375 × 0.9375 × 3 (mm³). Each lesion of interest was contoured by a physician on the post-Gd T1-weighted images obtained pre-RT, 2W and 1M post-RT. The general Toft model was used to calculate the rCBV and K^{trans} maps as described previously (4).

2.3.2 Probability Density Functions of Physiological Parameters—To analyze the rCBV distributions in lesions and subsequent changes during treatment, a probability density function (PDF) of rCBV of a lesion was generated using a non-parametric PDF estimator. The PDF consists of 150 evenly-spaced points to cover the range of rCBV values for all lesions of interest. A value of PDF at a point x , $H(\text{rCBV} = x)$, of a lesion was calculated as:

$$H(\text{rCBV}=x) \equiv n_i: x - \varepsilon \leq \text{rCBV}_i \leq x + \varepsilon \quad (1)$$

where n_i was the number of voxels within $|\text{rCBV}_i - x| < \varepsilon$, and ε was a smooth factor and set as $\varepsilon = \frac{\sigma}{4}$ where σ denotes the standard deviation of rCBV distribution in the tumor. After calculating Pre-RT and 2W PDFs for each lesion ($H_{\text{Pre}}(x)$ and $H_{2\text{W}}(x)$, respectively), $H(x)$ was normalized to have an area under the PDF curve equal to one ($\int H(x)dx = 1$), see Fig. 1(a). Then, the normalized $H_{\text{Pre}}(x)$ s of all lesions were summed to generate a pooled PDF (H_p) of brain metastases, in which each lesion contributes equally regardless of its size.

2.3.3 Probabilistic Membership Function—Previous studies have suggested that the rCBV distribution of a brain tumor is abnormal compared to normal cerebral tissue, as elevated rCBV in a subvolume of the tumor and low rCBV in another one (5). A renormalization of tumor vasculature, such as decreasing the elevated rCBV and increasing the low one, could be an indicator of tumor response to treatment (6). Our goal is to find a set of probability functions that are associated with high, intermediate and low rCBV classes. Hence, the pooled $H_p(\text{rCBV})$ pre-RT is partitioned into three classes using fuzzy-c-means (FCM) clustering analysis by minimizing an objective function J_m :

$$J_m = \sum_{i=1}^N \sum_{j=1}^C P_j(\text{rCBV}_i)^m \| \text{rCBV}_i - c_j \|^2, 1 \leq m < \infty \quad (2)$$

where c_j is a prototype vector of the j th class, $P_j(rCBV_i)$ is a probabilistic membership of a rCBV value belonging to the j th class, and m is a fuzzy exponent and chosen as 2. The solutions of Eq (1) are determined iteratively by:

$$C_j = \frac{\sum_{i=1}^N P_j(rCBV_i)^m \cdot rCBV_i}{\sum_{i=1}^N P_j(rCBV_i)^m}, \quad (3)$$

$$P_j(rCBV_i) = \frac{1}{\sum_{k=1}^C \left[\frac{\|rCBV_i - C_j\|}{\|rCBV_i - C_k\|} \right]^{\frac{2}{m-1}}} \quad (4)$$

until reaching stopping criteria. The probabilistic membership function, $P_j(rCBV_i)$, is a new representation of a rCBV value of a tumor voxel (mathematically transfers the data from an image space into a new space) see Fig. 1(b). Note that the FCM analysis does not classify a rCBV value into a single class (no hard threshold) rather assigns a probability belonging to a class. A similar computation is applied to K^{trans} .

2.3.4 Physiological-parameter Defined Tumor Subvolume—Our primary interest is to test if a change in the subvolume of tumor defined by high, intermediate or low rCBV classes is related to tumor response to therapy. We define a subvolume (SV) of a tumor with low, intermediate or high rCBV using $P_j(rCBV)$, and calculate a percentage change in SV from Pre-RT to 2W:

$$\widehat{\Delta SV}_{pre \rightarrow 2w, j}(rCBV) = \frac{GTV_{2w} \cdot \int P_j(x) H_{2w}(x) dx - GTV_{pre} \cdot \int P_j(x) H_{pre}(x) dx}{GTV_{pre} \cdot \int P_j(x) H_{pre}(x) dx} \cdot 100, j \in \{low, intermediate, or high\} \quad (5)$$

A similar calculation is applied to K^{trans} .

2.3.5 Association of the Physiological-parameter Defined Tumor Subvolume with Response Endpoint—A percentage change in gross tumor volume (GTV) from pre to post RT was used as an endpoint for response assessment. Several patients did not have 3 or 6 months post treatment imaging follow-ups. For the patients in whom 3 and 6 months post-RT images were available, there were good correlations in the GTV changes between 1 and 3 months post RT and between 3 and 6 months post RT (data not shown). Also, previous studies indicate that brain metastases exhibit little pseudo-response and pseudo-progression one month after RT (7). Therefore, we used a percentage change in the GTV from Pre-RT to 1 month post RT, $\widehat{\Delta GTV}_{pre \rightarrow 1M Post-RT}$, as a measure of tumor response to therapy. From Pre-RT to 1M Post-RT, 16 tumors had a decrease in the GTV at least 25%, defined as responsive, 11 tumors had an increase at least 25%, defined as progressive, and the remaining 18 were defined as stable. We noticed that there were heterogeneous responses of multiple lesions from a single patient. Thus, each lesion was considered independently.

Statistical Analysis: First, we tested if there were any significant differences in changes of $\widehat{\Delta SV}_{pre \rightarrow 2w, j}(rCBV)$ between responsive, stable, and progressive tumors using Mann-Whitney *U* Test. Similar tests were applied to changes in $\widehat{\Delta SV}_{pre \rightarrow 2w, j}(K^{trans})$. To justify multiple comparisons (6 parameters), a p -value < 0.01 was considered as significance. Next,

we performed a *Receiver Operating Characteristic* (ROC) analysis to evaluate sensitivity and specificity of the significant metrics identified in the previous test for predicting responsive tumors using software package ROCKIT (8). Also, we compared these newly developed metrics with the conventional ones: a percentage change in the GTV from Pre-RT to 2W, $\hat{\Delta} GTV_{pre \rightarrow 2W}$, and a change in the mean rCBV (K^{trans}) values of a tumor from pre-RT to 2W, $\hat{\Delta} \mu_{pre \rightarrow 2W}(rCBV(K^{trans}))$, for predicting post treatment response. The significant difference of the area under ROC curves (AUC) between the metrics were compared by *t*-test, for which the standard error and the difference between the two AUCs were calculated by the method proposed by DeLong et al. (9). Also, the leave-one-out technique was used to evaluate the prediction risk of the metrics. Furthermore, we estimated the sample size required for validation of the results in an independent study with $\alpha=0.05$ and power of 0.8 using the data in the current study.

2.3.6 Tumor Subvolume Defined by Combined Physiological Parameters—

Finally, we tested if combining the physiological parameters of rCBV and K^{trans} could improve prediction for tumor response. First, a joint histogram of rCBV and K^{trans} of a lesion is computed, e.g. $H(rCBV = x, K^{trans} = y)$. Then, a joint probability function, $P_{j,k}(rCBV, K^{trans}, \alpha)$, is defined as follows:

$$P_{j,k}(rCBV, K^{trans}, \alpha) = \frac{P_j(rCBV) + \alpha \cdot P_k(K^{trans})}{1 + \alpha}, j, k \in \{low, intermediate, or high\} \quad (6)$$

where α is a weighting factor of the two parameters. Applying the joint probability function to Eq. (5), a percentage change in the subvolume of a tumor defined by rCBV and K^{trans} classes from Pre-RT to 2W is given by:

$$\begin{aligned} \widehat{\Delta} SV_{pre \rightarrow 2W, j, k}(rCBV, K^{trans}, \alpha) \\ = \frac{GTV_{2W} \cdot \int \int P_{j,k}(x, y, \alpha) \cdot H_{2W}(x, y) dx dy - GTV_{pre} \cdot \int \int P_{j,k}(x, y, \alpha) \cdot H_{pre}(x, y) dx dy}{GTV_{pre} \cdot \int \int P_{j,k}(x, y, \alpha) \cdot H_{pre}(x, y) dx dy} \cdot 100, j, k \in \{low, intermediate, or high\} \end{aligned} \quad (07)$$

We selected the weighting factor α that led to a maximum area under the ROC curve for predicting tumor response.

3. Results

3.1 Probability Function Maps

Examples of maps of the probability functions belonging to the high rCBV class, high K^{trans} class and combination of two of a responsive and a stable lesion Pre-RT and at 2W are shown in Fig. 2. Note that the spatial distribution of the probability function map of the high rCBV class of a lesion can be different from one of the high K^{trans} class, and both can change from Pre-RT to 2W. For the responsive lesion, the voxel probability functions belonging to the high rCBV class were reduced to almost zero from Pre-RT to 2W, and for the stable lesion the reduction was in a much smaller extent.

3.2 Physiological-Parameter Defined Subvolumes

We found that the responsive tumors showed a greater decrease in the high-rCBV subvolume of the tumors from Pre-RT to 2W than the progressive tumors ($p < 0.0072$) and a group of combining the progressive and stable lesions ($p < 0.0057$). Also, the decrease in the high-rCBV sub-volume of the responsive tumors was marginally different from the stable ones ($p = 0.033$) (Table 2). Similar but much weaker trends were observed in the decrease of

the high- K^{trans} subvolumes of the tumors between the groups. The percentage decrease in the tumor subvolumes defined by both high-rCBV and high- K^{trans} classes with an equal weighting (described in 2.3.6) from Pre-RT to 2W differentiated the three groups with improved statistical significances, compared to using either variable alone. Specifically, the responsive group differed significantly from the progressive group ($p=0.0012$) and from the group of combining the progressive and stable tumors ($p=0.0017$). For the conventional metrics, a greater decrease was observed in the mean tumor rCBV from Pre-RT to 2W in the responsive group than in the stable tumors ($p<0.0049$) and the group of combining the stable and progressive ones ($p<0.0066$). Also, a decrease in the GTVs of the responsive tumors from Pre-RT to 2W was greater than in the progressive tumors significantly ($p<0.0039$) but marginally from the group of combining the progressive and stable tumors ($p<0.0124$).

3.3 Predictive Values of the Physiological-Parameter Defined Subvolumes

In prediction of post-RT response, the areas under the ROC curves were 0.80 ± 0.07 ($\pm$ SEM), 0.70 ± 0.08 , 0.67 ± 0.08 and 0.60 ± 0.08 For $\hat{\Delta}SV_{\text{pre} \rightarrow 2\text{w}, \text{high}}(\text{rCBV})$, $\hat{\Delta}\mu_{\text{pre} \rightarrow 2\text{w}}(\text{rCBV})$, $\hat{\Delta}SV_{\text{pre} \rightarrow 2\text{w}, \text{high}}(K^{\text{trans}})$, respectively (Fig. 3) indicating that the high-rCBV defined subvolume of the tumor performed the best in predicting the responsive tumors. The change in the subvolume defined by the high-rCBV and high- K^{trans} classes, $\hat{\Delta}SV_{\text{pre} \rightarrow 2\text{w}, \text{high}, \text{high}}(\text{rCBV}, K^{\text{trans}}, \alpha)$, resulted in the largest AUC, 0.86 ± 0.06 . The pair-wise comparison of the ROC curves revealed that $\hat{\Delta}SV_{\text{pre} \rightarrow 2\text{w}, \text{high}, \text{high}}(\text{rCBV}, K^{\text{trans}}, \alpha)$ was a predictor slightly but not significantly better than $\hat{\Delta}SV_{\text{pre} \rightarrow 2\text{w}, \text{high}}(\text{rCBV})$ ($p > 0.18$), or $\hat{\Delta}\mu_{\text{pre} \rightarrow 2\text{w}}(\text{rCBV})$ ($p > 0.05$). However, both $\hat{\Delta}SV_{\text{pre} \rightarrow 2\text{w}, \text{high}}(\text{rCBV})$ and $\hat{\Delta}SV_{\text{pre} \rightarrow 2\text{w}, \text{high}, \text{high}}(\text{rCBV}, K^{\text{trans}}, \alpha)$ were predictors significantly better than $\hat{\Delta}GTV_{\text{pre} \rightarrow 2\text{w}, \text{high}}$ ($p = 0.02$ and $p = 0.01$, respectively). Finally, $\Delta(x00302)\mu_{\text{pre} \rightarrow 2\text{w}}(\text{rCBV})$ was a predictor better but not significantly than $\hat{\Delta}GTV_{\text{pre} \rightarrow 2\text{w}}$ ($p > 0.4$). Also, the application of the leave-one-out technique resulted in the average AUCs of 0.857 ± 0.062 ($\pm$ SEM), 0.79 ± 0.0672 , and 0.68 ± 0.087 for $\hat{\Delta}SV_{\text{pre} \rightarrow 2\text{w}, \text{high}, \text{high}}(\text{rCBV}, K^{\text{trans}}, \alpha)$, $\hat{\Delta}SV_{\text{pre} \rightarrow 2\text{w}}(\text{rCBV})$, and $\hat{\Delta}GTV_{\text{pre} \rightarrow 2\text{w}}$, respectively, suggesting no significant bias in the computed ROCs. Also, it requires a sample size of 110 lesions with 39 responsive ones to validate the results in an independent study.

Discussion and Conclusion

In this paper, we proposed a new approach to delineate the subvolumes of a tumor defined from physiological imaging-parameters and related their early changes to treatment response in patients who had brain metastases and were treated by WBRT. Our proposed approach analyzes the heterogeneous distributions of physiological and/or biological imaging-parameters of the tumors, then assigns each tumor voxel a probabilistic membership function belonging to the physiological/biological classes defined in a sample of tumors, and then calculates the related subvolumes in each tumor. In the application of our approach to rCBV and K^{trans} images of brain metastases, we found that a percentage decrease in the tumor subvolumes defined by the high-rCBV class from Pre-RT to 2 weeks after the start of RT predicted volumetric tumor response one month after RT. The ROC analysis showed that this new metric was significantly better than the decrease in the gross tumor volume (GTV) observed during the same time interval for predicting post-therapy response, suggesting that physiological imaging adds discriminatory information compared to the volumetric change. The framework presented in this study can be applied to other physiological, metabolic or molecular images, e.g., apparent diffusion coefficient and ^{11}C -Methionine PET, to delineate a different physiological-parameter defined subvolume of a tumor. A subvolume of the tumor defined in such way could be a candidate as a boost target.

Our proposed approach differs from the method that generates the parametric response map (PRM) (10) and the one that uses hard thresholding to divide the tumor volume (11). In the

PRM method, after co-registration of a pair of images acquired at two different time points over therapy, a voxel-to-voxel comparison is applied to the images, and a response value is assigned to each voxel according to its change above or below a cutoff threshold. Although analyzing a voxelwise change in a tumor is an interesting approach, mis-registration of the image voxels, particularly in region where a tumor shrinks or grows during the time interval, could compromise the result. In addition, the PRM-based analysis considers an absolute change in $rCBV/K^{trans}$, regardless of the original value of the physiological parameters, whereas an increase/decrease in the low or high-perfused voxels may have a very different implication. For example, a decrease in regions with high perfusion may be more related to treatment response than a decrease in low-perfused areas. Also, while using a threshold value to segment a tumor volume is simple, the binary decision discards parameter continuity at the threshold value. Furthermore, finding an adequate threshold value is always a challenge, and often done empirically and sometimes arbitrarily. In contrast, our approach does not depend upon voxelwise accuracy of image registration or use any hard threshold to determine the subvolume of the tumor. It is worth to point out that our proposed method incorporates the tumor volume into analysis, and thus a change in the defined subvolumes represents both physiological and morphological changes in a tumor, which could increase the sensitivity in prediction of tumor response to therapy as well. Also, although our method does not rely on accuracy of image registration, spatial information of the subvolume of physiological imaging parameters at each time point of measurement is well preserved as shown in Fig 2.

The previous studies have shown that a high mean or regional value of CBV or K^{trans} in the brain tumor prior to therapy is correlated with a high tumor grade (5), and worse outcome (6). A reduction in the high CBV and/or K^{trans} in brain tumors during radiation therapy is associated with better outcome (6). All these suggest that high-CBV and/or K^{trans} in the brain tumor, as an imaging-defined tumor “phenotype”, and the related changes during therapy could be important prognostic and predictive indicators. Our results indicate that the early change in the high rCBV-defined subvolume of the tumor has the potential to be used for selecting the lesion and defining the target for intensified treatment. To improve the performance of the proposed metric (from AUC=0.86), our general approach can be used to test whether including other physiological imaging parameters into analysis, e. g. apparent diffusion coefficient or ^{11}C -MET PET, by creating a joint probability function and joint histogram, can improve prediction of treatment response. This type of analysis can help determine whether multiple physiological and metabolic imaging parameters provide complementary or redundant information. Also, it is interesting to further establish the relationship between the imaging-defined and molecular biology-defined “phenotypes” in the tumor and response to radiation, as it has been shown in a previous study that poor perfusion in head and neck squamous cell carcinoma xenografts is associated with less radiation-induced double-strand DNA damage (12). Therefore, a poorly perfused subvolume of head and neck cancers could be a candidate for boost target (13). The similar concept could also apply to Glioblastoma Multiforme. Here, we tested our proposed methodology in brain metastases, the most common form of intracranial tumors exceeding the number of primary brain tumors by at least ten times and occurring in approximately 25% of all cancer patients (14), for which the focal treatment and early response assessment are becoming more important due to the decrease in neurocognitive status after WBRT (15). However, further development and testing of this method using larger database and other types of tumors warrants its value for outcome prediction and therapy guidance.

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Fig. 1.

(a) The Pre-RT rCBV histogram of a typical lesion (from patient #13) with a tumor volume of 1.26 cm^3 . (b) The pooled PDF (light gray) of the Pre-RT rCBV from all the lesions and the three probability membership functions determined by FCM clustering. The pooled PDF is partitioned into three classes: low (dot-dashed), intermediate (dashed) and high (solid) rCBV classes. rCBV: regional cerebral blood volume, PDF: probability density function.

Fig. 2.

Top row: Pre-RT T1 weighted image (left), and rCBV (middle) and K^{trans} (right) maps of a patient with two brain metastases; Middle and Bottom rows: Probability function maps of the high-rCBV class (Left column), high- K^{trans} class (Middle column) and combination of the two (Right column) overlaid on T1-W images Pre-RT (middle row) and 2W (bottom row). The anterior lesion is responsive and posterior one is stable.

Fig. 3. Left: ROC curves of the metrics listed in Table 2 for predicting responsive tumors; Right: AUC vs α in Eq. (6). FPR: False Positive Rate; TPR: True Positive Rate; AUC: Area Under Curve;

Table 1

Patient characteristics information

Pt. No.	Gender/Age (Y)	Histology	No. of lesions	Volume range (cm ³)	Total accumulated dose/Fx (Gy)	Concurrent drug treatment
1	F/54	BC	3	4.23 - 11.78	37.5/2.5	None
2	M/63	RCC	2	13.23 - 14.67	30/3	Bortezomib
3	M/41	M	3	0.150 - 1.24	37.5/2.5	Bortezomib
4	F/60	NSCLC	1	0.518	37.5/2.5	None
5	F/52	M	1	2.74	37.5/2.5	Bortezomib
6	F/45	M	1	2.07	30/3	Bortezomib
7	M/49	M	2	0.171 - 4.09	30/3	Bortezomib
8	F/51	NSCLC	3	0.503 - 4.55	30/3	Bortezomib
9	M/61	M	4	6.64 - 17.67	37.5/2.5	Bortezomib
10	M/52	NSCLC	1	0.479	30/3	None
11	F/55	M	2	0.421 - 0.545	30/3	Bortezomib
12	M/76	M	1	0.680	30/3	Bortezomib
13	F/46	M	6	1.25 - 1.95	30/3	Bortezomib
14	F/57	M	2	0.941 - 1.58	30/3	Bortezomib
15	F/64	NSCLC	1	0.108	37.5/2.5	None
16	M/60	M	3	0.179 - 1.31	30/3	Bortezomib
17	F/74	M	4	0.690 - 5.81	30/3	Bortezomib
18	M/43	H&N SCC	1	0.601	30/3	None
19	M/58	NSCLC	3	2.38 - 10.69	30/3	None
20	F/66	NSCLC	1	0.954	37.5/2.5	None

Abbreviation: Pt. No. = patient number; Y = year; F = female; M = male; BC = breast cancer; RCC = renal cell carcinoma; M = melanoma; NSCLC = non-small cell lung cancer; and H&N SCC = head and neck squamous cell carcinoma.

Table 2
Differences between Responsive, Stable and Progressive Tumors

Metric	Group of lesions				
	R vs. S	S vs. P	R vs. P	R vs. {S & P}	
	p-value				
$\hat{\Delta}SV_{pre \rightarrow 2w, j}(rCBV)$	j=low	0.1086	0.2517	0.6392	0.1803
	j=intermediate	0.2771	0.3339	0.0513	0.0900
	j=high	0.0338 [*]	0.3568	0.0072 ^{**}	0.0057 ^{**}
$\hat{\Delta}SV_{pre \rightarrow 2w, k}(K^{trans})$	k=low	0.1012	0.8750	0.1910	0.0773
	k=intermediate	0.3088	0.2909	0.8243	0.5613
	k=high	0.6663	0.0162 [*]	0.0406 [*]	0.4992
$\hat{\Delta}SV_{pre \rightarrow 2w, high, high}(rCBV, K^{trans}, 1)$	0.0218 [*]	0.0758	0.0012 ^{**}	0.0017 ^{**}	
$\hat{\Delta}SV_{pre \rightarrow 2w, high, high}(rCBV, K^{trans}, 0.6)$	0.0199 [*]	0.0687	0.0012 ^{**}	0.0015 ^{**}	
$\hat{\Delta}\mu_{pre \rightarrow 2w}(rCBV)$	0.0049 ^{**}	0.2336	0.1088	0.0066 ^{**}	
$\hat{\Delta}\mu_{pre \rightarrow 2w}(K^{trans})$	0.5233	0.1704	0.5704	0.8775	
$\hat{\Delta}GTV_{pre \rightarrow 2w}$	0.1086	0.0653	0.0039 ^{**}	0.0124 [*]	

Abbreviations: GTV = gross tumor volume; R = responders; S = stables; P = Progressive; ^ The optimum value of α is 0.6, see the results of the ROC analysis.

* : P<0.05;

** : P<0.01.