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REVIEW ARTICLE

Computerized PET/CT image analysis in the evaluation of tumour response to therapy

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ABSTRACT

Current cancer therapy strategy is mostly population based, however, there are large differences in tumour response among patients. It is therefore important for treating physicians to know individual tumour response. In recent years, many studies proposed the use of computerized positron emission tomography/CT image analysis in the evaluation of tumour response. Results showed that computerized analysis overcame some major limitations of current qualitative and semiquantitative analysis and led to improved accuracy. In this review, we summarize these studies in four steps of the analysis: image registration, tumour segmentation, image feature extraction and response evaluation. Future works are proposed and challenges described.

Current cancer therapy strategy is mostly population based; it is developed from a certain patient group (disease site and tumour stage) and applied to new patients belonging to the same group. However, there are large differences in tumour response to such population-based therapy, implying that there are still biological and clinical heterogeneity even among patients within the same group. It is therefore important for the treating physicians to know individual tumour response so that they can determine whether to continue, change or abandon a population-based treatment strategy. Furthermore, accurate and early evaluation of tumour response is critical in clinical trials designed to test the effectiveness of new cancer therapies.

Traditionally, response of solid tumours to cancer therapy is evaluated visually or measured with anatomic changes in tumour diameters using CT imaging according to the Response Evaluation Criteria in Solid Tumours (RECIST) or World Health Organization (WHO) criteria.^{1–3} Fluorine-18 fludeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) imaging, which measures functional (metabolic activity) changes, has shown advantages over anatomic imaging as a response evaluation tool in many malignancies.^{3–8} Metabolic response is evaluated visually and measured semiquantitatively with changes in tumour standard uptake value (SUV) using ¹⁸F-FDG-PET imaging according to the PET Response Criteria in Solid Tumors (PERCIST)³ or the European Organization for Research

and Treatment of Cancer (EORTC)⁹ criteria. SUV is calculated as:

$$SUV = \frac{Q}{\frac{Q_{inj}}{W}} \quad (1)$$

where Q is the tumour radiotracer concentration (MBq l^{-1}) measured by PET scanner within a region of interest (ROI); Q_{inj} is the decay-corrected injected activity (MBq); and W is the body weight (kg).⁹ SUV can be normalized to lean body mass (SUV_{lbm}) or body surface area (SUV_{bsa}) instead of body weight used in Equation (1).³ Generally, the maximum SUV within a tumour (SUV_{max}) is used for evaluation, while the mean SUV in a peak uptake region (SUV_{peak}) or in the tumour (SUV_{mean}) are sometimes reported.³ At present, although radiologists and nuclear medicine physicians evaluate tumour response mainly in CT and PET, respectively, they often use PET and CT as a complementary modality to achieve more complete and more accurate assessment. Despite these encouraging results, the reported accuracy for predicting response to therapy using PET/CT is low, with averaged sensitivity, specificity and accuracy all around 70% (range, 30–100%^{3,10–12}). We propose that in order for clinicians to confidently make critical treatment decisions, a higher predictive accuracy ($\geq 90\%$) is required in both sensitivity and specificity.

In recent years, many studies proposed the use of computerized PET/CT image analysis in the evaluation of

tumour response. Results showed that computerized analysis overcame some major limitations of current qualitative and semiquantitative analysis and led to improved accuracy. In this review, we summarize these studies in four steps of the analysis: image registration, tumour segmentation, image feature extraction and response evaluation. This review focuses on computerized methods; includes only patient studies; mainly concerns with solid tumour response to chemotherapy (CTx), radiotherapy (RT) and chemoradiotherapy (CRT) (excludes surgery); and considers clinical PET/CT images only (excludes dynamic PET and methods for image reconstruction).

IMAGE REGISTRATION BETWEEN BASELINE AND EVALUATION PET/CTS

In computerized PET/CT image analysis, PET and CT images are analysed simultaneously rather than read separately by a nuclear medicine physician and a radiologist. The baseline PET/CT and evaluation PET/CT are aligned with image registration techniques rather than aligned visually. Registering serial PET/CT images provides new opportunities to quantify changes at the original tumour site and to model changes as a function of spatial location. Image registration is the process of aligning the evaluation PET/CT (moving image) into the image co-ordinate system of the baseline PET/CT (fixed image) with a transformation model. The transformation model refers to a function that maps the co-ordinate of each pixel in the moving image to the co-ordinate system of the fixed image (Figure 1). This mapping procedure is also called “image warping” and the transformed moving image is called “warped image”. Most PET/CT images are acquired with a combined PET/CT scanner where the PET image is hardware registered to the CT image from the same session. If somehow the PET and CT images from the same session are not registered, an image registration (generally called co-registration) can be used to align them. Since the PET scans suffer from lack of anatomic details and poor image resolution, usually the serial image registration is based on the CT images—the evaluation CT is registered to the baseline CT, and then the resulting transformation model is applied to transform the evaluation PET to the baseline imaging (PET/CT) space. Nonetheless, van Velden et al¹³ showed that (low-dose) CT-based registration had worse performance than did PET-based registration. This poorer performance may be expected owing to the poorer contrast and increased noise of the low-dose CT

images used in that study. Furthermore, the performance was evaluated using the similarity between the volume of interest (VOI) defined by 50% SUV_{max} threshold ($VOI_{50\%}$) in the evaluation PET and the warped baseline $VOI_{50\%}$. This performance metric was defined in PET images and thus higher performance for PET-based registration may be expected.

Image registration algorithms can be largely classified into rigid registration and deformable registration according to the output transformations. General image registration is a well-developed field,^{14,15} therefore this review includes only those studies related to tumour response evaluation with PET/CT.

Rigid registration

Rigid registration is one of the simplest forms of image registration. It preserves the topology of the anatomical structures by allowing only rotations and translations in the transformation. Although rigid registration is straightforward, it has been shown to achieve good alignment between baseline and evaluation scans in tumour response assessment studies^{12,16–19} (Table 1). Necib et al¹² reported their study in metastatic colorectal tumour response assessment using PET/CT scans acquired before and during CTx. They first conducted a rigid registration to register CT scans. The transformation was then applied for the alignment of PET scans. The PET findings in 78 lesions correlated well with the RECIST response assessment. In the study by Tan et al,^{17,18} the pre-CRT and post-CRT ^{18}F -FDG-PET/CT scans of patients with oesophageal cancer were similarly rigidly registered. The changes of comprehensive spatial temporal features from ^{18}F -FDG-PET scans were found to be useful for the assessment of response to CRT. Vera et al¹⁹ applied similar rigid registration to align baseline and mid-therapy ^{18}F -FDG-PET/CT scans to monitor the early tumour metabolic response to CRT of patients with oesophageal cancer. The results showed that the changes in ^{18}F -FDG uptakes provided prognostic information for the early tumour metabolic response. Aristophanous et al¹⁶ examined 12 patients with non-small-cell lung cancer (NSCLC). Three-dimensional (3D) ^{18}F -FDG-PET/CT scans were acquired before RT and after RT. Four-dimensional (4D) scans with five phases were obtained right after the completion of 3D scans. The results demonstrated that the 4D-PET scans captured larger changes in ^{18}F -FDG uptake from pre-RT to post-RT than did 3D-PET scans and could potentially solve the issue of signal loss in 3D-PET scans owing to respiratory motion.

Deformable registration

Rigid registration can align the baseline and evaluation scans efficiently. However, since these scans are acquired at different time points (before and during/after treatment), complex deformable distortions, such as shrinking, folding and stretching, may occur in organs (e.g. stomach, breast and oesophagus) and soft tissue owing to tumour shrinkage; weight loss or gain; respiration; changes in patient positioning; or movement during the image acquisition procedure. Rigid registration cannot compensate for deformable distortions, thus may lead to misregistration between baseline and evaluation scans. Deformable image registration attempts to solve this issue by providing more detailed local transformation (displacement field) between the fixed and the moving images.

Figure 1. Image registration is the process of mapping the moving image to the co-ordinate system of the fixed image with a transformation model.

Table 1. Positron emission tomography/CT-based tumour response assessment studies using rigid registration, deformable registration or rigid registration followed by (+) deformable registration algorithms

Study	Type of registration	Abnormality	Treatment	Scanning time
Aristophanous et al ¹⁶	Rigid	Non-small-cell lung cancer	RT	Before and after
Necib et al ¹²	Rigid	Metastatic colorectal cancer	CTx	Before and after
Tan et al ^{17,18}	Rigid	Oesophageal cancer	CRT	Before and after
Vera et al ¹⁹	Rigid	Oesophageal cancer	CRT	Before and during
Cannon ²⁰	Deformable	Head and neck cancer	RT or CRT	Before and after
Roels et al ²¹	Deformable	Rectal cancer	CRT	Before, during and after
van Velden et al ¹³	Deformable	Advanced colorectal carcinoma	CTx	Before and after
Due et al ²³	Rigid + deformable	Head and neck cancer	RT	Before and after
Li et al ²⁴	Rigid + deformable	Breast cancer	CTx	Before, during and after
Yip et al ^{25,26}	Rigid + deformable	Prostate cancer	Molecular targeted therapy or CTx	Before and during

CRT, chemoradiotherapy; CTx, chemotherapy; RT, radiotherapy.

Many deformable registration algorithms have been proposed^{14,15,27} and used in tumour response studies. Cannon²⁰ showed that “Demons”-based deformable registration improved the accuracy, compared with rigid registration, in assessment of tumour response with SUV_{peak} and VOI_{50%} in head and neck cancer. Roels et al²¹ investigated the use of MRI and ¹⁸F-FDG-PET/CT for rectal tumour response to CRT. Images acquired before, during and after CRT from 15 patients were registered using B-spline registration with mutual information as similarity metric. The results showed that the integration of MRI and ¹⁸F-FDG-PET/CT improved the measurement of tumour volume. To improve the efficiency of the deformable registration, usually the images are first roughly aligned using rigid registration, and then a deformable registration is applied to the rigidly registered images for fine tuning of the alignment between images. This strategy has been used for the tumour response assessment studies of head and neck cancer,²³ breast cancer²⁴ and prostate cancer.^{25,26}

In general, deformable registration approaches assume that all structures in the moving image can find their correspondence in the fixed image.²⁸ However, this assumption may not be valid in the case of tumour response studies. The changes in tumour size, that is, tumour shrinkage or even disappearance, can occur as the treatment progresses, producing uncertainty in the correspondence between the baseline and the evaluation scans. Because of the changes in tumour volume, deformable registration may lead to the appearance of “fake tumour tissues” in the warped images.²⁹ These unattainable tissues can result in errors in the assessment of tumour response. To address this and other issues, Varadhan et al³⁰ constructed a comprehensive framework for the validation of deformable image registration. This framework evaluates the performance of deformable image registration using (1) inverse consistency error (between forward

and inverse registrations); (2) anatomical correspondences between original and deformed image sets by quantitatively comparing the original organ contours with those obtained from warping the original contours with the displacement field derived from registration; and (3) physical characteristics of the displacement field, namely the Jacobian and harmonic energy, for quantifying the preservation of topology, physical feasibility and smoothness of the deformation.

TUMOUR SEGMENTATION

The current tumour response evaluation criteria (visual, RECIST and PERCIST) are non-volumetric and do not need segmentation of the tumour volume. Computerized evaluation approaches provide volumetric information and thus need segmentation of tumours. Tumour segmentation can be performed either manually by physicians or (semi-)automatically using image analysis tools. The accuracy of a tumour segmentation method has been hard to evaluate in patients owing to the lack of ground truth. In response evaluation that involves two or more serial image studies, the reproducibility of a segmentation method is as important as its accuracy.

Manual delineation

In diagnostic imaging, generally there is no need to segment a tumour volume. In RT treatment planning, tumour segmentation or target delineation is a critical process. The gross tumour volume (GTV) is manually delineated by the radiation oncologist on CT, with the aid of PET, MRI and other information about the size, shape and location of the tumour. Because of the uncertainties in microscopic extension of the tumour, in manual contouring and in patient set-up, as well as other uncertainties, disease-dependent margins (typically 0.5–2.0 cm, but can be up to 5 cm) are used to expand the GTV

into a planning target volume. Leong et al²² described a rigorous manual delineation protocol for oesophageal cancer. For the CT alone data set, GTV included the primary tumour in the oesophagus, which was defined as regions of abnormal oesophageal wall thickening, plus regions of tumour described on oesophagoscopy, and regional lymph nodes ≥ 10 mm in maximal diameter. The entire axial area of oesophagus was included. For the PET/CT data set, GTV was defined using the complementary features of PET and CT—a visual interpretation of the PET image was used to determine the nature of a lesion and the CT image to determine its anatomical boundary. In cases where no boundary was visible on CT (e.g. cranial or caudal extent of primary tumour), the ^{18}F -FDG-avid tumour volume was defined using a qualitative visual assessment of the PET image displayed on a liver-SUV-normalized greyscale.

Although Leong et al²² and MacManus et al³¹ have shown that visual interpretation of the PET image was more accurate and reproducible than thresholding-based semiautomatic segmentation methods, manual contouring has large interobserver and intraobserver variations and is time consuming.³² Therefore, manual contouring is generally not used for tumour response evaluation involving serial image studies.

Semiautomatic segmentation

On positron emission tomography only

Many solid tumours (including lung, gynecological and oesophageal cancer) are ^{18}F -FDG-avid and appear much more prominent in ^{18}F -FDG-PET images than in anatomic CT or MRI images. This observation along with the essential fact that PET captures functional information motivated many groups to develop semiautomatic tumour segmentation methods on PET. Zaidi and El Naqa³³ gave a comprehensive review on semiautomatic tumour segmentation methods on PET that included (1) thresholding methods, (2) variational approaches, (3) learning methods and (4) stochastic modelling-based techniques. Variational approaches utilize the intensity variation between the tumour and the surrounding tissues for the segmentation task. These include edge detector, watershed transform, gradient-based methods, active contour models and level set methods. Learning methods include classification methods [e.g. artificial neural network and support vector machine (SVM)] and clustering methods (e.g. k-means and fuzzy C-means). They also summarized the advantages and limitations of five strategies used for the assessment of PET tumour segmentation accuracy. These include manual segmentation by experts, the use of simulated or experimental phantom studies with known tumour volumes, the comparison with correlated anatomical GTVs defined on CT or MRI, and the comparison with tumour volumes measured on the macroscopic specimen derived from histology. Simulated or experimental phantoms are mostly too simplified to represent the complex human anatomy and physiology. The methods and results from such studies are often not generalizable to patient studies. PET-GTV is generally different from anatomic GTVs defined on CT or MRI. Such difference is expected, as PET images the function of tissues rather than the structure of tissues. Since none of these imaging modalities can be considered as ground truth, comparing PET-GTV to anatomic GTVs has limited value. The idea of comparing PET-GTVs

with histology tumour volumes is attractive. However, there are large uncertainties in many steps of the procedure, including resecting the tumour, slicing and histology processing, imaging and denoting tumour areas in each slice, and reconstructing and aligning the histology tumour volume with *in vivo* PET/CT images. The combined impact of these uncertainties led to poor and rather suspicious results of such comparison (Dice similarity coefficients < 0.70 ³⁴).

The Turku PET symposium organized a challenge to delineate tumours on PET images³⁵ (http://www.turkupetcentre.net/PET_symposium_XII_software_session/ContouringChallengeResults/index.php) using two phantoms and three head and neck tumours. 13 groups presented their methods that included manual contouring, thresholding, region growing, watershed, gradient based, pipeline (multistep) and graph based (multimodality). The general accuracy scores were low (mean Dice similarity coefficient of 0.61 for patients), mainly owing to the heterogeneity in tumour uptake and blurred edges between tumour and normal tissue. Their results revealed benefits of high levels of user interaction with simultaneous visualization of CT images and PET gradients.

On CT only

Semiautomatic tumour segmentation methods were developed on CT for only a few diseases that show marked difference in CT attenuation between the tumour and the surrounding normal tissues. These include mainly lung tumour and liver tumour in contrast-enhanced CT (CECT). Lung nodule (can be malignant or benign) segmentation has been well studied in computer-aided diagnosis (CAD) systems. El-Baz et al³⁶ gave a comprehensive review of CAD systems for lung cancer that includes a review of 11 categories of segmentation methods. These include thresholding, mathematical morphology, region growing, deformable model, dynamic programming, spherical/ellipsoidal model fitting, probabilistic classification, discriminative classification, mean shift, graph-cuts and watersheds. The success rates of these methods were 80–95%. Segmentation of solitary and large solid lung nodules is technically straightforward, but problems arise when targeting (1) small nodules, (2) nodules attached to vessels, (3) nodules attached to parenchymal wall and diaphragm, and (4) ground-glass opacity nodules. The success rates for these challenge cases were 70–80%. El-Baz et al³⁶ also presented works that were designed to address these challenge cases. As an example, Zhao et al³⁷ developed a modified 3D multicriterion segmentation algorithm. This algorithm applied pre-defined size constraints to remove surrounding blood vessels and required a rough manual ROI to separate the adjacent mediastinum or the liver.

The Medical Image Computing and Computer Assisted Intervention Society organized a 3D Liver Tumour Segmentation Challenge 2008 (http://grand-challenge.org/All_Challenges) using 30 liver tumours (hepato-cellular carcinoma, hemangioma and metastasis). 14 groups presented their methods that included interactive graph-cut, thresholding, level set, region growing, and statistics-based and deformable models. The total accuracy scores of these methods were low (approximately 70%), mainly owing to the challenges in the segmentation of lesions with low contrast compared with normal liver tissue and lesions with heterogeneous CT attenuation.

On positron emission tomography/CT

Inherently, it is more advantageous to combine PET and CT images in defining the tumour volume, since they provide additional information compared with PET only and CT only. However, since PET and CT images capture fundamentally different information of a tumour, the two sources of information can be either complementary or contradictory. Furthermore, other factors, including patient motion (physical or physiological such as respiratory), image artefacts, and difference in image resolutions, all add to the complication of this problem. The success of a PET/CT tumour segmentation algorithm relies on effective combination of PET and CT information.

Some existing single-modality segmentation algorithms can be extended to multimodality segmentation. These include

classification- or clustering-based algorithms with inherent capability to handle multidimensional data,^{38,39} deformation shape (active contour) model⁴⁰ and graph-based segmentation.^{41,42} Yu et al³⁸ extracted PET and CT texture features and used them in a decision tree-based K-nearest-neighbour classifier, which was trained with manual contours, to label each voxel as either “normal” or “abnormal”. The limitation of such voxelwise classification or clustering algorithm was the loss of spatial connectivity. To address this issue, El Naqa et al⁴⁰ developed an active contour model using multivalued level sets with empirical weighting factors of PET and CT images. Bagci et al⁴¹ developed a graph-based random walk image segmentation that used a combined (product) graph with empirical weighting factors of PET and CT images. In general, it is challenging to identify the appropriate weighting factors for each modality for a disease site. Han et al⁴² developed a graph-based

Figure 2. Co-segmentation of the tumour in both positron emission tomography (PET) and CT images. Typical lung tumour segmentation in three-plane views. (a–c) Two-dimensional slices of a three-dimensional CT image with the reference standard (red/dark grey) and outlines of spherical initialization (green/light grey and yellow/white). (d–f) Proposed cosegmentation results in the CT image. (g–i) Cosegmentation results in the PET image. Reproduced from Song et al⁴³ with permission from IEEE. Colours appear only in the online version.

Markov random field segmentation with a regularized energy term that penalizes the segmentation difference between PET and CT. In recognition of possible differences of tumour volume defined in PET from that defined in CT, Song et al⁴³ extended the work of Han et al to generate tumour volumes in both modalities, rather than a compromised identical one (Figure 2). Both works required empirical determination of multiple parameters. Tan et al⁴⁴ developed a multimodality adaptive region-growing algorithm with combined PET and CT similarity criteria. Although most multimodality segmentation studies showed improved accuracy compared with single-modality algorithms, more studies are needed to validate these algorithms.

IMAGE FEATURES AS PROGNOSTIC OR PREDICTIVE FACTORS

With the emerging PET/CT performed at multiple time points for each patient, it becomes more important to analyse the serial images quantitatively, select and combine complementary information from the two sources—PET for functional information and CT for anatomic information, for accurate and personalized evaluation of tumour response to therapy. The bountiful information extracted from images was traditionally called image features, while recently the term Radiomics has been proposed specifically for medical images with the hypothesis that genomic and proteomic patterns can be quantified with image features.⁴⁵

CT features

Assessment of the change in tumour burden or tumour response is an important feature of the clinical evaluation of cancer therapeutics.¹ Traditionally, response of solid tumours to cancer therapy is evaluated visually or measured with anatomic changes in tumour diameters using CT imaging according to the RECIST or WHO criteria.^{1–3} Briefly, RECIST¹ defines complete response (CR) as disappearance of all target lesions; partial response (PR) as at least 30% decrease in the sum of (the largest) diameters (in the axial plane) of target lesions from the baseline; progressive disease (PD) as at least 20% increase and an absolute increase of at least 5 mm in the sum of diameters; and stable disease as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Recent studies show that new CT features, including volumetric, attenuation, morphologic, structure and texture descriptors, have advantages over the RECIST and WHO criteria in certain tumour types. Both RECIST and WHO criteria are linear measurements of tumour size, which have limitations related to technical variability, tumour morphology and reader decisions. With thin-section CT, it is possible to measure tumour volume using segmentation methods with adequate spatial resolutions,^{37,46} which overcomes some of the limitations of linear measurements. Changes in attenuation in CECT were shown to correlate better with response than did changes in tumour size in hepatocellular carcinoma⁴⁷ and gastrointestinal stromal tumour.⁴⁸ One advantage of attenuation features is that they can take into consideration tumour necrosis.⁴⁷ In colorectal liver metastases, morphological evaluation based on metastases, changing from heterogeneous masses into homogeneous hypoattenuating lesions, had

a statistically significant association with pathological response and survival, whereas RECIST did not.⁴⁹ Adding structural features (the presence or absence of marked central necrosis) to morphology, attenuation and size features in CECT was found to be more accurate than response assessment by RECIST in renal cell carcinoma.⁵⁰ CT texture features characterizing the spatial variations of tissue density were shown to be prognostic factors in NSCLC^{51,52} and oesophageal cancer.⁵³

Positron emission tomography features

In recent years, ¹⁸F-FDG-PET imaging, which measures functional (metabolic activity) changes, has shown advantages over anatomic imaging as a response evaluation tool in many malignancies.^{3–8} For example, in NSCLC^{4,54} and oesophageal cancer,^{6,11,55–58} ¹⁸F-FDG-PET imaging has been shown to have superior results in predicting survival and pathological response to therapy compared with conventional CT imaging. Both EORTC⁹ and PERCIST³ have developed guidelines for the methodology of evaluating tumour response with serial ¹⁸F-FDG-PET, with the goal of achieving standardization in clinical trials. Despite these encouraging results, the reported accuracy for predicting response to CRT using PET/CT is often not high enough (<90%) for clinicians to confidently make critical treatment decisions. For example, a pooled sensitivity of 67% (range, 33–100%) and specificity of 68% (range, 30–100%) were reported in 20 studies for oesophageal cancer.¹¹ Furthermore, none of these studies has demonstrated both high sensitivity and high specificity.

The majority of the published ¹⁸F-FDG-PET studies quantify therapeutic response in tumours with SUV_{max}.^{20,59,60} In these studies, changes in SUV_{max}, or sometimes SUV_{max} pre-therapy or post-therapy only, are correlated to post-therapy pathological response or survival, or both. SUV_{max} is a single-point estimate that ignores changes in the distribution of ¹⁸F-FDG uptake within a tumour and in the extent of metabolic abnormality. However, it is known that most solid tumours consist of various malignant and non-malignant components so that they show significant heterogeneity in both the degree and distribution of ¹⁸F-FDG uptake. Heterogeneity in ¹⁸F-FDG uptake is associated with important biological and physiological parameters^{61–65} and has been shown to be prognostic in many cancers.^{61,62,64–68} Another limitation of SUV_{max} is that it exhibits dependence on image noise and image resolution.^{3,69–71} Recent studies suggest that new PET/CT features considering spatial information, such as tumour volume,⁷² total glycolytic volume,³ standardized added metabolic activity (total excess tumoural SUV above the tumour background),⁷³ SUV histogram distance,¹⁸ tumour shape,^{67,74} texture features^{52,65–67,75,76} and cumulative SUV–volume histograms^{67,77} are more informative than SUV_{max} and tumour diameters for the prediction of tumour response. Particularly, Tan et al¹⁷ demonstrated that comprehensive spatial–temporal ¹⁸F-FDG-PET features (intensity, texture and shape) were more useful predictors of pathological tumour response to CRT than were conventional SUV measures in oesophageal cancer (Figures 3 and 4). Leijenaar et al⁷⁶ showed that the majority of these PET-derived features had both a high test–retest (71%) and interobserver (91%) stability, suggesting that further research is warranted.

RESPONSE EVALUATION

PET/CT has been utilized to evaluate or predict tumour response in a number of malignancies. Schwarz et al⁷⁸ correlated the changes in cervical tumour ¹⁸F-FDG uptake with tumour response and survival. Janssen et al⁷⁹ and Hatt et al⁸⁰ both showed that PET/CT after the first 2 weeks of CRT provided the best pathological response prediction for locally advanced rectal cancer. Munden et al⁸¹ and McKeown et al⁸² reviewed the usage of PET/CT for response assessment in oesophageal cancer and colorectal cancer, respectively. Many studies have regarded PET/CT as both a predictor of treatment response and a prognosticator for NSCLC.^{83,84} A systematic review of PET for prediction of tumour response to neoadjuvant therapy in patients with oesophageal cancer revealed mixed results.¹¹

Conventional method: cut-off value of a single measurement

Most published PET/CT tumour response criteria were based on cut-off values of a single measurement such as change in SUV_{max} .^{59,60} The optimal cut-off values defining response varied considerably for different diseases as well as for the same disease. For NSCLC, the criteria for tumour response included 50%⁸⁵ or 80% decrease in SUV_{max} ⁸⁶ and SUV thresholds ranging from 2.5 to 4.5 after CRT.⁸³ For oesophageal cancer, criteria for tumour response varied from 20% to 81% decrease in SUV_{max} in 20 studies.¹¹ Janssen et al showed that 43% decrease in SUV_{max} on PET/CT taken at Day 15 of CRT was the best predictive factor for pathological response of rectal tumour.⁷⁹ Oh et al⁸⁷ showed that CR of cervical cancer on post-therapy PET/CT can be predicted accurately by 59.2% decrease in SUV_{max} .

Predictive model: logistic, support vector machine

The current approach of using cut-off value of a single measurement for tumour response is simple, but it has several limitations. The single measurements, tumour diameters and SUV_{max} assess anatomic response and functional response independently. They ignore potentially important spatial information such as tumour heterogeneity and tumour shape. The aforementioned considerable variations in optimal cut-off values (even for the same disease) suggested their dependence of specific data set and thus limited their use in other data sets. Finally, the reported accuracy in tumour response evaluation with PET/CT is low, with averaged sensitivity, specificity and accuracy all around 70% (range, 30–100%^{3,10–12}), and few studies have demonstrated both high sensitivity and high specificity.

As described above, many new image features have been extracted to characterize various properties of a tumour in PET and CT. These features contain new and potentially more important information than do traditional PET/CT response measures. In order to take advantage of multiple features, advanced response predictive models have been proposed. Vaidya et al⁵¹ showed that multivariable logistic regression (LR) improved the prediction of local failure for NSCLC by combining complementary PET and CT features. Zhang et al⁸⁸ constructed SVM models using selected features from (1) conventional PET/CT response measures, (2) clinical parameters and demographics, (3) comprehensive spatial-temporal ¹⁸F-FDG-PET features, and (4) all features. The modelling process is shown in Figure 5. With cross-validation, the models achieved 100% sensitivity and 100% specificity for the

Figure 3. Illustration of an intensity feature quantifying the skewness of standard uptake value (SUV) histogram in pre-chemoradiotherapy positron emission tomography for oesophageal tumour. (a) A responder tumour with (b) SUV histogram, where skewness = 1.63; (c) a non-responder tumour with (d) SUV histogram, where skewness = 0.66. Reproduced from Tan et al¹⁷ with permission from Elsevier.

Figure 4. Illustration of three texture features quantifying the standard uptake value heterogeneity in post-chemoradiotherapy positron emission tomography for oesophageal tumour. Three-plane views of (a) a responder tumour where inertia = 3.5, correlation = 0.12 and cluster prominence = 1254.4; (b) a non-responder tumour in which inertia = 5.5, correlation = 0.07 and cluster prominence = 6155.3. Reproduced from Tan et al¹⁷ with permission from Elsevier.

prediction of pathological tumour response to CRT in patients with oesophageal cancer. The authors compared the performance of LR and SVM models. When there are more candidate features (feature Groups 3 and 4), SVM achieved significantly higher accuracy than did LR because SVM has been proved to be able to extract complex relationships among a large number of features.⁸⁹ On the other hand, when there are a small number of candidate features (feature Groups 1 and 2), LR achieved better results than did SVM.

DISCUSSION AND FUTURE WORKS

While excluded from this review owing to its length, two aspects are worth mentioning here. Although SUV measured on a static PET scan are most widely used in routine clinics, SUV are “semi-quantitative” indices that depend on the time of measurement and

do not consider physiological changes.⁹⁰ By contrast, full quantitative analysis uses kinetic compartment modelling on dynamic PET scans to derive the metabolic rate for glucose.⁹⁰ Such quantitative analysis uses a more complex model of the underlying physiology and considers the effects of confounding factors. Therefore, it can provide more accurate response assessment than SUV, particularly in tumours with relatively low metabolic activity. Owing to the “semiquantitative” nature of SUV, they depend upon image acquisition and reconstruction parameters among many other factors. The readers are referred to a comprehensive review by Boellaard.⁹¹ That review provides the typical range and maximum effect of factors, including technical errors, biological factors (uptake period, patient motion) and physical factors (acquisition parameters, image reconstruction parameters). They found that many factors have a relatively small effect (<15%) on SUV, yet the

Figure 5. Illustration of tumour response modelling using support vector machine. ¹⁸F-FDG, fluorine-18 fludeoxyglucose; PET, positron emission tomography; SVM, support vector machine.

accumulation of many small errors can lead to substantial differences in SUV among sites. These factors impact all SUV-based image analysis, including tumour segmentation,⁹² image feature extraction⁹³ and response evaluation.^{91,94} Many groups recognized the importance of harmonizing these factors and published recommendations for standardization of both biological and physical factors.^{94,95}

It is important to validate the accuracy of image registration and tumour segmentation methods, the usefulness of image features, and the generalizability of response models, which are often developed on small retrospective data sets, in large retrospective and prospective data sets. These are works in progress by several co-operative groups, including the Quantitative Imaging Network, Quantitative Imaging in Cancer: Connecting Cellular Processes with Therapy consortium and the American Association of Physicists in Medicine task group 211 that is building a benchmark for PET/CT tumour segmentation. There is also great need for clinical and biological interpretation of the advanced PET/CT image features, which are new to physicians and biologists.

A large number of PET/CT image features (>100) can be extracted using computerized approaches.¹⁷ In principle, one can select important features and feed them to tumour response evaluation models.⁸⁸ There are, however, limitations for this approach. The first limitation is the difficulty to relate many image features to biological or clinical knowledge because they are defined in complex mathematical formulas. The second limitation is that even with feature selection, the number of selected features may still be large compared with the number of patients in a study. This makes the generalization of the resulting response models unstable. To overcome these limitations, we propose to identify and use only a few important image features that capture the underlying physiological processes during cancer therapy. These features are likely specific for each disease and therapy combination. This approach requires computational scientists to work closely with clinicians and biologists. One step towards such an approach was proposed by Orlhac et al,⁹⁶ who sorted image features with high correlations ($r > 0.80$) into one feature group, thus reducing a total of 41 features into 11 distinct groups.

On the other hand, we propose to develop a response modelling approach that is robust for different malignancies and different

types of tumour response evaluations. Although there have been approaches identified for many cancer malignancies, there is no single approach that performs well for every site. Similarly, a variety of approaches were applied for different types of response evaluations (e.g. survival, response or prognostic factors). It could be promising to develop a hybrid approach that combines the strength of each predictive modelling approach to offer a direct off-the-shelf solution for tumour response modelling. Prior to response modelling, it is important to identify an optimal, smaller feature set to maintain clinical relevance and prevent model overfitting. Advanced feature selection process needs to be utilized to remove redundant features that introduce collinearity and noise into the models. Furthermore, feature selection bias needs to be eliminated either through frequency distribution of the features obtained during cross-validation or using advanced techniques such as calculation of information criteria.

Although not widely used in clinics, quite a few new PET tracers, including ¹⁸F-3'-deoxy-3'-fluorothymidine (FLT) that measures cell proliferation,^{97,98} ¹⁸F-fluoromisonidazole that measures hypoxia^{99,100} and others^{101–103} have brought enthusiasm in the evaluation of tumour response for various disease sites. A recent review suggested that FLT-PET has a positive role in predicting therapy response, especially in brain, lung and breast cancers.¹⁰⁴ However, different FLT-SUV measures (maximum, peak, mean or total SUVs) resulted in substantial variation of individual tumour response assessments,¹⁰⁵ thus requiring further study on optimization of FLT-PET-based quantification. The aforementioned concepts and methods are generally applicable to any tracer and therapy where PET/CT is used for response evaluation.

Challenges in implementing the computerized PET/CT image analysis for tumour response evaluation include harmonization of physiological and imaging parameters,⁹⁵ delineating the tumour volume in multimodality (PET/CT) images, identifying a few features that truly capture biological changes correlated with tumour response for a specific disease and therapy, validating the results in large, multicentre patient data sets, vendor implementation and ultimately clinical acceptance.

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