



# Predicting response to radiotherapy in tumors with PET/CT: when and how?

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**Abstract:** Radiotherapy is one of the main methods for tumor treatment, with the improved radiotherapy delivery technique to combat cancer, there is a growing interest for finding effective and feasible ways to predict tumor radiosensitivity. Based on a series of changes in metabolism, microvessel density, hypoxic microenvironment, and cytokines of tumors after radiotherapy, a variety of radiosensitivity detection methods have been studied. Among the detection methods, positron emission tomography-computed tomography (PET/CT) is a feasible tool for response evaluation following definitive radiotherapy for cancers with a high negative predictive value. The prognostic or predictive value of PET/CT is currently being studied widely. However, there are many unresolved issues, such as the optimal probe of PET/CT for radiosensitivity prediction, the selection of the most useful PET/CT parameters and their optimal cut-offs such as total lesion glycolysis (TLG), metabolic tumor volume (MTV) and standardized uptake value (SUV), and the optimal timing of PET/CT pre-treatment, during or following RT. Different radiosensitivity of tumors, modes of radiotherapy action and fraction scheduling may complicate the appropriate choice. In this study, we will discuss the diverse methods for evaluating radiosensitivity, and will also focus on the selection of the optimal probe, timing, cut-offs and parameters of PET/CT for evaluating the radiotherapy response.

**Keywords:** Radiosensitivity; positron emission tomography-computed tomography (PET/CT); PET/CT parameters; optimal cut-offs; textural features

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## Introduction

Traditionally, the American Joint Committee on cancer (AJCC) tumor-node-metastasis (TNM) staging system is the important basis for the selection of tumor treatment methods (1). Although TNM staging reflects entire disease status, it cannot accurately assess individual tumor burden or biologic activity. Therefore, TNM staging alone cannot comprehensively assess the treatment response and

prognosis of patients. As one of the main methods for tumor treatment, radiotherapy has improved in delivery technique to combat cancer, there is a growing interest for finding effective and feasible ways to predict tumor radiosensitivity.

Early evaluation of the efficacy of tumor radiotherapy could lead to a more patient-tailored approach. If long term treatment effect of patients could be predicted during RT, then the individual treatment plans could be modified. For example, if a tumor is predicted to have a good response

to RT, it seems to be worth to perform RT as a treatment method. Otherwise, if a tumor is predicted to be radio-resistant, it is better to modify the neoadjuvant treatment or to perform the surgery earlier and decrease radioresistance. How can we evaluate or predict the radiosensitivity of tumors? Radiosensitivity is associated with tumor proliferation, hypoxia, angiogenesis, apoptosis, autophagy and DNA or chromosome damage (2-5). Clone formation assay is the gold standard for detecting radiosensitivity, however, the clone formation assay requires collection of tumor tissue specimens and the operation is complicated and time-consuming. Therefore, it is imperative to find new methods for assessing the radiosensitivity of malignant tumors.

### **Diverse methods for evaluating radiotherapy response of tumors**

As the morphological imaging modalities, endorectal ultrasound, magnetic resonance (MR) and computed tomography (CT) are used to evaluate tumor treatment response, but it is difficult to use these modalities distinguishing fibrosis or early radiotherapy-induced inflammation from residual tumors. Therefore, the investigators have studied a variety of radiosensitivity detection methods based on a series of changes in hypoxic microenvironment, cytokines of tumors, microvessel density and metabolism after radiotherapy.

Recently, diverse magnetic resonance techniques are used to present functional and molecular imaging, such as diffusion-weighted MRI (DW-MRI) and dynamic contrast-enhanced MRI (DCE-MRI) (6). Some studies found that DWI had a value of evaluating radiosensitivity in cancer of brain, rectum, prostate, head and neck (7,8). Pan *et al.* demonstrated that apparent diffusion coefficient (ADC) value was correlated with the radiosensitivity of tumors (9). The advantages of MRI are that there is no radiation to the patient, the contrast agent is low in toxicity, and the cost is low affordable, but the technique is complicated and the quantitative analysis of the parameters is difficult to perform (6).

Dynamic contrast CT is also used as a means of evaluating radiosensitivity. Harvey found that dynamic contrast CT could accurately reflect tumor vascular perfusion, capillary permeability, so it could evaluate the radiosensitivity of tumors 1–2 weeks after radiotherapy

in prostate carcinoma, bronchial carcinoma and cervical cancer (10). However, Kimura found that dynamic contrast CT could not reflect the efficacy of radiotherapy within 3 months after treatment in hepatocellular carcinoma (11). The cost of dynamic contrast CT is low, but the calculation of quantitative and semi-quantitative parameters is complicated and it evaluates the radiosensitivity of tumors at a later time after treatment than other methods, moreover, there is radiation to patients.

Some molecular markers of tumors as radiosensitivity predictor are also under investigation. Xu *et al.* found that the expression of miR-185-3p and miR-324-3p before and after radiotherapy is associated with radiosensitivity in patients with nasopharyngeal carcinoma, the expression of miR-185-3p and miR-324-3p would decrease significantly after radiotherapy in patients with radioresistant tumors (12). Saito *et al.* found that the patients with a significant decrease in MIB-1 (an anti-Ki-67 monoclonal antibody) labeling indices after radiotherapy showed complete response after 1 year, so Saito concluded that MIB-1 labeling indices after radiotherapy could predict the radiosensitivity of hepatocellular carcinoma (13). There are also studies that considered the use of cytokines to detect radiosensitivity, including detection of chromosomal radiosensitivity and DNA double-strand break repair, but these are still in research stage (14). Furthermore, these detection methods are all invasive and difficult for clinical application.

For cancer patients, positron emission tomography (PET)/CT is often used for staging, restaging, long-term follow-up, treatment planning and treatment response prediction (15,16), furthermore, it can be used to optimize target volume delineation, as has recently been reported (17,18). The uptake of PET/CT developer tracer in the tumor may reflect tumor aggressiveness, which is closely related to the cellularity and proliferative activity of the tumor. PET/CT is a routine tool for response evaluation following definitive radiotherapy for cancers with a high negative predictive value, which can be used to avoid surgery following radiotherapy. Pre-treatment PET/CT is of value in predicting the response to radiotherapy and post-treatment PET/CT is helpful in assessing residual viable tumors. There are a number of studies on the predictive value of PET/CT before or after RT. Adversely, relatively little data are valid on the predictive value of PET/CT

during RT for tumors. The prognostic or predictive value of interim PET/CT is currently being investigated. Abgral *et al.* used PET/CT to evaluate metabolic changes during treatment, and found that PET/CT could be an available method for predicting tumor response to therapy and prognostic outcomes of cancer patients (19,20). PET is more and more extensively studied for early monitoring treatment response during radiotherapy in clinical or basic scientific researches. However, there are many unresolved issues, such as the optimal probe of PET/CT for radiosensitivity prediction, the selection of the most useful PET/CT parameters and their optimal cut-offs, and the optimal timing of PET/CT during RT.

Therefore, we suggest that PET/CT is more effective for evaluating the treatment response during radiotherapy, it can predict the treatment response of the patient earlier.

### The probe of PET/CT for radiosensitivity prediction

Tumor proliferation is a factor closely related to both intrinsic radiosensitivity and tumor repopulation. Methods that can monitor tumor proliferation may have the effect in predicting tumor response. In certain tumor cell types, glucose metabolism measured by 2'-deoxy-2'-[18F]fluoro-D-glucose ( $^{18}\text{F}$ -FDG) PET/CT varies proportionally with the proliferative activity and the grade of malignant cells (21). Oh *et al.* found that  $^{18}\text{F}$ -FDG PET images may predict the treatment response after chemoradiotherapy in hypopharyngeal cancer (22).  $^{18}\text{F}$ -FDG is the most common PET tracer, however, it is also being challenged by novel positron emission agents.

Recently, there are many studies about the novel positron emission agents to predict radiosensitivity.  $^{18}\text{F}$ -Fluorothymidine ( $^{18}\text{F}$ -FLT) PET/CT is a non-invasive measurement assessing tumor proliferation. Accumulation of  $^{18}\text{F}$ -FLT is closely correlated with active cellular proliferation, it is significantly correlated with Ki-67 value detected by immunohistochemistry in lung and breast tumors (23). Zheng *et al.* found that  $^{18}\text{F}$ -FLT PET/CT has the potential to predict radiosensitivity in nasopharynx cancer xenografts nude mice models (24). Park *et al.* suggested that the alteration of tumor uptake in  $^{18}\text{F}$ -FLT PET might be available for early prediction of tumor response after chemoradiotherapy in patients with

esophageal cancer (25). Qi *et al.* revealed that parameters of both  $^{18}\text{F}$ -FDG and  $^{18}\text{F}$ -FLT PET had medium to strong correlation with tumor treatment response for chemoradiotherapy. Both  $^{18}\text{F}$ -FDG and  $^{18}\text{F}$ -FLT PET showed their potential to predict tumor treatment response. According to the preliminary results,  $^{18}\text{F}$ -FLT PET showed no advantage over  $^{18}\text{F}$ -FDG PET (26).

Bao *et al.* investigated the value of 2-(5-[18F] fluoropentyl)-2-methylmalonic acid ( $^{18}\text{F}$ -ML-10) PET/CT, which selectively reflected cells apoptosis, they found that  $^{18}\text{F}$ -ML-10 microPET/CT had the potential to predict radiosensitivity of NPC, however,  $^{18}\text{F}$ -FDG did not reveal the potential (27). Murayama *et al.* examined the tumor uptake of a new PET probe 18F-2-tert-butyl-4-chloro-5-{6-[2-(2-fluoro-ethoxy)-ethoxy]}-pyridine-3-ylmethoxy}-2H-pyridazin-3-one ( $^{18}\text{F}$ -BCPP-EF) and  $^{18}\text{F}$ -FDG in C3H/HeN mice, which were inoculated with murine squamous cell carcinoma SCCVII, they found the tumor uptake of  $^{18}\text{F}$ -BCPP-EF was increased dose-dependently early after radiotherapy while  $^{18}\text{F}$ -FDG uptake could not indicate tumor response. Their results demonstrated that  $^{18}\text{F}$ -BCPP-EF is a promising PET tracer for early prediction of tumor radiotherapy response (28). Wang *et al.* found that tumor uptake of 18F-fluoromisonidazole ( $^{18}\text{F}$ -FMISO) and  $^{18}\text{F}$ -FDG both had the potential to evaluate the radiosensitivity of C6 rat glioma cells *in vivo* and *in vitro* experiment (29).

So, the clinicians need take further studies to find out which is the most useful PET probe to evaluate the radiosensitivity of malignant tumors. In our opinion, the accumulation of  $^{18}\text{F}$ -FDG in tumors after radiotherapy may be interfered by the inflammation induced by the radiotherapy, so there may be some difficult for  $^{18}\text{F}$ -FDG PET/CT to evaluation of the radiosensitivity of tumors.  $^{18}\text{F}$ -FLT is an indirect marker of active cellular proliferation, and it can evaluate the radiosensitivity of tumors more efficiently.

### Selection of the useful PET/CT parameters to evaluate the radiosensitivity

Standardized uptake value max (SUVmax) is the commonest parameter of PET/CT. However, it does not measure heterogeneity or the volume of tumors, it only provides information for a single volumetric pixel in the tumor, it

ignores the intratumoral tracer spatial distribution and does not represent the overall tumor burden. Therefore, volumetric parameters, such as total lesion glycolysis (TLG) and metabolic tumor volume (MTV) were recently investigated. TLG and MTV which reflect metabolic activity of the whole tumor and tumor volume, respectively, are used as tumor prognostic predictors (30). Furthermore, partial-volume-corrected TLG was recently shown to correlate with overall survival (OS) in a large, prospective study (31).

Intratumoral heterogeneity is correlated with aggressive tumor behavior and a decreased response to treatment (32). How to quantify the intratumoral heterogeneity more accurately? A novel approach is to quantify spatial heterogeneity of metabolism and tissue density with textural features of PET/CT. Texture analysis data of pre-RT and post-RT PET depicts tumor heterogeneity. Texture feature-based analysis is known as radiomics (33), which is actively being investigated as a prognostic tool in clinical outcomes after radiotherapy (34,35). Recently, some studies suggested that texture feature analysis was an effective approach to reflect local FDG activity distribution, and it had the potential for evaluation of corresponding biological heterogeneity (36,37). Recently, baseline tumor textural features were shown to have a higher predictive value for chemoradiotherapy response and patient survival than SUV, TLG or MTV in  $^{18}\text{F}$ -FDG PET/CT images (38). Several textural features of PET/CT imaging have the potential for predicting treatment response or the survival of cancer patients (39,40). Therefore,  $^{18}\text{F}$ -FDG PET/CT textural features have been proposed to be valuable in response prediction (41-43). Which metabolic parameters measured at primary tumor has more significant value for predicting treatment outcomes remains a research issue, maybe we can combine two or more parameters to evaluate the radiotherapy response. Maybe PET/CT textural features is more efficiently than other parameters for predicting treatment outcomes, because it can quantify spatial heterogeneity of metabolism and tissue density of tumors.

### **Selection the optimal cut-offs of PET/CT parameters**

Cell proliferation occurs more actively when tumors have a higher PET/CT SUVmax. In other words, tumors with

a higher SUV have a shorter doubling time. Then, what is the optimal cut-offs of the PET/CT parameters? This is still in debate. Jo *et al.* demonstrated that the SUVmax (5.1) of  $^{18}\text{F}$ -FDG PET/CT may be a prognostic predictor for clinical outcome and the pattern of failure after RT in hepatocellular carcinomas patients. The high SUV group (SUVmax  $\geq 5.1$ ) manifested a better radiotherapy response than the low SUV group (SUVmax  $< 5.1$ ) (44). This might be due to higher FDG uptake indicates greater tumor cell activity or a higher division rate, or both (45). Furthermore, Melsens *et al.* found that a T/B (tumor to background)  $\geq 3.59$  on pre-treatment  $^{18}\text{F}$ -fluoroazomycin arabinoside ( $^{18}\text{F}$ -FAZA) PET/CT was optimal cut-off for predicting the poor RT response (specificity 71.4%, sensitivity 92.3%) in esophageal adenocarcinoma xenografts (46).

The percent of the SUV declined during the radiotherapy was also used to evaluate the radiosensitivity. In the study of Qi, the preliminary results reported that 70% SUVmax (the percent declined after 2 cycles of neoadjuvant chemotherapy) may be a promising cut-off for both FDG and FLT PET to predict tumor regression after chemoradiotherapy in nasopharyngeal carcinoma (26). Lin *et al.* (47) demonstrated nodal SUV mean and a reduction of nodal MTV and TLG  $> 50\%$  during RT were prognostic predictors in locally advanced head and neck squamous cell carcinoma. Chen *et al.* (48) identified that a lower reduction ratio of the SUVmax or a higher interim SUVmax at the primary tumor was a poor predictive factor in head and neck cancers. Yue *et al.* demonstrated that texture features analysis provided a feasible method for assessing and predicting radiotherapy response of pancreatic adenocarcinoma, based on the risk score of multivariate analysis, the low risk patient had a higher texture variation ( $> 30\%$ ), the high risk patient had a lower texture variation ( $< 15\%$ ) (49). The optimal cut-offs of PET/CT parameters are still under research, in different tumors or for different PET/CT probes, the optimal cut-offs are diverse.

### **The optimal timing of PET/CT during RT**

Pre-treatment PET is helpful in predicting the treatment response, while post-treatment PET is useful in discovering residual viable tumors. There are a number of studies on the predictive value of PET/CT before or after RT. Adversely, relatively little data are valid on the prognostic

value of PET/CT during RT for tumors. Assessment before or during radiotherapy is more beneficial for patients to modify the individual treatment plan and choose the appropriate treatment method in time. Moreover, the current data demonstrated that the optimal post-treatment  $^{18}\text{F}$ -FDG PET detection could be carried out during RT (50). However, the optimal timing of PET/CT during RT is also in research, the optimal time is diverse in different studies.

Performing  $^{18}\text{F}$ -FDG PET/CT during RT could be helpful in distinguishing inflammatory changes from metabolic changes and it helped to modify treatment plans as early as necessary. Intriguingly, some investigators found that MTV and the SUV<sub>max</sub> before chemoradiotherapy are associated with OS, local control in head and neck cancer (51,52), and response to therapy in nasopharyngeal carcinoma (53). Oh *et al.* measured the pre-treatment SUV, MTV, and textural features (contrast, complexity, busyness and coarseness) of tumors, and found that pretreatment textural features in the  $^{18}\text{F}$ -FDG PET could characterize intratumoral heterogeneity and identify patients with low response rates and poor disease-free survival (DFS) and OS outcomes in hypopharyngeal cancer (22).

The optimal timing in performing PET during therapy is now persistently debated. It is necessary to choose an optimal time for second PET. In the study of Tandberg DJ, the PET was performed at a median of 32.4 Gy during treatment, they found that the volumetric PET features such as SUV<sub>max</sub>, SUV<sub>mean</sub>, MTV and TLG during treatment were the most feasible predictors of treatment response in esophageal cancer (54). Garibaldi *et al.* demonstrated that FDG PET/CT images carried out earlier than the third to fourth week of RT (i.e., 2 weeks after the start of RT) was more favorable in head and neck cancer (55). Kim found that during RT (3th-4th week) the primary tumor with higher TLG on FDG PET/CT had a poor prognosis for OS and progression-free survival (PFS) in head and neck cancer patients (56). A prospective trial indicated that a PET/CT carried out in the second week of neoadjuvant chemoradiotherapy could distinguish poor responders with an accuracy of 78% and a sensitivity of 94% in rectal cancer (57). A study of non-small cell lung cancer in China demonstrated that a decline in MTV and SUV of intra-treatment PET/CT after 40 Gy of radiotherapy were more

pronounced in patients who responded well to treatment (58). A Belgian study indicated that intra-treatment SUV<sub>max</sub> at 47 Gy of RT in head and neck cancers was significantly associated with OS (59). Therefore, there are emerging data that an intra-treatment PET may also be of significant prognostic utility.

Uptake of  $^{18}\text{F}$ -FDG in solid tumor is influenced by many different biological factors, including molecular, such as oncogene expression, and pathophysiological aspects such as tumor perfusion, tumor heterogeneity, apoptosis and viable cell fraction, amount of inflammatory cell infiltration, effects of hypoxia and lastly also by substrate utilization. In addition, different radio-sensitivities of tumors, modes of radiotherapy action and fraction scheduling may complicate the appropriate choice. So, the optimal timing of PET/CT is still under research. According to most of authors including ours, the optimal timing in performing PET during therapy is 2th-4th week, and it is an early enough time point to monitor treatment approaches accordingly.

## Conclusions

Early evaluation of the efficacy of tumor radiotherapy could lead to a more patient-tailored approach. Based on a series of changes in metabolism, microvessel density, hypoxic microenvironment, and cytokines of tumors after radiotherapy, a variety of radiosensitivity detection methods have been studied. PET/CT is often used for staging, restaging, long-term follow-up, treatment planning and treatment response prediction. Moreover, PET/CT is a routine tool for response evaluation following radiotherapy for cancers with a high negative predictive value. However, there are many unresolved issues, such as the optimal probe of PET/CT for radiosensitivity prediction, the selection of the most useful PET/CT parameters, their optimal cut-offs and the optimal timing of PET/CT during RT (*Table 1*). Uptake of PET/CT probe in solid tumor is influenced by many different biological factors, so the PET/CT in predicting the radiotherapy response of different tumors has diverse results. Different radio-sensitivities of tumors, modes of radiotherapy action and fraction scheduling may complicate the appropriate choice. So, how to selection the optimal probe, timing, cut-offs and parameters of PET/CT are still under research.



**Table 1** A summary of the main literature about the value of PET/CT in predicting radiosensitivity of tumors

Author	Probe	Parameters	Optimal timing	Optimal cut-offs	Tumor type
Zheng (24)	<sup>18</sup> F-FLT	The percent of injected dose per gram (%ID/g) T/M	Pretreatment (T/M0) and 24 h after irradiation (T/M1)	2.38 for T/M0, -0.15 for (T/M1-T/M0)	Nasopharyngeal carcinoma (NPC) xenografts
Park (25)	<sup>18</sup> F-FLT	SUVmax	Before and after 2 cycles of chemotherapy	The percent change of SUVmax >40%	Esophageal cancer
Qi (26)	<sup>18</sup> F-FDG/ <sup>18</sup> F-FLT	SUVmax	Before and after 2 cycles of chemotherapy	The percent change of SUVmax >70%	Nasopharyngeal carcinoma
Bao (27)	<sup>18</sup> F-ML-10	T/M	24 to 48 h after irradiation	Decline of T/M	NPC xenografts
Murayama (28)	<sup>18</sup> F-BCPP-EF	SUV	After irradiation	0.6	Murine squamous carcinoma
Wang (29)	<sup>18</sup> F-FMISO	SUVmax	Before and after treatment	Decline of SUVmax	C6 rat glioma cells <i>in vivo</i> and <i>in vitro</i>
Jo (44)	<sup>18</sup> F-FDG	SUVmax	Pretreatment	5.1	Hepatocellular carcinoma
Melsens (46)	<sup>18</sup> F-FAZA	T/B ratio	Pretreatment	3.59	Esophageal adenocarcinoma xenografts
Lin (47)	<sup>18</sup> F-FDG	SUVmax, MTV, TLG	During the third week of RT	3.05 for SUVmax, reduction of more than 50% for MTV and TLG	Locally advanced mucosal HNSCC
Oh (22)	<sup>18</sup> F-FDG	Textural features	Pretreatment		Hypopharyngeal carcinoma
Chen (48)	<sup>18</sup> F-FDG	SUVmax	Intra-treatment PET at 41.4–46.8 Gy of RT	Reduction ratio of SUVmax <0.64	Advanced pharyngeal cancers
Yue (49)	<sup>18</sup> F-FDG	Tumor locoregional texture	Pre and post RT	Texture variation >30%	Pancreatic adenocarcinoma
Akagunduz (51)	<sup>18</sup> F-FDG	MTV, maximum lean body mass corrected SUV (SULmax)	Before treatment	14 for MTV, 10.15 for SUVmax	Head and neck cancer
Tandberg (54)	<sup>18</sup> F-FDG	MTV, TLG	Intra-treatment PET at a media of 32.4 Gy RT		Esophageal cancer
Kim (56)	<sup>18</sup> F-FDG	TLG	Third to fourth week during RT	19	HNSCC
Roedl (57)	<sup>18</sup> F-FDG	TLG	In the second week of chemoradiotherapy	TLG decreased by 78%	Adenocarcinoma of the esophagus
Huang (58)	<sup>18</sup> F-FDG	SUV, MTV	Before and following 40 Gy RT with 2 cycles of CT	37.2 for SUVmax, 41.7 for SUVmean, 29.7% for MTV	Non-small cell lung carcinoma
Farrag (59)	<sup>18</sup> F-FDG	SUVmax	Before and during the treatment after 47 Gy RT	8.11 for pretreatment SUVmax, 4.03 for the intra-treatment SUVmax	Head and neck cancer

T/M, tumor to muscle ratio; T/B, tumor to background ratio; PET/CT, positron emission tomography-computed tomography; FLT, fluorothymidine; FDG, fluoro-D-glucose; SUV, standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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