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Viable tumor volume: volume of interest within segmented metastatic lesions, a pilot study of proposed computed tomography response criteria for urothelial cancer

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Abstract

Objectives—To evaluate the ability of new computed tomography (CT) response criteria for solid tumors such as urothelial cancer (VTV; viable tumor volume) to predict overall survival (OS) in patients with metastatic bladder cancer treated with cabozantinib.

Materials and Methods—We compared the relative capabilities of VTV, RECIST, MASS (morphology, attenuation, size, and structure), and Choi criteria, as well as volume measurements, to predict OS using serial follow-up contrast-enhanced CT exams in patients with metastatic urothelial carcinoma. Kaplan-Meier curves and 2-tailed log-rank tests compared OS based on early RECIST 1.1 response against each of the other criteria. A Cox proportional hazards model assessed response at follow-up exams as a time-varying covariate for OS.

Results—We assessed 141 lesions in 55 CT scans from 17 patients with urothelial metastasis, comparing VTV, RECIST, MASS, and Choi criteria, and volumetric measurements, for response assessment. Median follow-up was 4.5 months, range was 2–14 months. Only the VTV criteria demonstrated a statistical association with OS ($p = 0.019$; median OS 9.7 vs. 3.5 months).

Conclusion—This pilot study suggests that VTV is a promising tool for assessing tumor response and predicting OS, using criteria that incorporate tumor volume and density in patients

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receiving antiangiogenic therapy for urothelial cancer. Larger studies are warranted to validate these findings.

Keywords

Segmentation; tumor burden assessment; cancer; oncology

1. Introduction

Standardized response criteria were developed in the 1970s to address the need for objective evaluation of tumor activity during oncologic treatment [1]. The Response Evaluation Criteria in Solid Tumors (RECIST) were published in 2000 by an international collaboration that included the European Organisation for Research and Treatment of Cancer, the National Cancer Institute of the United States (NCI), and the National Cancer Institute of Canada Clinical Trials Group [2]. RECIST evaluates metastatic tumor burden on cross-sectional imaging modalities such as computed tomography (CT). It is based on nonoverlapping slices 0.5 cm thick and uses a unidimensional measure on axial images to evaluate changes in size of the target lesion post-therapy.

However, since RECIST was first developed and updated in 2009 [3], the advent of more advanced CT resolution and semiautomated and automated methods of image measurement have made volumetric assessment more feasible. Several groups have recommended the use of 3D measurements to assess tumor activity [4,5]. Yet despite recent advances in automated algorithms and increased availability of open-source tools [6], volumetric measurements have not been adopted in oncologic evaluations. The authors believe that increased accessibility of robust and more accurate automated 3D measurements will pave the way for this parameter to be incorporated into routine assessments of tumor burden in the near future.

Many antiangiogenic agents such as those that target vascular endothelial growth factor are approved by the U.S. Food and Drug Administration (FDA) and have been used successfully, either alone or in combination with chemotherapy, to treat multiple solid tumors such as renal cell carcinoma, colorectal cancer, non-small cell lung cancer, cervical cancer, glioblastoma, medullary thyroid cancer, hepatocellular carcinoma, and gastrointestinal stromal tumors (GISTs), among others. GISTs [7] have shown closer response-outcome relationships when density (attenuation) measurements have been incorporated in tumor response assessment [8]. However, RECIST does not account for changes in tumor density attenuation, a factor that may result in its underestimation of tumor response to therapies targeting angiogenesis [9,10].

About 500,000 people in the United States are living with bladder cancer (metastatic urothelial carcinoma or non-transitional cell carcinoma of the bladder, urethra, ureter, or renal pelvis). More than 73,000 new cases of bladder cancer are diagnosed annually, and over 15,000 (1 in 42) Americans will die this year from this disease [11]. Yet no new FDA-approved treatments have been developed in the last 25 years [12]. Antiangiogenic targeted agents such as cabozantinib are currently being tested in clinical trials [13]. Incorporating

automated methods that take tumor volume and attenuation distribution into account could help assess response to agents that target the tumor vasculature.

Recent studies [14-16] in metastatic cancer imaging have demonstrated the value of going beyond the use of axial dimensions (as in RECIST), and now take into account tumor density and/or a selective region of interest (ROI). For example, criteria that incorporate attenuation into tumor measurement include MASS (morphology, attenuation, size, and structure) [14], SACT (size and attenuation CT) [15], and modified versions of the Choi criteria (mChoi) [7], [16].

The MASS criteria takes necrosis into consideration by determining “marked central necrosis” such as decreased attenuation to that approximating water density, or central fill-in where a previously low density mass appears to enhance centrally. The Choi (and modified Choi) uses ROI around each tumor, with a mean of all HU values considered along with the longest axis measurements.

Here we introduce a new method of tumor response assessment called VTV (viable tumor volume), which employs automated density and volumetric assessment. VTV accounts for volumetric Hounsfield unit (HU) changes throughout the lesions to quantify changes in viable vs. necrotic tumor tissue. The purpose of the study reported here was to develop new CT imaging criteria for predicting overall survival (OS) in patients with advanced urothelial cancer treated with cabozantinib.

2. Materials and Methods

2.1. Patient population

Patients with advanced metastatic urothelial carcinoma or non-transitional cell carcinoma of the bladder, urethra, ureter, or renal pelvis, including but not limited to squamous cell, neuroendocrine, and adenocarcinoma (including urachal and sarcomatoid), were enrolled in a HIPAA-compliant, open-label, prospective, single-arm, phase II clinical trial of cabozantinib that was approved by the NCI's Institutional Review Board. Patients had to have progressive metastatic disease, defined as new or enlarging lesions on cross-sectional imaging with at least one measurable site of disease according to RECIST 1.1, on prior standard chemotherapy. Patients received 60 mg/day of oral cabozantinib in continuous 28-day cycles. The primary objective was to determine patients' response rate to therapy. A secondary objective was to compare alternative criteria for assessing radiologic response to treatment in metastatic target lesions, including semiautomated volume, SACT, MASS, Choi, and VTV. Patients remained on study until disease progression by RECIST 1.1 and were followed for survival after progression.

2.2. Imaging

CT scans of chest, abdomen, and pelvis were acquired at baseline (pretreatment) and at 8-week intervals following treatment initiation (post-treatment follow-up) using any of the following scanners: Siemens Definition, Biograph or Flash (Siemens Healthcare USA; Malvern, PA), Philips Brilliance (Philips Healthcare; Andover, MA), Toshiba Aquilion ONE™ Vision CT (Toshiba Medical Systems Corporation; Tochigi, Japan), or GE

Lightspeed (GE Medical Systems; Waukesha, WI). Patients with nonmeasurable (i.e., bone-only) disease by RECIST or who had < 2 i.v. contrast-enhanced CT scans were excluded. All patients received contrast-enhanced CT scans using 0.6- to 2.5-mm collimation, 120 kVp, 150–240 reference mAs (with dose modulation), and 0.6- to 0.75-sec rotation time. Images were pushed to our picture archiving and communication system (PACS) as contiguous 5 × 5-mm and 2 × 1-mm overlap axial slices for volumetric and density assessments, coronal, and other reformats. Scans were obtained with patients coached to full inspiration, supine from chest to pelvis in one acquisition, and with weight-based (2 mg/kg) i.v. contrast (Isovue 300 at 2 mL/sec) after a 70-sec delay.

2.3. Image analysis/tumor measurement criteria

A semiautomated PACS tool (Carestream Health; Rochester, NY) segmented volumes by density thresholds to represent viable (50–180 HU) or necrotic (0–50 HU) tissue. Scans were evaluated independently with lesion borders confirmed by consensus of the investigating radiologists (LF, ET) and oncologist (AA). Target lesion measurements by RECIST were compared with measurements obtained by MASS, Choi, and VTV criteria. Imaging response by MASS categorization was termed favorable, indeterminate, or unfavorable.

Lesions were assessed on the portal venous phase for all available CT exams (during treatment period) using a semiautomated PACS toolkit. All patients with CT exams acquired during the treatment period were assessed for OS and date of first partial response (PR). Criteria for tumor evaluation are summarized in Table 1. For all criteria used for tumor evaluation, selection of target lesions followed RECIST 1.1 parameters (2 lesions/organ, 5 total/patient/exam; 1.0 cm in long axis for solid tumors and 1.5 cm in short axis for lymphadenopathy; absolute change of 5 mm) [17]. Response categories were the same as RECIST [18] and included the following:

- Complete response (CR): disappearance of all target and nontarget lesions, and all lymph nodes must be 10 mm in short axis.
- Partial response (PR): > 30% decrease in the sum of longest diameters (target lesions) compared to baseline.
- Progressive disease (PD): > 20% increase in the sum of longest diameters, appearance of 1 new lesions, or unequivocal progression of nontarget lesions.
- Stable disease (SD): neither partial response nor progressive disease.

Target lesions initially selected by an oncologist were measured according to RECIST 1.1, MASS, Choi, and VTV criteria by two radiologists with 20 years of combined experience.

Because of limited numbers of PRs at the 2-month evaluation, imaging responses by VTV criteria were initially pooled into only 2 categories: SD+PR, and PD. Total lesion volume was determined using semiautomated segmentation tools with manual contour edits as needed. Lesion borders were reviewed and confirmed by a tumor-measurement radiologist prior to density assessment. All volume, size, and volumetric density measurements of target

tumors were recorded for baseline and follow-up CT scans. (See Appendix 1 for details of registration and automation for VTV criteria.)

For MASS criteria assessments, we defined “marked central necrosis” as a change in lesion attenuation from solid to near fluid density in > 50% of the lesion. We defined “marked decreased attenuation” as a reduction (≥ 40 HU using a circular ROI) in all or almost all lesion attenuation. Target lung lesions were not evaluated for features of MASS criteria because of partial volume effect limitations with CT. The response criteria based on these findings were termed, as per Smith et al. [14], favorable response, indeterminate response, and unfavorable response.

Using mChoi criteria, tumor attenuation was measured slice-by-slice with a custom ROI along the lesion border, avoiding partial volume effects on borders. We then calculated mean volumetric density of all target lesions. Percent change in mean volumetric tumor attenuation for each patient was used to evaluate response. Good response was defined as a 10% decrease in mean tumor size (by axial measurements) or a 15% decrease in mean tumor attenuation. Patients not meeting good response criteria were described as having a poor response [7].

2.4. VTV

VTV combines volumetric segmentation capability with density analysis (See Appendix 2). Recent studies have demonstrated considerable interobserver variability in the use of rigid ROI tools to assess attenuation in contrast-enhanced CT [19]. As an assessment tool, volume of interest (VOI) that incorporates all tumor voxels has been shown to be more comprehensive and consistent than a single ROI or multiple ROI placed within an axial tumor slice (Fig. 1) [20]. Another study has demonstrated the application of volumetric histograms and the rationale for chosen thresholds [21].

Combining automated segmentation capability with a tool for assessing volumetric density (voxels of attenuation) creates histograms of attenuation that are partitioned into thresholds of a less perfused tumor (0–50 HU, or VTV-low) and a more viable tumor (50–180 HU, or VTV-high). For total volumetric HU, the range was 0–180 to eliminate or minimize skewing from lung or nearby vessels included in segmentations. We applied the same threshold for extrapulmonary lesions, such as in liver and lymph nodes. Change in total voxels over time determined response.

VTV measurements were made using RECIST-defined lesions. Adjustments to the segmented contours were made using the LiveWire tool within our PACS (Carestream Health; Rochester, NY). After satisfactory demarcation, a radiologist reviewed lesion boundaries and confirmed results.

2.5. Histograms

A histogram tool was used separately on each lesion following segmentation. Histogram data were entered into a spreadsheet that included HU summary statistics (HU: mean, median, range, standard deviation) and the proportion of voxels within the thresholded area (cited as the mass number). Figure 2 shows a volumetric histogram that shifts to the left

when a tumor becomes necrotic, allowing the radiologist to quantify necrosis that otherwise could only be assessed subjectively.

Response determinations using volumetric percent change were similar to Choi in that a 30% reduction represented PR and a 20% increase represented PD.

For each lesion, we examined HU threshold subsets:

- VTV-low: 0–50 HU (necrotic/cystic components)
- VTV-high: 50–180 HU (mixed live/dead/cystic components)
- VTV-total: 0–180 HU (represents the entire tumor of interest—e.g., not artifact, fat, calcification, or vessel; probable tumor or semitumoral tissue components)

After we gathered histogram data for each of the HU thresholds for each lesion, we summed mass values for each HU subset for each patient. We partitioned density ranges (low, high, and total) to compare predictability based on level of presumed tumor necrosis. This provided a binary subset of necrosis or not necrosis that appeared useful in phantom trials.

2.6. Statistical Analysis

RECIST response classification (PR, SD, PD) was adapted for Choi and VTV criteria and Kaplan-Meier curves were constructed for each set of criteria. A 2-tailed log-rank test compared OS based on early response (first or second restaging, or 2 to 4 months) determination (SD+PR vs. PD). Because the data suggested that a PR was sometimes initially determined at or beyond the first 2-month evaluation, the impact of time to classification as a PR (at any follow-up exam by each of several methods) on survival was determined by a Cox proportional hazards model using time to PR (or its absence) as a time-varying covariate for OS. Volume, size, and volumetric density measurements of target tumors were recorded at baseline and follow-up CT scans.

3. Results

Evaluable patients ($n = 17$, first 17 consecutive patients enrolled in trial) included 12 men and 5 women (mean age 62 years) who had a total of 141 lesions on 55 baseline and follow-up CT exams. Sites of disease included lymph nodes ($n = 14$), lung ($n = 6$), liver ($n = 6$), soft tissue ($n = 3$), bone ($n = 3$), and kidney ($n = 2$). Thirteen of 17 patients (76%) had 2 sites of disease. Four patients had only one site of disease: 2 in the lymph nodes and 2 in the lung. Median follow-up was 4.5 months (1 restaging scan), range was 2–14 months (1–7 restaging scans).

VTV revealed a statistical association between initial response determinations (with binary tumor response classified as either SD or PR) of total and low-attenuation volume change and OS (2-tailed; $p = 0.019$). Patients with lower-attenuating lesions (presumed tumor necrosis) had the most significant survival prediction using VTV.

The estimated time to complete VTV segmentations and histogram analysis was approximately 10 minutes per lesion.

Other criteria (MASS, mChoi) showed weak ($p = 0.083$) or no association ($p = 0.58$).

When time to classification of PR was evaluated as a time-varying covariate, low-attenuation VTV change demonstrated a trend toward an association with OS ($p = 0.087$; hazard ratio [HR] 0.16; 95% CI on HR: 0.02–1.30). RECIST, MASS or Choi criteria could not demonstrate any association between response determined at any follow-up timepoint and OS. The effect could not be assessed by RECIST, VTV-high, or VTV-total because all PRs determined using these methods were in surviving patients and thus there was no means for estimating the association of responses with death using these measures.

Figure 3 shows how lung lesions that became necrotic to the point of cavitation affected response by VTV, Choi, and MASS, but not by RECIST (minimal size change). Figure 4, which outlines survival curves, shows that only VTV-low or VTV-total determined significant differences between PD and SD+PR.

4. Discussion

Our results suggest that incorporating volumetric measurement and attenuation in tumor response assessment may identify treatment efficacy as early as the first restaging.

To overcome the limitations of traditional tumor response criteria, we developed a combined attenuation and volumetric assessment, termed VTV, to quantify volumetric changes in viable vs. necrotic tumor tissues that respond to antiangiogenic therapy. Recent studies in the imaging of metastatic lesions demonstrate the added value of accounting for tumor attenuation and volume over a selective ROI beyond the axial dimensions accounted for by RECIST [4,5,7-10]. Volume is not assessed by RECIST, MASS, or Choi, and although MASS and mChoi take lesion attenuation into consideration, they are limited to axial ROI. Automated quantification tools are now commercially available within PACS, offering advanced software features that measure volumetric size (rather than 2D measurements) and attenuation (not just ROI on the axial plane alone).

Performing complex volumetric size and attenuation segmentations/determinations within PACS will become more feasible as the technology becomes more accessible to users and it is incorporated into standard radiologic assessments in oncology. Redefined segmentation procedures will allow for more comprehensive assessments. Using automated methods that take volumetric characterization of attenuation distribution into account should help to assess underlying structural changes. A more extensive examination of the relationships between changes in tumor volume, attenuation, and texture and patient outcomes should promote accelerated software development and practical implementation of volumetric tumor analysis.

The VOI algorithm used within our PACS uses normalization to account for all HU values within the volume sampled to avoid negative values (rather between 0 and 1). An extension of this analysis uses kurtosis and texture of densities to characterize thresholded groups of similar-size voxels is a useful method for assessing changes in tumor pattern [22]. Assessing textural changes in tumors with thresholding attenuation values also appears useful for

excluding extreme values due to unrelated tissue (fat, bone, calcifications) and CT artifacts (beam hardening).

In GIST patients treated with tyrosine kinase inhibitors, Choi criteria predict outcomes better than RECIST when i.v. contrast attenuation change is assessed in addition to RECIST size measurements [9]. Studies in patients treated with similar antiangiogenic targeted chemotherapeutic agents also support the use of attenuation as an additional evaluative criterion, especially in highly vascular tumor types [14]. We assessed VOI because the lesions were already segmented for volumetric size. Measuring volumetric size and attenuation is now possible within our PACS, and our new VTV method predicts treatment efficacy as early as the first follow-up CT.

Limitations of this pilot study include a small sample size and potential for tumor attenuation variability across scanners and i.v. contrast administration. Nevertheless, findings from this trial may guide future research. We chose metastatic urothelial carcinoma as a model for cancers with a generally short treatment course to demonstrate the utility of multidimensional assessments in cancers where oncologists make rapid treatment changes. While antiangiogenic agents are effective and FDA-approved for many solid tumors, no antiangiogenic agent is yet approved for the treatment of urothelial carcinoma, although many are in clinical trials. Our use of multiple readers could introduce bias; however, we did not have the resources for additional reads. Because of the mathematical relationship between linear and volume measurements, we elected to use percent change values similar to established criteria (Choi). The appropriateness of these thresholds for volumetric change criteria is uncertain. This is true with volumetric size and the threshold of densities we choose (selected by unpublished phantom trials). The authors note the additional time to segment and analyze lesions take additional time that we believe is not yet feasible in routine workflows.

Variable factors limit the confidence interval for tissue-specific values assessed in this study. Variables such as i.v. contrast administration, amount and timing, cardiac function, inter- and intrascanner variability (some with iterative reconstruction, further varying pixel values), temperature, and reconstruction kernel/noise also affect assessment of HU values. Additionally, since different tube voltage (kVp) settings can affect HU, we kept kVp constant at 120 for consistency.

6. Conclusion

VTV is a more comprehensive approach to assessing tumor burden that quantifies volume and attenuation, reflecting the effect of treatment on tumors. This pilot study suggests that determining tumor attenuation and volume by VTV may predict OS on the first follow-up CT, potentially outperforming other established criteria.

Appendix 1

Registration and lesion management application (algorithm/software) within PACS

Automated registration and semiautomatic segmentation of target lesions were performed on serial CT scans using PACS Lesion Management Algorithm radiology imaging software (Carestream Health v.12.0; Rochester, NY).

Baseline and follow-up CT scans were manually opened and globally registered to align axial planes between the 2 scans. The global registration algorithm employed a fully automated volumetric voxel-based rigid registration algorithm [23]. Tumors were manually located by single-clicking on the tumor or by extending a measurement marker across conglomerated or abutting lesions. PACS software then performed a refined registration, modifying the initial global registration dataset to enhance selected metastatic tumor localization across serial exams [24]. The software automatically segmented the target tumor on both CT scans using enhanced tumor edge detection (not necessarily defining separate lesions) [25]. PACS software automatically coupled segmentation and tumor measurements, providing the longest axial tumor length, perpendicular to longest axial length, short axis, tumor VOI, and mean HU in the segmented area.

Typical segmentation outline edits using a freeform segmentation tool exclude nontumoral components. The lesion tracking tool automatically localizes and segments lesions on post-treatment exams.

Appendix 2

VTV method

The steps required to segment each lesion, follow up, and obtain a histogram for analysis are as follows:

1. Segment lesions (other than liver or lung) using a general segmentation tool.
2. Edit segmentation contours; confirm with radiologist.
 - a. Use LiveWire for incomplete or oversegmentation events.
 - i. Right-click on segmented lesion; select “Correct with LiveWire.”
 - ii. Acts like a magnet. Click to start. Contours based on local threshold (green). Double-click when cut is made.
 - iii. Repeat on each slice.
 - iv. Select “Crop Segmentation from this Plane” for oversegmentation of an additional axial slice.
 - b. To complete segmentation, select “Accept Lesion Segmentation.”

- c. Since the follow-up tool does not work in all instances, link the segmented lesion by right-clicking on it. Select “Define Follow-up Set” and click on the follow-up segmented lesion (should see a star when hovering over lesion).
 - d. Verify lesions on bookmark table (icon with 2 stars).
 - e. Create report when the latest exam is open.
- 3. For each lesion, use histogram to get mass value (number of voxels).
 - a. Right-click on segmented lesion and select “Show Histogram.”
 - b. Partition lesion into 2 subsets based on attenuation threshold.
 - i. Low: 0–50 HU (type ‘0’ in Min text block, ‘50’ in Max)
 - ii. High: 50–180 HU (can subtract from Low)
 - iii. Total: 0–180 HU (Low+High = Total)
 - c. Record mass # (# of voxels in partitioned set) and average HU in XL.
- 4. Combine HU subsets across lesions to get one value for each subset. Enter into SVOI master data. I.e., sum all the 0–50 HU voxels for all lesions in this exam, etc., and sum the 50–180 HU subset.
- 5. Take summed value for subset and compare to equivalent value in later exams to assess tumor response. i.e., compare follow-up #1 (sum all voxels for all lesions in the 0–50 HU subset) to baseline (sum all voxels for all lesions in the 0–50 HU subset).
- 6. Response is defined as percent change in number of voxels in a subset over time.
 - a. Roughly, volume equivalent of Choi size change (i.e., least restrictive criteria).
 - b. Increase of 20% = progression (for Volume, Low, High, Total)
 - c. Decrease of 30% = Partial Reponse

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Highlights

It is clear that 2D axial measurements are incomplete assessments in metastatic disease; especially in light of evolving antiangiogenic therapies that can result in tumor necrosis.

Our pilot study demonstrates that taking volumetric density into account can better predict overall survival when compared to RECIST, volumetric size, MASS and Choi.

Although volumetric segmentation and further density analysis may not yet be feasible within routine workflows, the authors believe that technology advances may soon make this possible.

Figure 1. VTV comprises the segmented VOI and captures areas otherwise missed by ROI, which is limited to axial slice.

Figure 2. Attenuation Assessment

A volumetric attenuation histogram that has shifted to the left on first follow up exam, reflecting potential mediastinal tumor necrosis following antiangiogenic therapy. The baseline axial CT on top shows greater enhancement of the lesion. The CT at (below) shows lower attenuation throughout, indicating necrosis. The corresponding histogram of densities CT essentially quantifies the presumed necrosis.

Figure 3.

Example application of volumetric attenuation demonstrating lung metastasis that becomes cavitary. Note the linear measurements are similar, whereas the volume of remaining tissue is significantly less in this patient responding to therapy.

a .

b .

c .

Figure 4.

Kaplan-Meier curves for VTV [4a], RECIST 1.1 MASS, and Choi [4b] for survival. Only VTV-low / VTV-total (lower histogram threshold) showed a significant difference ($P = 0.019$) in survival between patients with disease progression and patients with stable disease or response to treatment.