Assessing the Many Faces of Tumor Response with Advanced Therapies: Viable Tumor Volume

Les Folio, DO, MPH, MSc, MAS
Col (ret) USAF
Lead Radiologist for CT, NIH CC
Adjunct Clinical Professor of Radiology, George Washington University Hospital
Disclosures, Disclaimers, Conflicts of Interest

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   The NIH Clinical Center PACS shown here
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Overview

• Background: limitations of axial-only criteria (e.g. RECIST)
• Introduction to semi-automated volumetric segmentations
• Pilot volumetric criteria: Viable Tumor Volume (VTV)
• Methods, results, discussion, limitations in urothelial trial
• Ongoing VTV testing in other cancers
• Limitations, challenges applying volumetric criteria
• Future: total body segmentation, cancer cohort heatmaps
• Conclusions
Issues with RECIST

- Not adapted to specific tumor types, newer target agents
- Outgrew original intent; only select lesions (subjective)
- Two dimensional (becoming outdated)
  - Volumetric assessment capability becoming widespread
- Only anatomical assessment; functional characteristics not considered
  - IV contrast enhancement or activity
- Time consuming
  - Especially without automation or digital data management
  - Still handwriting on paper forms
### Tumor Criteria: Taking Necrosis Into Account

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Size</th>
<th>Attenuation/HU</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST 1.1</td>
<td>Linear</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Choi</td>
<td>Linear</td>
<td>Area</td>
<td>N/A</td>
</tr>
<tr>
<td>Modified Choi</td>
<td>Linear</td>
<td>‘Volume’</td>
<td>N/A</td>
</tr>
<tr>
<td>SACT</td>
<td>Linear</td>
<td>Volume</td>
<td>Central necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diffuse decrease</td>
</tr>
<tr>
<td>MASS</td>
<td>Linear</td>
<td>Area</td>
<td>Central necrosis (single lesion)</td>
</tr>
<tr>
<td>VTV</td>
<td>Volume</td>
<td>Volume</td>
<td>Central necrosis vs. viable tumor</td>
</tr>
</tbody>
</table>
Example Successful Segmentation and Resultant Measurements in Melanoma

LTT Finds & measures all (most) previously segmented lesions; then a RECIST report is generated.

Automated Registration, Segmentation, and Measurement of Metastatic Melanoma Tumors in Serial CT Scans

Acad Radiol 2013
Semi-automated Segmentation

- Lesion Management Application in PACS
  - Performs well in lung: 95%
  - Less successful in liver, other organs, nodes
    - Most often needed manual fine tuning with Livewire

- Histograms analyzed of all lesions all voxels
  - Following volumetric segmentation
  - Threshold selected from 0 to 180 HU
    - Established from earlier study on an FDA CT phantom *

* Folio L. European Congress of Radiology presented Mar 2013
  http://dx.doi.org/10.1594/ecr2013/B-0209
AJR: Automation more consistent and more efficient than manual

With LMA most had no difference between observers

LMA was faster than manual; especially on follow-up exam.

Likely due to one click Lesion Tracking Tool

VTV first validated in Cabozantinib (tyrosine kinase inhibitor) Results in all the tumor response “faces”

Vascular Tumor Burden (VTB)

- Amount of vascularized tumor within attenuation thresholds
- Derived from freeform ROI target lesion margins on axial CT
  - Same section that was chosen for RECIST determination

Conclusion:
- Better predicts Metastatic RCC Response to Antiangiogenic Therapy

Smith AD. Vascular Tumor Burden as a New Quantitative CT Biomarker for Predicting Metastatic RCC Response to Antiangiogenic Therapy. Radiology. 2016 Nov.
Viable Tumor Volume (VTV)

• Takes volumetric density of each lesion into account
  – On CECT* following segmentation within PACS
    • Carestream Health (Rochester, NY)
      – version 12.0

• Considers all voxels in segmented volume
  – Not limited to single slice

• Note the MPVR of all target lesions as discrete objects

* Contrast Enhanced Computed Tomography
Volumetric Segmentation

• Recently available within PACS
  – Carestream Health (Rochester, NY), version 12
  – Near future possibility within workflow

• Our Experience with PACS segmentation
  – Success rates in metastatic melanoma
  – Automated volumetric consistency and efficiency


Volumetric Density Histogram

- Example enhancing metastatic tumors
- Histogram analysis shows shift towards necrosis
  - Reflecting treatment success
VTV Methods

- Assessed 141 metastatic urothelial lesions
  - Compared VTV with existing and density criteria
  - RECIST, SACT, MASS, Choi and volume (size only)
  - Baseline and serial follow-up CT exams (n=55)
    - In 17 patients with metastatic bladder cancer
    - Treated with cabozantinib (tyrosine kinase inhibitor)

- VTV response pooled into two categories
  - Stable Disease + Partial Response
  - Progressive Disease

- Each criteria plotted on Kaplan-Meier curves
  - 2-tailed log-rank test applied
Volume of Interest (VOI); Viable Tumor Volume (VTV)

- Volumetric histogram HU analysis
  - VOI now in v12.0
    - Traditional Region of Interest (ROI) is only 2 Dimensional
- VTV assesses all voxels, accounts for periphery

Volumetric Density Histogram

- Volumetric histogram represents all HU voxels
  - Within segmented volume
- X axis is range of HU, y axis number of voxels
- Shift of histogram values to left correlates with less enhancement seen in necrosis

*Note shift to left over time in this responder; from Avg HU from 92 to 51*
Baseline

First Follow up (2 months)
Tumor necrosis analogy

Assume antiangiogenic therapies convert golf balls into ping pong balls (much less mass)

Diameter (RECIST, nor volumetric size) does not assess this
- Cabozantinib resulting in necrosis (cavitation)

Baseline, 1.8 cm

Following first treatment 1.7 cm
RECIST, Volumetric: “Stable Disease”
VTV: “Complete Response”

Golf ball ≈ solid enhancing mass

Ping Pong ball ≈ necrotic cavity

4.1 cm
37 cc

4.3 cm
40 cc
Results: Associations

• Statistical association between initial response determinations of VTV total and low (2-tailed; $p = 0.019$)
• Patients with lower-attenuating lesions (presumed tumor necrosis) had the most significant survival prediction using VTV.
• Other criteria (MASS, mChoi) showed weak ($p = 0.083$) or no association ($p = 0.58$).
Viable Tumor Volume: Results

- Assesses metastatic lesion volume density
  - Presumed viable tumor verses necrotic portions
- VTV closest trend towards association
  - Toward time to developing PR: $p = 0.087$
  - Hazard ratio = 0.16; 95% with CI: 0.02 to 1.30
- VTV better reflects tumor burden over other criteria in our study
  - May predict outcomes earlier
VTV Response correlated best with Overall Survival (OS) Compared to other criteria
VTV correlates better with OS over RECIST

Also better than mChoi, SACT and volumetric size alone

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

Les Roger Folio, Elyrim B. Turkbey, Seth M. Steinberg, Andrea B. Apolo
Current NCI Cancer Cohorts Applying VTV
(All using RECIST 1.1 or immune criteria primarily)

- Muscle Invasive Urothelial
- Chordoma
- Desmoid tumor
- Adenoid cystic carcinoma (ACC)
  - Inter and intra observer variation assessed
- Kaposi Sarcoma (Solomon lung segmentation (ref))
- HER2 Breast:
  - autologous dendritic cell vaccine
VTV in Adenoid Cystic Carcinoma (ACC)

- Analyzed CT and MRI exams on 20 patients with locally advanced, recurrent or metastatic ACC treated on a phase 2 clinical trial with vorinostat.
- Compared volumetric to linear RECIST criteria correlating to clinical benefit, progression free survival, overall survival and stable disease duration >6 months.
- Also assessed VTV inter and intra-observer variability
- Work in progress, preliminary results promising
- **Hypothesis:** Volumetric criteria; especially with volumetric density more adequately assess tumor burden than RECIST criteria, relating better to OS, PFS and stable disease > 6 months.
Limitations, challenges applying volumetric criteria

• Resources needed to assess volumetrics are not trivial*
  – Technology has advanced, however few apply routinely
  – 3D lab, staffing, training, oversight, time, money

• Did not compare to other advanced techniques not available
  – Smith
  – Ganeshen, Goh Texture analysis

• Variability: preliminary results show significant variability
  – We selected a challenging cancer to compare 3 observers

Discrete Object Heatmaps of all Volumes

• Find other slides, poster by Offrie
• 40xx urothelial cancer patients (Total Tumor Volume)
  – Better represented tumor burden
  – Resources
• Volumetric segmentations performed on all lesions > 1cm
  – Thousands of volumes
  – All exams throughout trial
• Volumes displayed as discrete objects in PACS
  – Carestream Health
  – All superimposed by NLM in Matlab to create heatmaps
  – Baseline and last follow up compared, male female distribution difference
Can overlay all cancer patients in select cohorts with images of volumetrically segmented tumor lesions (and skin masks) by linearly mapping with MatLab® to a standard mean size creating a superimposed Color gradient Cohort Heatmap.

Note the 3D rendered lesions are discrete objects showing overlapping lesion frequency or distribution (red = most lesions) of soft tissue metastasis. May help with distribution likelihood.
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Thanks for your attention

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FIRST IN HUMAN
BEFORE THE BREAKTHROUGH COMES THE TRIAL

narrated by Emmy® winner Jim Parsons
produced and directed by Emmy® winner John Hoffman
executive produced by Emmy® winner Dyllan McGee
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• Folio LR, Sandouk A, Huang J, Solomon JM, Apolo AB. (2013). Consistency and Efficiency of CT Analysis of Metastatic Disease: Semiautomated Lesion Management Application Within a PACS. AJR;201:3, 618-625

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