

WHITE PAPER

# Expanding the Power of PET with PERCIST

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# Expanding the Power of PET with PERCIST

## Introduction: Evaluation of Treatment Response in Oncology

Accurate monitoring of patient response to cancer therapy is vital both for the provision of effective treatment and the development of novel therapies. Distinguishing those patients who are responding to a particular treatment, from those who are not, as early as possible, can maximize effectiveness of patient care. Non-responders can then be moved to a different, more effective treatment regimen earlier, sparing patients unnecessary toxicity and morbidity from ineffective therapy, and resulting in overall cost saving to payors.

Although overall survival provides the definitive measure of therapy success, it is hampered by its inability to provide early feedback and the difficulties in separating out the effectiveness of the multiple treatment strategies employed over the course of a patient's care cycle. As such, surrogate measures for survival, such as progression-free survival or response rate are commonly used. Imaging-based assessment of treatment response is able to provide early indication of treatment effectiveness and is widely used to aid patient management and evaluate novel therapies.

## Morphological Response Assessment: RECIST and WHO

Anatomical imaging modalities such as CT and MRI allow the accurate assessment of changes in tumor size over the course of therapy, a measure that is often, but not always, related to overall survival. The World Health Organization (WHO) criteria<sup>1</sup> and the Response Evaluation Criteria in Solid Tumors (RECIST)<sup>2</sup> provide standardized methodologies for assessing treatment response. As such, they have catalyzed the adoption of anatomical imaging modalities in determining the efficacy of treatment for solid tumors in drug development and for regulatory approval, where reproducible, quantitative results are of particular importance.

Morphological criteria for complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) have been established with RECIST and RECIST 1.1.<sup>3</sup> However, with increasing adoption of metabolic imaging with PET and PET/CT, particularly with <sup>18</sup>F-FDG imaging in initial staging and follow up of a variety of cancers, there appears to be a need to modify these criteria and base them not only on tumor size, as measured by morphological imaging modalities like CT, but also on tumor metabolism parameters, like standardized uptake value (SUV), as measured by PET. Since many newer cancer therapies may be more cytostatic than cytotoxic, good tumor response may be associated predominantly with a decrease in metabolism, even in the absence of a major reduction in tumor size. Further, metabolic response as a leading indicator of tumor response to therapy may be even more predictive of outcome than morphological measures. It is in this context that a new criteria of therapy response assessment, PET Response Criteria In Solid Tumors, or PERCIST 1.0, was proposed by Wahl and colleagues<sup>4</sup> based on PET metabolic criteria.

## PET/CT Based Response Assessment: PERCIST 1.0

### *Response Assessment with PET*

The discrepancy between tumor response and decrease in lesion size is very apparent in lymphoma. Presence of residual masses on CT during chemotherapy follow-up with PET/CT, in spite of significant decrease in tumor metabolism and <sup>18</sup>F-FDG uptake, is common. Similar situations during therapy are common in several tumors including Gastrointestinal Stromal Tumors (GIST), breast carcinoma, etc.

Attempts have been made to combine CT and PET information for effective therapy response assessment. Choi et al<sup>5</sup> correlated changes in tumor size and density on CT with changes in glucose metabolism based on SUVmax, in 173 GIST lesions in 36 patients undergoing treatment with imatinib mesylate (Gleevec™). There was significant decrease in both tumor density and SUVmax with Gleevec™ therapy. Seventy percent (14/20) of the patients with tumors that showed response on FDG PET exhibited at least a partial response by a change in tumor density. Tumor size was found to have decreased significantly 2 months after treatment in all 20 FDG PET responders. However, in 75 percent of the patients, the disease was stable according to the traditional tumor response criteria of RECIST. This suggested that RECIST, using only tumor size, was unreliable for monitoring GIST during therapy although tumor density measurement and FDG PET SUVmax were reliable quantitative indicators.

Limitations of RECIST in predicting response are also apparent from the results of the SHARP trial<sup>6</sup> in which sorafenib, an inhibitor of vascular endothelial growth factor receptor, was used in a trial of 602 patients with hepatoma who had not received previous therapy. Only 2 percent of the treated group demonstrated a partial response by RECIST. However, the clearly prolonged

survival of patients with advanced hepatocellular carcinoma treated with sorafenib, which was associated with radiologically stable disease, demonstrates the efficacy of therapy in spite of the lack of response by RECIST criteria.

### *The PERCIST 1.0 proposal*

Standardized quantitative assessment of metabolic tumor response with PET necessitates a consistent and reliable measure of tumor activity. PERCIST recommends using lean body mass normalized SUV (SUVlbm<sup>7,8</sup> or SUL (Wahl et al<sup>4</sup>)), due to its reduced dependence on patient weight as compared to the standard body weight normalized SUV (SUVbw).

SUV-based quantification reduces variation due to injected radionuclide dose and patient weight; however, inter-observer differences in defining the boundary of a tumor represent another significant source of variation. Typically, this is avoided by taking the value of the single voxel with the maximum intensity (SUVmax). A major drawback of this approach though is its susceptibility to noise in the data.

PERCIST recommends computing the SUL Peak Value, which it defines as the largest possible mean value of a 1 cm<sup>3</sup> spherical VOI positioned within a tumor. By strictly defining the dimensions and positioning of the VOI, inter-observer variation is removed, and the averaging of multiple voxels reduces the susceptibility to noise. Details of the computation of the Peak Value in syngo TrueD can be found in the following sections.

PERCIST also recommends comparing the variability in SUL between time points for reference VOIs positioned either in the right lobe of the liver or the descending aorta. By stipulating that this variation should be less than 20 percent or 0.3 SUL mean units, the influence of non-pathologic variability in PET quantification across multiple time points can be reduced. Liver and mediastinal uptakes are recommended since they are usually stable over time. Mean SUL in the liver was 1.49+/- 0.25 and 1.45+/- 0.20 in test/retest studies in Wahl et al<sup>4</sup>.

The reference VOIs are also used in the PERCIST analysis to define a threshold for selecting reportable lesions. For a reference VOI positioned in the liver, this threshold is calculated as:

$$(1.5 \times \text{SUL mean}) + (2 \times \text{SUL SD of mean}).$$

For a reference VOI in the descending aorta, it is calculated as:

$$(2 \times \text{SUL mean}) + (2 \times \text{SUL SD of mean}).$$

In view of the widely experienced value of sequential PET/CT evaluation of tumor metabolism as an indicator of true therapy response, and the complexity of the quantitative indexes involved, the PERCIST guidelines advocate simple measurement and documentation criteria to assess therapy response accurately<sup>9-12</sup>. It is of utmost importance to adhere to a standardized protocol of PET/CT scanning including injected dose, post injection delay, reconstruction parameters and SUV normalization approaches. In PERCIST,

response to therapy is evaluated as a continuous variable and expressed as a percentage change in SUL Peak for the most active lesion at each time point (or optionally the sum of up to 5 lesion SUL Peaks) between the pre- and post-treatment PET/CT studies. A complete metabolic response (CMR) is defined as visual disappearance of all metabolically active tumor and a drop in SUL Peak to that of the background. A partial metabolic response (PMR) is defined as at least a 30 percent and 0.8 unit decrease in SUL Peak between the most intense pre-therapy lesion and the most intense post-therapy lesion. Progressive metabolic disease (PMD) involves at least a 30 percent increase in SUL Peak or the appearance of new lesions. Stable metabolic disease (SMD) is the classification if the criteria for CMR, PMR or PMD are not met.

This criterion of 30 percent or more decrease in SUL Peak as a criterion for PMR is subject to modification based on the disease progress. In lymphoma, a higher cut-off (e.g. 65 percent drop in Peak SUL in mid therapy) may be required for accurate response evaluation. Similar high thresholds for PMR may be required for GIST as well.

Criteria for defining progressive disease can also be complicated by choice of the lesion assessed. It may be difficult for the most intense lesion to increase in uptake by 30 percent since it may be already performing glycolysis at the maximum possible level, depending on its blood supply. In such situations, a 30 percent increase in SUL of another lesion, which is not with the highest uptake in the first study, may be regarded as indicative of progressive disease. Appearance of fresh lesions, even in presence of SUL decline of existing lesions, is to be regarded as indicative of progressive metabolic disease, as reported by Wahl et al<sup>4</sup>.

Finally, PERCIST recommends that for cases where there is no <sup>18</sup>F-FDG avidity, or that are technically unsuitable for PERCIST assessment, response evaluation should defer to morphologically based RECIST 1.1.

The following flow charts summarize how to use PERCIST for response assessment, with Figure 1 outlining the analysis of each time point and Figure 2 describing the assessment of response between analyzed time points. Full details of PERCIST can be found in Wahl et al<sup>4</sup>.

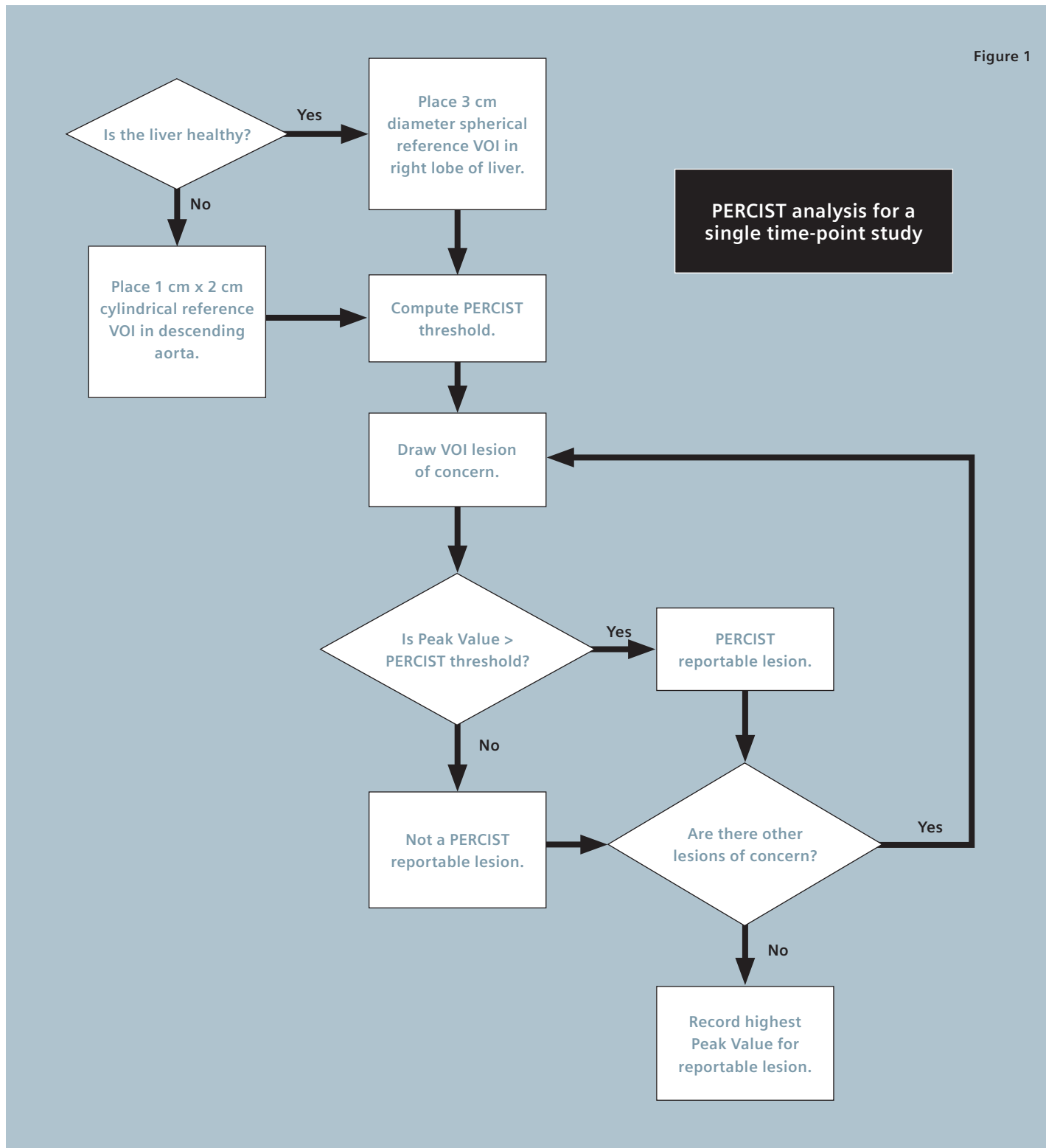


Figure 2

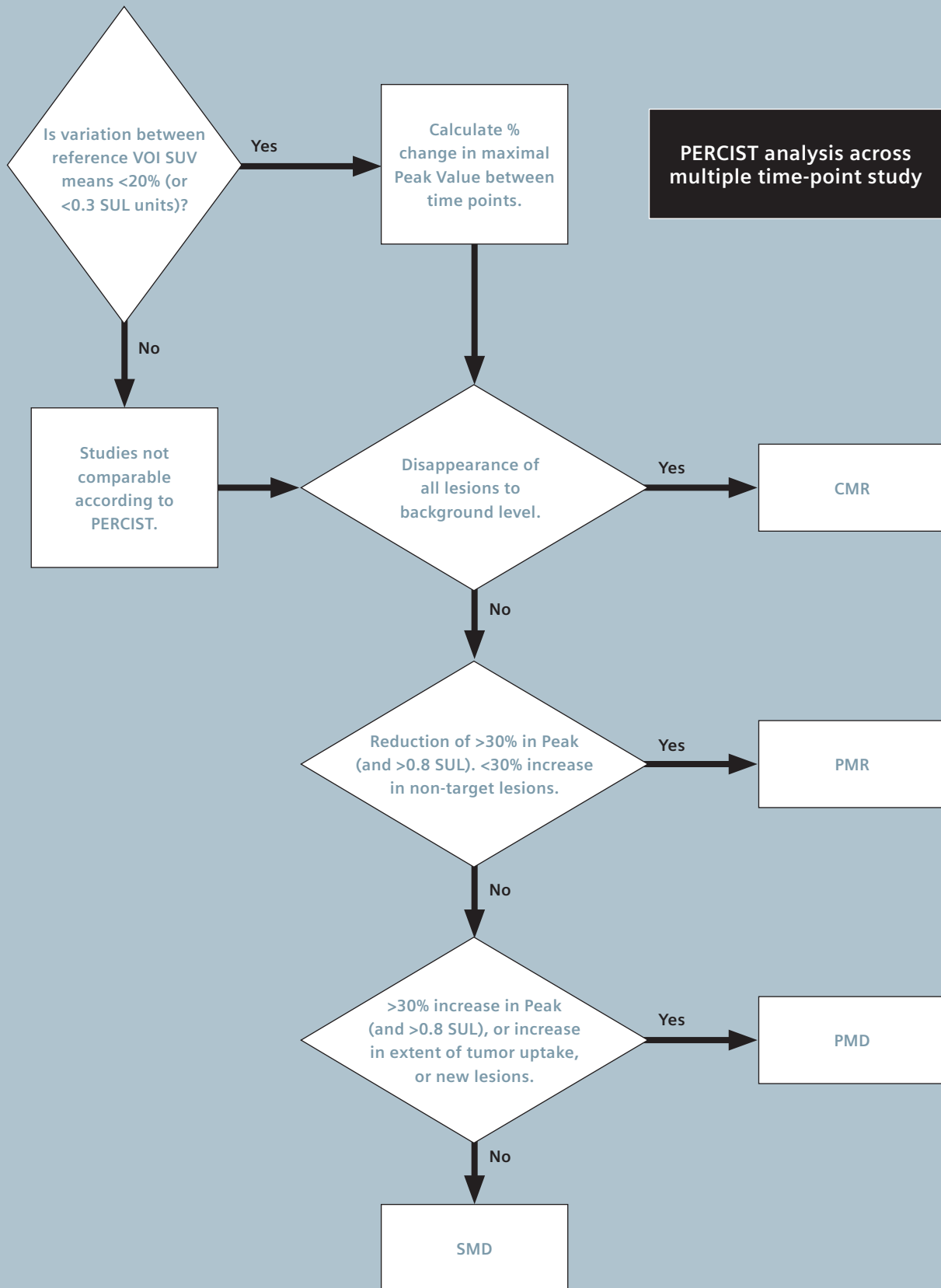
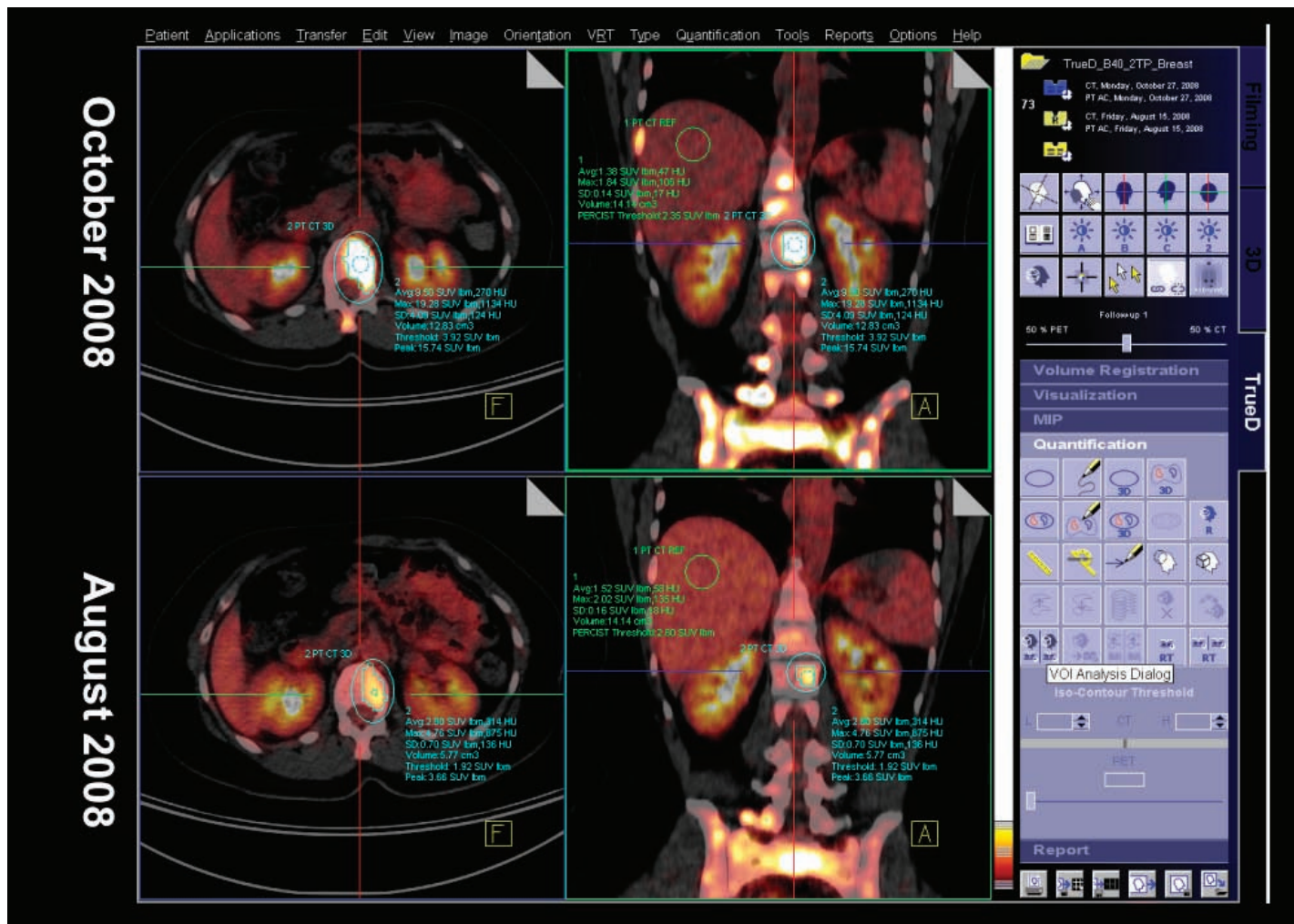


Figure 3. Data courtesy of Northwestern University, Chicago, IL, USA



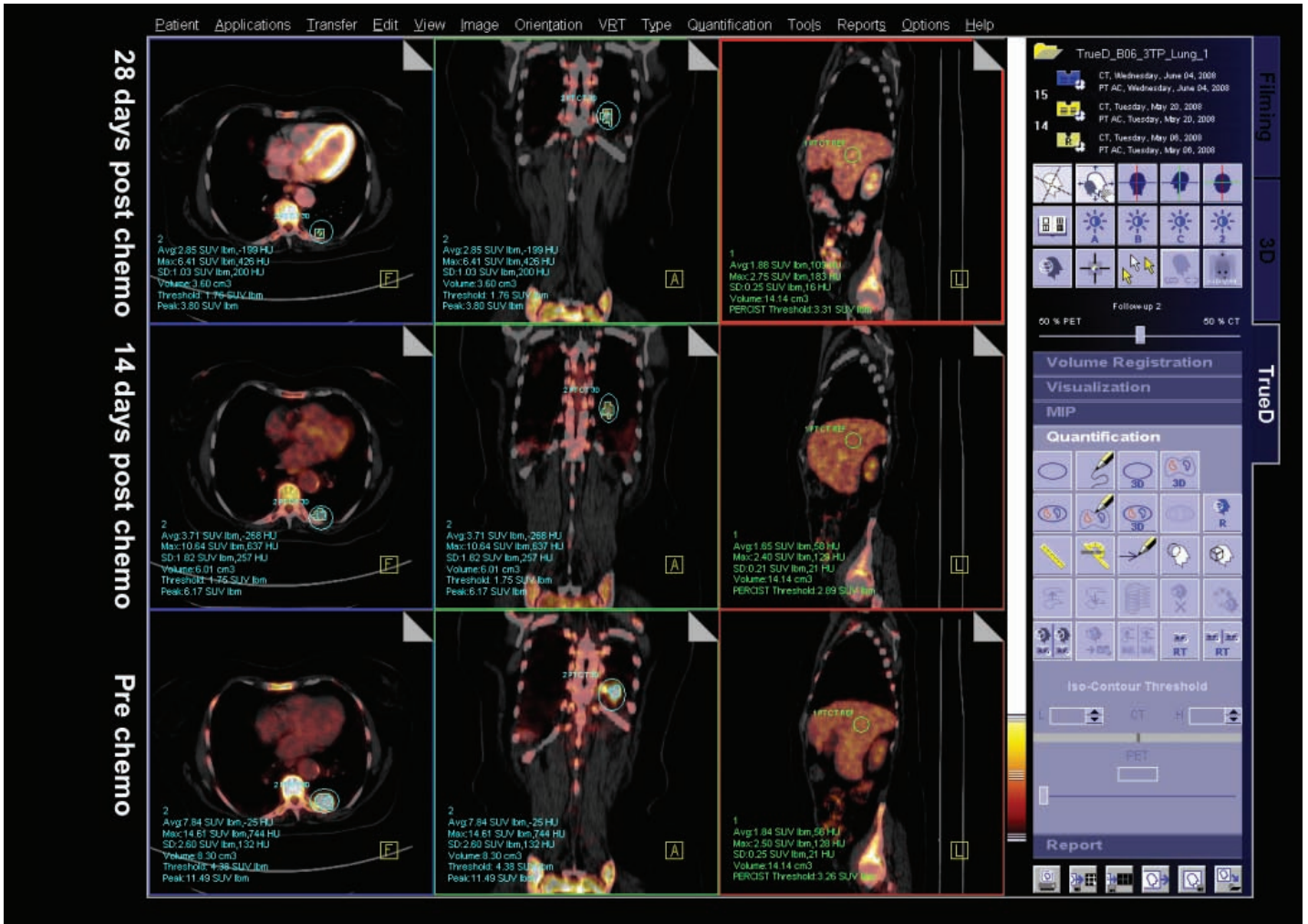
### Clinical examples

A few clinical examples of sequential PET/CT studies evaluated with reference to PERCIST criteria would be illustrative of its clinical value.

The first case (Figure 3) shows a patient with breast carcinoma on chemotherapy who underwent sequential <sup>18</sup>F-FDG PET/CT imaging on a Biograph™ TruePoint™ 40 system. The initial study, performed in August 2008, shows multiple skeletal metastases. However, the follow-up study, performed in October 2008, showed further increase in number, size and intensity of uptake in the skeletal metastases, suggesting failure of chemotherapy. The reference VOI was positioned in the right lobe of the liver for each study

and showed an average SUL of 1.52 for the initial study and 1.38 for the follow up study. As this variation was less than 20 percent and 0.3 SUL, the studies could be evaluated using PERCIST. The PERCIST SUL thresholds computed from these reference VOIs were 2.60 and 2.35, respectively. The hottest lesion in the initial study, a vertebral lesion, showed a Peak SUL of 3.66, increasing to 15.74 in the follow up study; both values were above the corresponding PERCIST SUL threshold. Since this lesion remained the hottest in the follow up scan, the SUL Peak for the study increased 330 percent. Combined with the increase in number, size and intensity of uptake in the skeletal metastases, this increase in SUL Peak clearly indicated progressive metabolic disease.

Figure 4. Data courtesy of University of Tennessee Medical Center, Knoxville, TN, USA



The next study (Figure 4) shows a three-time point  $^{18}\text{F}$ -FDG PET/CT study, performed on a Biograph™ TruePoint™ 6 system before and during chemotherapy, in a patient with lung carcinoma. A pre-therapy PET/CT study was followed by studies after 2 weeks and 4 weeks. Sequential images show significant decrease in intensity of uptake as well as lesion size with chemotherapy. The reference VOI was positioned in the right lobe of the liver for each study and showed an average SUL of 1.84 pre-chemotherapy, 1.65 two weeks post-chemotherapy and 1.88 four weeks post-chemotherapy. Again, the variation was within acceptable bounds and the PERCIST SUL thresholds computed from these reference VOIs were 3.26, 2.89 and 3.31 respectively. The hottest lesion in the pre-chemotherapy study, a lung lesion, showed a Peak SUL

of 11.49, decreasing to 6.17 two weeks post-chemotherapy and 3.80 after four weeks. This overall reduction in Peak SUL of nearly 67 percent, combined with no increased activity in non-target lesions, indicates partial metabolic response. Complete metabolic response was not achieved as the SUL Peak for the most recent study remained above the PERCIST threshold. These findings are summarised in the trending chart in Figure 5. Trend chart analysis is able to assess Peak SUL levels for multiple identified lesions and determine the highest Peak SUL from the lesion group for each study allowing optimized evaluation of sequential PET/CT studies to assess tumor response to therapy.

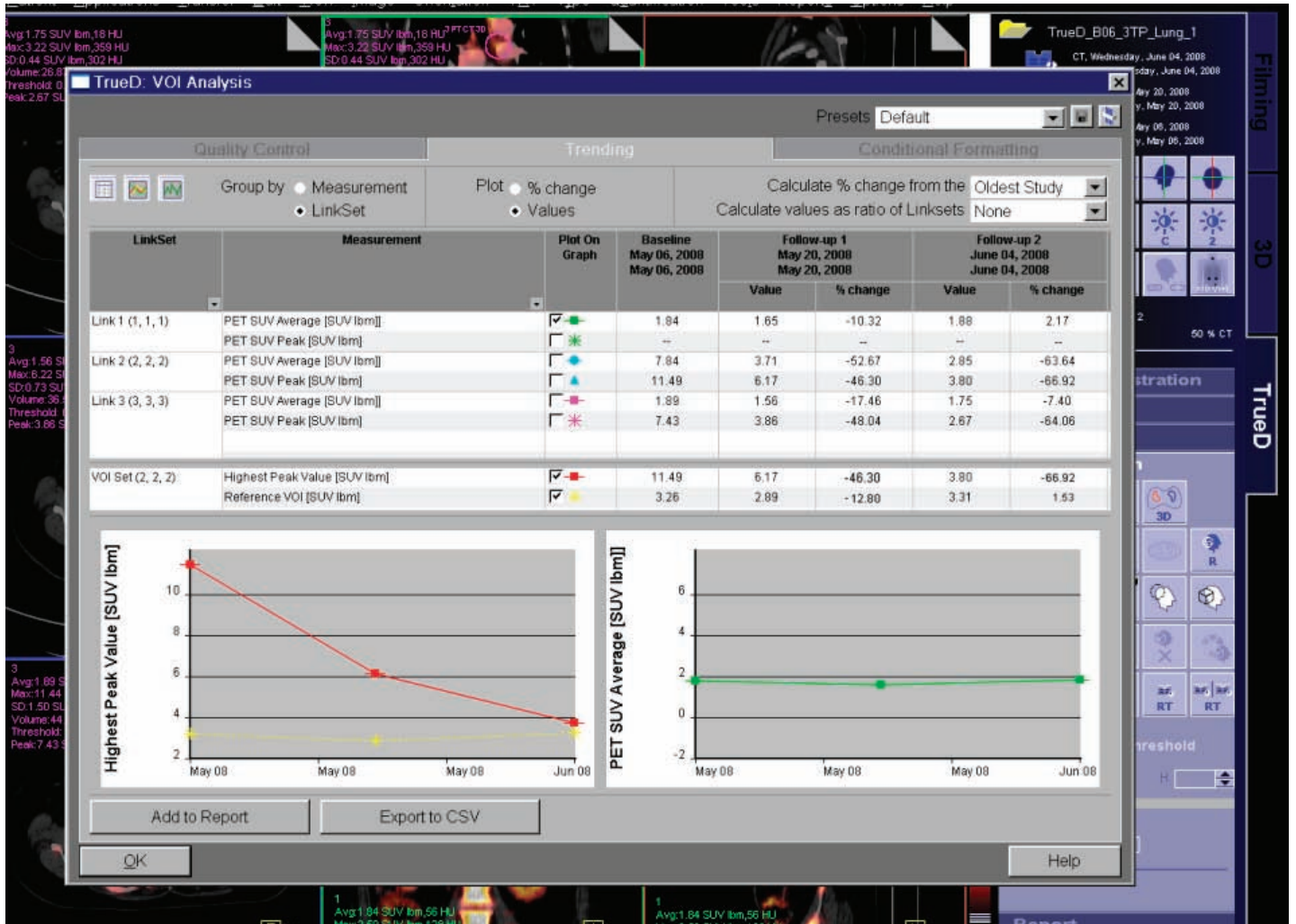
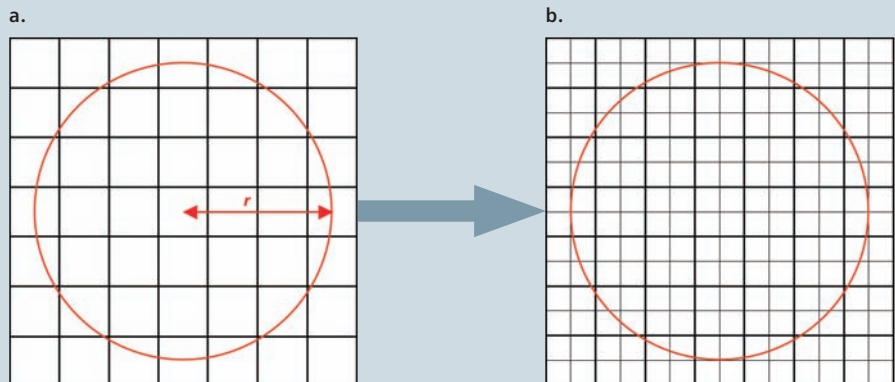


Figure 5

Figure 6. 2-D example of Peak Kernel construction. (a) Peak Kernel initialized with sufficient voxels to enclose sphere of radius ( $r$ ). (b) Kernel voxels supersampled in this example, with a supersampling factor of 2 along each axis. (c) Supersampled voxels with center inside sphere identified. (d) Fraction of supersampled voxels within sphere assigned to original voxels. (e) Resulting Peak Kernel. Note, actual kernel computed in 3-D.



## Implementation

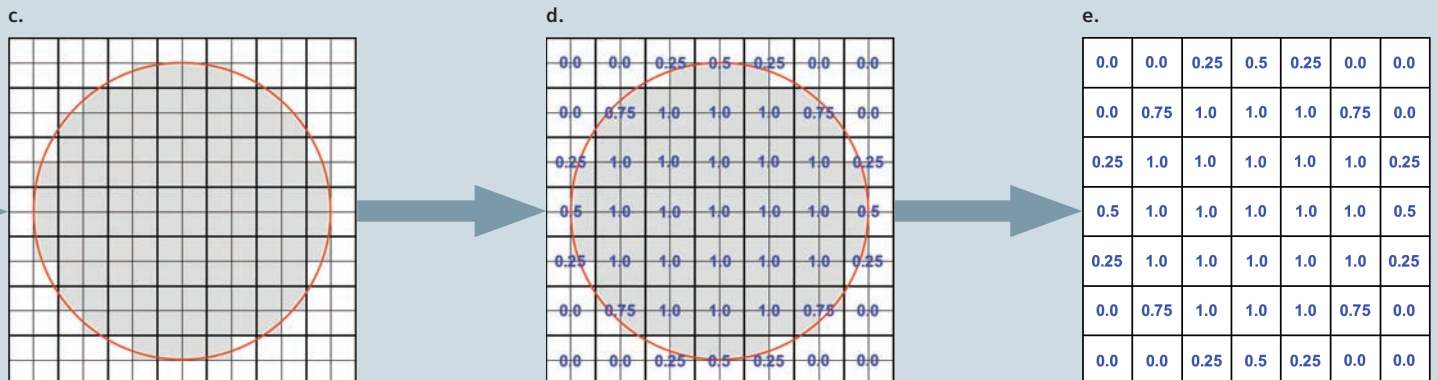
The key parameter used in the PERCIST analysis is the SUL Peak. Wahl et al<sup>4</sup>. define this value as the largest possible mean value of a 1 cm<sup>3</sup> spherical VOI positioned within a tumor or hotspot, using SUL (or SUVlbm) as the reported unit. This section describes the technical details of the computation of the Peak Value in *syngo* TrueD in order to provide clarity and remove any ambiguity. Note that in *syngo* TrueD, the Peak Value is available for any selected units and not restricted to SUVlbm.

Computation of the Peak Value for a tumor or hotspot can be divided into two steps:

1. *Computation of the mean activity concentration within a 1 cm<sup>3</sup> spherical VOI centered on a particular voxel.*
2. *Identification of the voxel within the tumor or hotspot having the highest mean activity concentration.*

For the first step, we compute the mean activity within a 1 cm<sup>3</sup> spherical VOI by constructing a Peak Kernel that allows us to account for the contribution of partial pixels at the edge of the spherical VOI. Consideration of partial voxels is of particular importance in computing the Peak Value given the small size of the spherical VOI relative to the typical PET voxel size.

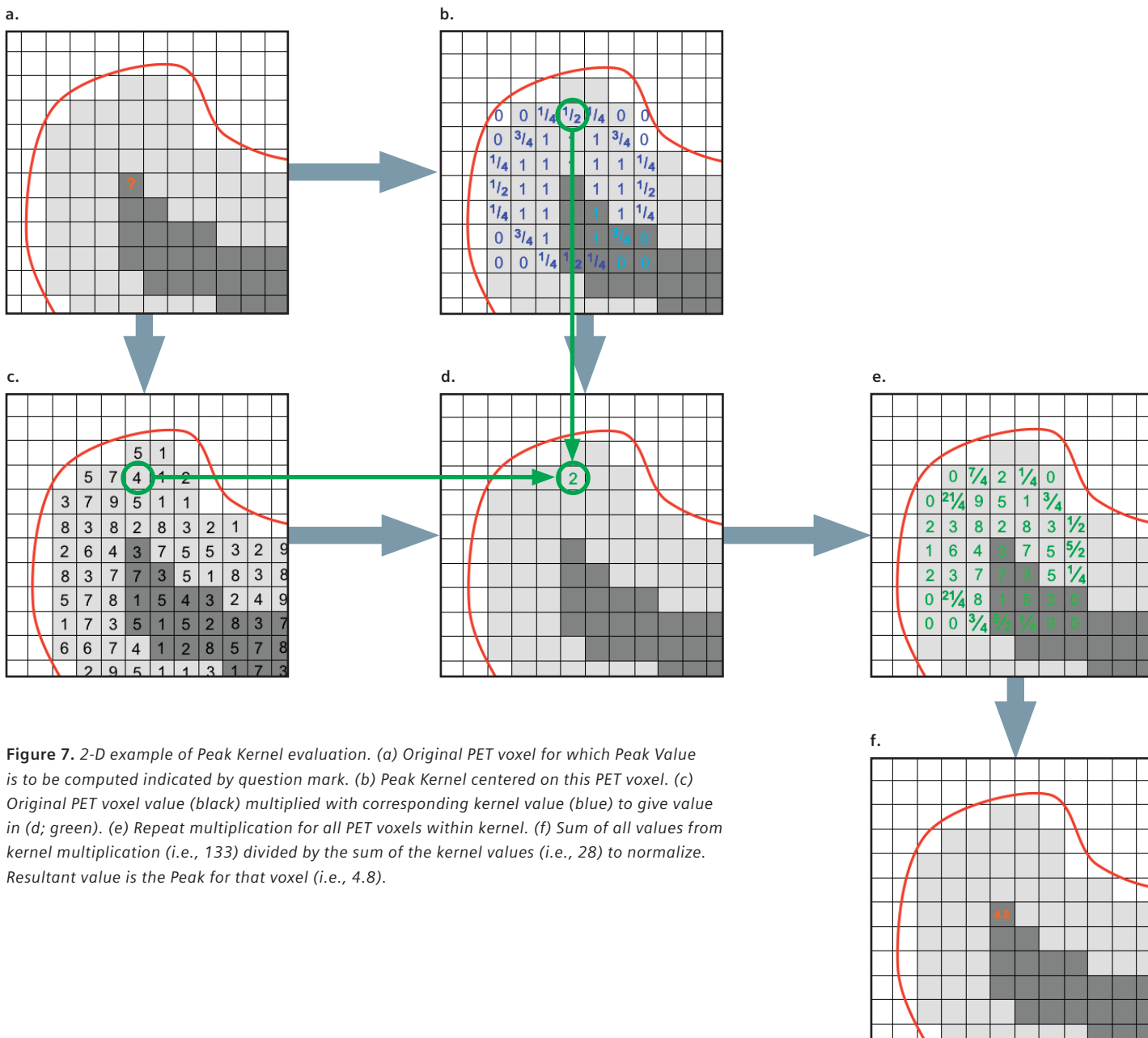
The Peak Kernel is constructed at the resolution of the PET data voxels with the fraction of each voxel contributing to the spherical VOI calculated by supersampling each these voxels and computing the proportion of these supersampled voxels whose centers lie within the sphere (Figure 6).



Once constructed, the Peak Kernel can then be used to evaluate a Peak Value for any voxel in the PET image. This is performed by aligning the center voxel of the Peak Kernel with the chosen image voxel, multiplying the value of each kernel voxel with the corresponding voxel in the image, summing these values, then normalizing the result by dividing it by the sum of kernel voxel values. The final result is the Peak Value for that voxel (Figure 7).

For a VOI defined in *syngo* TrueD, a Peak Value is computed, as described above, for each voxel within the VOI upon which the Peak Kernel can be centered without any non-zero elements of the kernel falling outside the boundary of the VOI (Figure 8).

Following evaluation of the Peak Kernel for all possible PET voxels within the VOI, the Peak Value for the VOI is that of the voxel with the highest individual Peak Value (Figure 9).





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