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Spatial-Temporal FDG-PET Features for Predicting Pathologic Response of Esophageal Cancer to Neoadjuvant Chemoradiotherapy

Shan Tan, Ph.D.^{*,†}, Seth Kligerman, M.D.[‡], Wengen Chen, M.D., Ph.D.[‡], Minh Lu, M.D.[‡], Grace Kim, M.D.^{*}, Steven Feigenberg, M.D.^{*}, Warren D. D'Souza, Ph.D.^{*}, Mohan Suntharalingam, M.D.^{*}, and Wei Lu, Ph.D.^{*}

^{*}Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, USA.

[‡]Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland School of Medicine, Baltimore, USA.

[†]Department of Control Science and Engineering, Huazhong University of Science and Technology, Wuhan, China.

Abstract

Purpose—To extract and study comprehensive spatial–temporal ¹⁸F-FDG PET features for the prediction of pathologic tumor response to neoadjuvant chemoradiotherapy (CRT) in esophageal cancer.

Methods and Materials—Twenty patients with esophageal cancer were treated with trimodality therapy (CRT plus surgery) and underwent FDG PET/CT scans both before (pre-CRT) and after (post-CRT) CRT. The two scans were rigidly registered. A tumor volume was semiautomatically delineated using a threshold of standardized uptake value (SUV) > 2.5, followed by manual editing. Comprehensive features were extracted to characterize the SUV intensity distribution, spatial patterns (texture), tumor geometry, and associated changes resulting from CRT. The usefulness of each feature in predicting pathologic tumor response to CRT was evaluated using the area under the receiver operating characteristic curve (AUC).

Results—The best traditional response measure was maximum SUV (SUV_{max}) decline (AUC 0.76). Two new intensity features (SUV_{mean} decline and skewness) and three texture features (inertia, correlation, and cluster prominence) were found to be significant predictors with AUCs 0.76. According to these features, a tumor was more likely a responder when the mean SUV decline was larger, when there were relatively fewer voxels with higher SUVs pre-CRT, or when FDG uptake post-CRT was relatively homogeneous. All of the most accurate predictive features were extracted from the entire tumor rather than from the most active part of the tumor. For SUV intensity features and tumor size features, changes were more predictive than pre- or post-CRT assessments alone.

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Correspondence author: Wei Lu, Ph. D., Department of Radiation Oncology, University of Maryland School of Medicine, 22 South Greene Street, Baltimore, MD 21201, Tel: 410-706-6511, Fax: 410-328-2618, wlu@umm.edu.

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Conclusion—Spatial–temporal FDG PET features were found to be useful predictors of pathologic tumor response to neoadjuvant chemoradiotherapy in esophageal cancer. Key words: FDG PET/CT, Tumor response, Esophageal cancer, Quantitative image analysis

Keywords

FDG PET/CT; Tumor response; Esophageal cancer; Quantitative image analysis

INTRODUCTION

Esophageal cancer remains one of the most lethal malignancies. Historically, the primary treatment strategy has been surgery (esophagectomy) (1). Trimodality therapy, consisting of concurrent chemoradiotherapy (CRT) followed by surgery, has recently been used for managing this disease. The adoption of this approach was supported by the results of Phase II and III randomized trials that showed greater long-term overall and progression-free survival (1) or disease-free survival (2) with trimodality therapy than surgery alone. However, the question of whether the addition of surgery to CRT provides an advantage over CRT alone remains controversial (3). Randomized trials reported equivalent 2-y overall survival rates (range: 28%–40%) for the two treatment strategies (4, 5). Moreover, surgery after CRT is associated with significantly higher mortality (9%–12%) and morbidity (30%) than CRT alone (mortality: 0.8%–3.5%) (4, 5).

Despite these data, strategies forgoing surgery may be inappropriate for many patients. Local failure rates for CRT alone can exceed 50%, and evidence suggests that surgery after CRT improves local control (4, 5). Several investigators have shown recently that patients who responded to CRT had good prognoses (survival and local control) regardless of whether they underwent surgery, whereas patients who did not respond to CRT had poor prognoses—but surgery improved survival in these patients (3–5). With the uncertain benefit and added mortality and morbidity of surgery after CRT and the high local failure rate for CRT alone, it becomes critical to accurately identify patients who respond to CRT so that surgery may be safely deferred. It is equally important to accurately identify patients who do not respond to CRT so that surgery can be considered.

¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has shown promising results in predicting pathologic response to and long-term prognosis after CRT in esophageal cancer, but accuracy is still low (6). Westterterp et al. showed that PET had similar accuracy (sensitivity, 71%–100%; specificity, 55%–100%) to and was more feasible than endoscopic ultrasonography, whereas the accuracy of CT was significantly lower (7). In a review of 20 studies, Kwee found that the sensitivity and specificity of PET ranged from 33% to 100% and from 30% to 100%, respectively, with pooled estimates of 67% and 68% (6). Monjazebe et al. demonstrated that PET complete response after CRT alone predicted improved survival and local control rates that were equivalent to those with trimodality therapy (3).

Almost all FDG PET studies quantify therapeutic response in tumors using the maximum standardized uptake value (SUV_{max}) of FDG within a tumor (8). Changes in SUV_{max} and sometimes SUV_{max} pre- or post-CRT alone are correlated with post-CRT pathologic tumor response or survival. However, SUV_{max} is a single-point estimate, and most solid tumors include various malignant and nonmalignant components and show significant heterogeneity in both degree and distribution of FDG uptake. Heterogeneity in FDG uptake may be associated with important biological and physiologic parameters (9, 10) that have been shown to be prognostic factors in many cancers (10, 11). Another limitation of SUV_{max} is that noise effects are substantial (12). Recent studies suggest that spatial PET/CT features,

including tumor volume (12), tumor shape (11), total glycolytic volume (12), and texture features (10, 11), are more informative than SUV_{max} for the prediction of tumor response.

The objective of this study was to extract comprehensive spatial–temporal tumor features from PET/CT images and assess their usefulness in predicting pathologic tumor response to neoadjuvant CRT in esophageal cancer.

MATERIALS AND METHODS

Patient Cohort

This retrospective study was approved by our Institutional Review Board. The cohort included 20 consecutive patients with esophageal cancer (Table 1), who were treated with trimodality therapy from 2006 to 2009 and underwent both pre- and post-CRT PET/CT imaging at our institution. The median age for patients was 64 y. Staging was according to AJCC Cancer Staging Manual sixth edition. The 2 patients with M1a disease had extensive local–regional lymph node disease, but no distant metastases were evident outside the treatment field. Therefore, they, like the other 18 patients in the study, underwent resection after CRT.

PET/CT Imaging—Pre-CRT PET/CT imaging was performed ~3–5 wk before CRT, and post-CRT imaging was performed 4–6 wk after completion of CRT but before surgery. All PET/CT studies were performed with an integrated 16-slice Gemini PET/CT scanner (Philips Medical Systems; Cleveland, OH). Following an institutional standard protocol, each patient fasted for a minimum of 4 h before intravenous injection of 12–14 mCi ^{18}F -FDG. Whole-body PET and CT imaging was started 60 min after tracer injection. PET images were attenuation corrected and reconstructed with a maximum likelihood algorithm. Resolution for PET images was $4.0 \times 4.0 \times 4.0$ mm³ and for CT images was $0.98 \times 0.98 \times 4.0$ mm³.

Chemoradiotherapy

All patients were treated with external-beam radiotherapy with concurrent chemotherapy. A radiation dose of 50.4 Gy (1.8 Gy/d, 5 d/wk) was delivered using CT simulation and 3D or intensity-modulated radiation therapy treatment planning. Chemotherapy consisted of cisplatin (100 mg/m²) administered intravenously on d 1 of wk1 and 5 and 5-fluorouracil (1,000 mg/m²) administered daily as a continuous intravenous infusion over 4 consecutive d in wk1 and 5.

Pathologic Assessment

Surgical resection (Ivor–Lewis, transhiatal, or 3-field esophagectomy) was performed 1–7 wk after post-CRT PET/CT imaging. Resected surgical specimens were submitted to a pathologist for evaluation. Specimens were serially sectioned every 2–4 mm, microscopically examined, and semiquantitatively categorized into 3 groups: pathologic complete response (pCR), microscopic residual disease (mRD), or gross residual disease (gRD), according to the amount of residual viable carcinoma observed in relation to areas of fibrosis (13). In this study, both pCR and mRD were considered as evidence of response (responders) because they are associated with similar survival rates (13, 14). Patients with gRD were considered to be nonresponders.

Spatial–Temporal PET Features

To extract the spatial–temporal PET features for response assessment, we performed the following PET/CT image analysis using open source software (Insight Segmentation and Registration Toolkit [ITK]; National Library of Medicine, Bethesda, MD)(15).

Image Registration—A rigid registration (VersorRigid3DTransform in ITK)(15) technique was used to register the post-CRT CT to the pre-CRT CT by maximizing their normalized correlation. To achieve higher registration accuracy in the tumor area, registration was constrained within a rectangular chest region excluding the arms and head. Next, the results were visually examined and adjusted if deemed necessary by a radiologist (SK). The resulting registration transform was directly applied to register the post-CRT PET to the pre-CRT PET. PET intensity was converted to SUVs, and a difference image (diff-SUV) was calculated as pre-CRT SUV minus post-CRT SUV. All images were then aligned spatially. The registration algorithm was optimized and tested on simulated CT images with known rotations up to 10° and/or translations up to 10 cm. The registration error was <0.5 voxel in the simulation study. In patients, no obvious misalignments were observed.

Tumor Volumes of Interest—Two tumor volumes of interest (VOI) were semi-automatically delineated for the tumor on the pre-CRT SUV image and for the metabolically residual tumor on the post-CRT SUV image, respectively. A rough volumetric rectangle enclosing a tumor was defined by a nuclear medicine physician (WC). A tumor VOI was then delineated using a Connected Threshold method in ITK (15), which started at the SUV_{max} point and iteratively appended all surrounding voxels with SUVs ≥ 2.5 to the current VOI. A morphologic opening filter was applied to smooth the VOI surface while preserving its dominant shape. The radiologist (SK) reviewed the results and manually edited the VOI when necessary. The resulting VOI represented the entire hypermetabolic tumor volume and was denoted as $VOI_SUV_{2.5}$. Another tumor VOI was defined as the $3 \times 3 \times 3$ -voxel cube centered at the SUV_{max} point, representing the peak metabolically active part of the tumor, and was denoted as VOI_SUV_{peak} .

Feature Extraction—Various features that described the SUV intensity distribution, texture, and geometry of each tumor VOI were extracted as potential predictors of response. SUV intensity and texture features were computed in VOIs that were delineated in the pre-CRT image, on the pre-CRT, coregistered post-CRT, and diff-SUV images, respectively. These features thus described the initial, residual, and changed SUV intensity and texture at the initial tumor location. Pre- and post-CRT geometry features were extracted from the VOIs delineated in pre- and post-CRT images, respectively. For each image and each VOI, nine intensity features, eight Haralick texture features (16), 15 geometry features (17, 18), and one volume-intensity feature were extracted (Table 2), resulting in 192 features for each tumor. We describe those features determined to have the highest predictive accuracy in four categories below.

Intensity Features: Intensity features quantify the level and distribution of FDG uptake. They were computed based on the histogram (17) of SUVs for all voxels within a tumor VOI. This category included the two traditional SUV response measures: SUV_{max} (maximum SUV) and SUV_{peak} (mean SUV within VOI_SUV_{peak}); and two new SUV intensity features: SUV_{mean} (mean SUV within $VOI_SUV_{2.5}$) and skewness, which is defined as:

$$s(x) = E \left[\left(\frac{x - m}{t} \right)^3 \right],$$

where x , m , and t are, respectively, the SUV, SUV_{mean} , and standard deviation within a VOI. Skewness quantifies the asymmetry of the SUV histogram.

Texture Features: Texture features quantify the spatial patterns, such as homogeneity, coarseness, and correlation, of FDG uptake (16). The SUVs within a tumor VOI were firstly normalized to range [0, 63]. The texture features were then computed based on the gray level co-occurrence matrices (GLCM) (16), using `itkScalarImageToTextureFeaturesFilter` in ITK (15). The texture features were averaged over eight spatial directions with offset 1. Let $G(i, j)$ represent the element of a normalized GLCM. $G(i, j)$ describes how often a voxel with SUV i occurs adjacent to a voxel with SUV j . The three important texture features were (15, 16):

1. Inertia: defined as:

$$\sum_{i,j} (i - j)^2 G(i, j).$$

Inertia measures the local SUV variation between a voxel and its neighbors.

2. Correlation: defined as:

$$\sum_{i,j} \frac{(i - \mu)(j - \mu)G(i, j)}{\sigma^2},$$

where

$\mu = \sum_{i,j} i \cdot G(i, j) = \sum_{i,j} j \cdot G(i, j)$ and $\sigma = \sqrt{\sum_{i,j} (i - \mu)^2 G(i, j) + \sum_{i,j} (j - \mu)^2 G(i, j)}$ are respectively the mean and standard deviation of the row sums of G . Correlation measures the extent to which a voxel is correlated with its neighbors.

3. Cluster prominence: defined as:

$$\sum_{i,j} ((i - \mu) + (j - \mu))^4 G(i, j).$$

Cluster prominence measures the nonuniformity of SUV distribution.

Geometry Features: Geometry features describe the shape, size, or relative position of a tumor VOI. Fifteen conventional geometry features were computed using the `itkLabelGeometryImageFilter` (18) and the label-object representation (17) in ITK. Three of these geometry features were of interest:

1. Roundness: defined as:

$$R = A/S,$$

where S is the area of a VOI and A is the area of a hypersphere with the same volume as the VOI. Roundness measures the degree to which the VOI is like a sphere;

2. Volume: volume of a VOI;
3. Major axis length (diameter): the major axis length or the longest diameter of a VOI, measured in 3D.

Geometry-Intensity Feature: Total Glycolytic Volume (TGV): defined as the product of volume and SUV_{mean} within a VOI. TGV measures the total metabolic activity (12).

Statistical Analysis

The accuracy of each feature to predict the pathologic tumor response to CRT was quantified using AUCs. An AUC of <0.7 was considered to have low diagnostic accuracy, $0.7-0.9$ to have moderate accuracy, and >0.9 to have high accuracy. In addition, the Mann-Whitney test was used to test the statistical significance at the 0.05 level.

RESULTS

Predicting Accuracy of Features

Features with the highest AUCs and not highly correlated (correlation coefficient <0.8) with others in each category are listed in Table 3, along with the VOIs and images from which they were extracted. Figure 1 shows example boxplots used to visually evaluate how well and in which direction a feature separated responders from nonresponders.

Traditional SUV Intensity Measures— SUV_{max} decline and SUV_{max} ratio were significant predictors and better than all SUV_{peak} measures (not shown). The larger the decline in SUV_{max} , the more likely the tumor was a responder (Fig. 1A).

New Spatial-Temporal Features—All of the most accurate spatial-temporal features in Table 3 were extracted from $VOI_SUV_{2.5}$, representing the entire hypermetabolic tumor volume. Their AUCs were higher than those (not shown) extracted from the peak area (VOI_SUV_{peak}).

Intensity Features: Two SUV intensity features were significant. One was SUV_{mean} decline; the larger the decline in SUV_{mean} , the more likely the tumor was a responder. The other was skewness pre-CRT; as illustrated in Fig. 2, a histogram with a more elongated tail on the higher SUV end or relatively fewer higher SUVs has a greater skewness. A tumor with a greater skewness was more likely a responder (Figs. 1B and 2).

Texture Features: Three texture features were significant, and all were extracted from the post-CRT SUV images: inertia, correlation, and cluster prominence. The lower the local SUV variation, the smaller the inertia. The more similar SUV a voxel had to its neighbors, the larger the correlation. The more uniform or less focal the SUV distribution, the smaller the cluster prominence. Smaller inertia, larger correlation, and smaller cluster prominence were positively associated with the likelihood that a tumor was a responder (Fig. 3).

Geometry Features: The less spherical the tumor or the larger decrease in tumor volume or tumor diameter, the more likely the tumor was a responder, although no geometry feature was significant.

Geometry-Intensity Feature: The larger the decline in TGV, the more likely the tumor was a responder, although this association did not reach the level of significance.

DISCUSSION

Two new PET intensity features and three PET texture features were found to be significant predictors of pathologic response to neoadjuvant CRT in esophageal cancer. They had the same or moderately higher AUCs than the traditional SUV response measures of SUV_{max} and SUV_{peak} . These features quantified novel spatial-temporal tumor characteristics that are

not conventionally captured and may be more useful than traditional SUV response measures in evaluation of tumor response.

Both biological and clinical data demonstrate that FDG uptake is related to cancer cell density. A significant decline in tumor FDG uptake indicates a loss of viable cancer cells and response to therapy (12). Both SUV_{mean} decline and SUV_{max} decline are measures of this change, with slightly higher accuracy using SUV_{mean} decline. Another intensity feature, skewness, provides new information on the statistics of SUVs within a tumor. The two tumors in Fig. 2 have very similar SUV_{max} but with different distributions at higher SUVs. According to skewness, the tumor that has fewer higher SUVs is more likely a responder. This suggests that examining the abundance of higher SUVs may be useful in addition to the degree of the highest SUV. In this study, texture features have higher accuracy than traditional SUV response measures, results similar to those reported by Tixier et al. and El Naqa et al. (10, 11). Inertia, correlation, and cluster prominence quantify the local spatial patterns of post-CRT SUV in terms of variation, correlation, and uniformity, respectively. For a tumor with homogeneous FDG uptake, the variation is lower, correlation is higher, and uniformity is higher (Fig. 3A), and vice versa for a tumor with heterogeneous FDG uptake (Fig. 3B). They all suggest that a tumor with homogeneous FDG uptake post-CRT is more likely a responder. A similar conclusion was drawn by Tixier et al. (10) for FDG uptake pre-CRT. The underlying biological mechanisms for the effect of FDG uptake heterogeneity on tumor response are not clearly understood (10, 11). However, we could reasonably hypothesize that in a responder, tumor cell metabolic activity may have been greatly suppressed to the level of surrounding normal tissue, resulting in homogeneous FDG uptake. No geometry features (including tumor volume, diameter, and shape) were significant predictors. This suggests that simple morphologic characteristics of esophageal cancer may be of little prognostic value, consistent with the low accuracy of CT-based features reported in this study and that of Westerterp et al. (7).

PET evaluation of tumor response is mainly based on changes in SUV (6, 12); however, in a few studies pre-CRT SUV alone was used (10, 19). Our results show that changes in SUV are more accurate predictors than either pre-CRT SUV or post-CRT SUV alone (Table 3). Also, changes in tumor size (volume and diameter) are more accurate predictors than pre-CRT or post-CRT tumor size alone. Texture features describing the spatial patterns of the residual FDG uptake are more accurate predictors than those of either the initial FDG uptake or of changes in FDG uptake.

Traditional SUV response measures (SUV_{max} and SUV_{peak}) were extracted from the most metabolically active part of a tumor. Table 3 shows that all of the most accurate predictive features in all categories, however, were extracted from the entire (hypermetabolic) tumor. For intensity features, SUV_{mean} decline has slightly higher AUC than SUV_{max} and SUV_{peak} . For texture and geometry features, the peak VOI is too small to extract any meaningful information. These results suggest that it may be useful to evaluate the response of the entire tumor in addition to its most active part. In this study, a threshold of $SUV = 2.5$ was used to assist the radiologist in defining tumor volumes. This threshold has been widely used for classifying FDG uptake in various cancers and has been shown to delineate esophageal tumors with reasonable accuracy (19, 20). Most thresholded volumes were contiguous and deemed reasonably accurate by the radiologist, with only minimal manual editing required, even in low-grade tumors. In only one patient, three adjacent hypermetabolic regions were barely disconnected and manual joining was required. We should point out that the delineated $VOI_{SUV_{2.5}}$ is not an exact representation of the underlying tumor cell–normal tissue boundary. The accuracy of tumor delineation in FDG PET imaging is limited by its spatial resolution, normal tissue uptake, and other factors. We and others have developed more advanced and more complicated methods that would generate somewhat different

tumor VOIs, but all would be much larger than $VOI_{SUV_{peak}}$. The conclusion that it may be useful to evaluate the response of the entire tumor is likely to be valid.

One limitation of this study is that only the predictive accuracy of each individual feature was examined. The fact that these features characterize different properties of a tumor suggests that they contain complementary information. We are developing machine learning methods that selectively combine features for more reliable prediction. Another limitation is that this is a retrospective study of a small patient cohort. The predictive accuracy and stability of the new features should be validated in a larger, prospective patient cohort.

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Summary

The accuracy of FDG-PET/CT in predicting response to chemoradiotherapy (CRT) is still low in esophageal cancer. By quantitatively analyzing FDG-PET/CT images both before CRT and after CRT, comprehensive spatial-temporal PET features were found to be useful predictors of pathologic tumor response, providing complementary information to traditional PET response measures.

Fig. 1. Boxplots for (A) SUV_{max} decline; (B) skewness; (C) inertia; (D) roundness.

Fig. 2. Skewness in pre-CRT PET. (A) A responder tumor with SUV histogram (B), skewness = 1.63; (C) A non-responder tumor with SUV histogram (D), skewness = 0.66.

Fig. 3. Texture features in post-CRT PET. Three-plane views of: (A) a responder tumor with inertia = 3.5, correlation = 0.12, and cluster prominence = 1254.4; (B) a nonresponder tumor with inertia = 5.5, correlation = 0.07, and cluster prominence = 6155.3.

TABLE 1Characteristics of Patients ($n = 20$)

Characteristic	No. of patients
Sex	
Male	18
Female	2
Primary site	
Proximal	0
Distal	20
Mid	0
Throughout	0
Histology	
Squamous cell carcinoma	3
Adenocarcinoma	17
Histologic grade	
Well differentiated	3
Moderately differentiated	10
Poorly differentiated	5
Unknown	2
TNM stage	
T1	0
T2	2
T3	18
T4	0
N0	6
N1	14
M0	18
M1 (M1a)	2
Pathologic response	
Pathologic complete response (pCR)	6
Microscopic residual disease (mRD)	4
Gross residual disease (gRD).	10

TABLE 2Spatial-temporal ^{18}F FDG-PET Features

Intensity Features
Minimum, Maximum, Mean, Standard Deviation, Sum, Median, Skewness, Kurtosis, Variance
Texture Features
Energy, Entropy, Correlation, Inverse Difference Moment, Inertia, Cluster Shade, Cluster Prominence, Haralick Correlation
Geometry Features
Volume, Major Axis Length, Minor Axis Length, Eccentricity, Elongation, Oriented Bounding Box Volume, Bounding Box Volume , Roundness, Region Ratio, Orientation, Feret Diameter, Number Of Lines, Perimeter, Physical Size, Flatness
Geometry-Intensity Feature
Total Glycolytic Volume

TABLE 3

AUCs and *p*-values of the most accurate SUV features for the prediction of pathologic response to neoadjuvant chemoradiotherapy in patients with esophageal cancer

Feature	VOI	Image*	AUC	<i>p</i> -value
Traditional SUV Intensity Features				
SUV _{max} decline [†]	SUV _{max} point	Pre, Post	0.76	0.05
SUV _{max} ratio [‡]	SUV _{max} point	Pre, Post	0.76	0.05
SUV _{max} Pre	SUV _{max} point	Pre	0.70	0.14
SUV _{max} Post	SUV _{max} point	Post	0.61	0.47
Intensity Features				
SUV _{mean} decline [†]	VOI_SUV _{2.5}	Diff	0.79	0.03
Skewness	VOI_SUV _{2.5}	Pre	0.76	0.05
Texture Features				
Inertia	VOI_SUV _{2.5}	Post	0.85	0.01
Correlation	VOI_SUV _{2.5}	Post	0.80	0.03
Cluster prominence	VOI_SUV _{2.5}	Post	0.78	0.04
Geometry Features				
Roundness	VOI_SUV _{2.5}	Pre	0.71	0.12
Volume change [†]	VOI_SUV _{2.5}	Pre, Post	0.71	0.12
Diameter change [†]	VOI_SUV _{2.5}	Pre, Post	0.64	0.30
Geometry-Intensity Feature				
TGV change [†]	VOI_SUV _{2.5}	Diff	0.74	0.08

* Pre = Pre-CRT SUV, Post = Post-CRT SUV, Diff = Pre - Post.

[†] Decline or change = Pre - Post.

[‡] Ratio = Post / Pre.