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Imaging for Response Assessment in Radiation Oncology: Current and Emerging Techniques

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SYNOPSIS

Imaging in Radiation Oncology is essential for the evaluation of treatment response in tumors and organs at risk. This influences further treatment decisions and could possibly be used to adapt therapy. This review article focuses on the currently used imaging modalities for response assessment in Radiation Oncology and gives an overview of new and promising techniques within this field.

Keywords

CT; MRI; PET; functional imaging; response assessment; tumor; organs at risk; Radiation Oncology

1. Introduction

Computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) play a major role in the assessment of tumor response. Moreover, these imaging modalities are increasingly used to evaluate treatment-related changes in normal tissue and correlate these findings with treatment-related toxicity. Especially in Radiation Oncology, the prediction of tumor response and radiation-induced normal tissue damage arouses more and more interest. The aim is to adapt therapy in cases of more aggressive tumors or severe changes in organs at risk (OARs). Because CT is increasingly used to dictate patient positioning, many CT images are produced, which has prompted many investigators to search for predictors of tumor control and normal tissue toxicity in CT. In contrast, MRI has not been afforded the same attention as CT owing to the fact that MRI cannot be directly used for modeling dose deposition. However, with advantages of no radiation dose and superior soft tissue contrast compared to CT, and with the rising availability of combined MR linear accelerators (MR Linacs) that facilitate online imaging during irradiation, MRI is also a promising alternative for response assessment already during the course of radiotherapy.

In the next sections we will give an overview of the current and emerging imaging techniques using CT, MRI and PET for response assessment of tumor and OARs.

2. Imaging Applications for Tumor Response Assessment

2.1. CT Approaches

Tumor response in CT is principally assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria¹. Simplified, a complete response is therein defined as disappearance of all so-called target lesions. Stable disease is the proper term if the sum of the longest diameter of target lesions is less than 30% decreased (otherwise partial response) and less than 20% increased (otherwise progressive disease). It is an inherent and important limitation, however, that's RECIST's response evaluation is only two-dimensional.

Another use for CT imaging is quantitative characterization of tumor function using dynamic contrast enhanced CT (DCE-CT). DCE-CT scans are repeatedly acquired for approximately 40 seconds after injecting iodine-based contrast agents². DCE-CT has gained popularity among radiation oncologists as a valuable tool to spatially map tumor vascular attributes like perfusion, permeability, and blood flow³. DCE-CT has shown promise in early and longitudinal assessment of tumor response to radiation therapy⁴, multi-parametric functional imaging characterization of radioresistant tumor subvolumes and adaptive radiotherapy^{2,5,6}. Studies assessing chronological changes in quantitative DCE-CT metrics like transfer coefficient (K-trans) and relative tumor blood volume (rTBV) have reported a dose and treatment modality-dependent correlation in various cancer sites such as head and neck cancers (HNC) and non-small cell lung cancer (NSCLC)^{7,8}. Nonetheless, as with all quantitative imaging biomarkers, the development of clinically applicable DCE-CT biomarker profiles in Radiation Oncology hinges on standardization and reproducibility assurance efforts that address technical validation and robustness issues⁹.

Dual energy CT (DE-CT) employs two x-ray sources of non-identical energies to acquire signal, rather than a single x-ray source used in traditional, single-energy CT (SE-CT)¹⁰. Because tissue x-ray attenuation varies with photon energy, dual-photon energies capture greater information about tissue density than does SE-CT¹¹. The most common use for DE-CT is to extract iodine contrast maps and correlate them with a variable of interest¹². For example, Bahig et al. described the first attempt to correlate DE-CT-derived iodine tissue concentration with oncologic outcomes in HNC¹³. Primary gross tumor volume (GTV) maximum voxel-wise iodine concentration, primary GTV kurtosis, nodal GTV volume, and nodal GTV iodine concentration standard deviation each predicted worse locoregional recurrence risk in a cohort of 25 laryngeal and hypopharyngeal cancer patients. DE-CT-derived iodine content also has the ability to differentiate metastatic, inflamed, and healthy lymph nodes¹⁴. Iodine maps derived by DE-CT may complement RECIST's two-dimensional limitation by identifying cases where tumor viability has indeed decreased despite no change in tumor size¹². Furthermore, they may also prove useful for risk-stratifying radiotherapy patients prior to radiation¹⁵.

An evolving approach is the use of radiomics features, which encompass a wide range of mineable multi-dimensional values that quantitatively describe tumor shape, intensity, and

texture¹⁶. Predictive radiomics biomarkers have been demonstrably informative in HNC, gastric cancer and lung cancer, among others¹⁷. In a study by Ramella et al.¹⁸, a combined signature of semantic and radiomics features derived from baseline CT could be correlated to rate of volumetric changes at subsequent time points in NSCLC. A similar study found a grey level co-occurrence matrix (GLCM) texture feature improved the capacity of a clinicopathological model to predict tumor shrinkage at mid-treatment course¹⁹. Other studies tracked the kinetics of radiomics features from sequential in-treatment CT images and demonstrated an association with subsequent response to radiation in HNC and NSCLC^{20,21}.

2.2. MRI Approaches

MRI is superior to CT for tumor response assessment in soft tissues when motion artifacts and tissue/air interfaces leading to susceptibility artifacts are negligible. As is the case for CT, the RECIST criteria¹ are commonly used for response assessment of solid tumors on MRI.

Other MRI response criteria have been implemented, including criteria that are specific to certain anatomic subsites and/or tumors (such as glioma). Similar to the RECIST criteria, they are based on lesion sizes as well. For example, the Macdonald criteria²² assess the size of contrast-enhancing tumor in T1 sequences, while an updated version of the Response Assessment for Neuro-Oncology (RANO) criteria were introduced in 2010²³ to allow for incorporation of T2/Flair changes as well.

Newer imaging techniques, like MR perfusion and spectroscopy, are still not adopted by these criteria although they are more accurate at differentiating between true progression and treatment-induced changes²⁴. This is especially a problem with the increasing use of immunotherapy²⁵. High-grade glioma usually presents with increased vasculature, and the relative blood volume is greater in tumor progression or recurrence than in necrosis or pseudoprogression. This can be measured by dynamic susceptibility contrast (DSC) perfusion MRI²⁶. Machine learning approaches have achieved some success at differentiating disease progression from pseudoprogression using diffusion-weighted imaging (DWI)²⁷ and DSC perfusion MRI²⁸. Arterial spin labeling measures perfusion using magnetically labeled blood as an endogenous tracer. Using MRS, active tumor tissue is defined as having an elevated choline level²⁹; lipid-lactate peaks, a decrease in N-acetyl-aspartate and a lack of choline elevation, however, is suspect for radiation necrosis^{30,31}.

Functional MRI has further potential to predict for tumor response. For example, high apparent diffusion coefficient (ADC) values pre-treatment derived from DWI associate with poor outcomes in HNC^{32,33}. Treatment responders showed a higher increase in ADC during the first weeks of radiotherapy than non- or partial-responders³². Dynamic contrast enhanced (DCE) imaging is comparably more invasive because it uses an intravenous contrast agent and is inconsistent in its response prediction for most of the parameters. K-trans seems most reliable, with higher values correlating with better tumor response^{34–36}. Other approaches include Blood Oxygen Level Dependent (BOLD) imaging which leverages the paramagnetic nature of deoxyhemoglobin to visualize a decrease in T2*³⁷. As

tumor hypoxia is known to adversely affect the outcome after radio- and/or chemotherapy, BOLD imaging may also be a predictive imaging biomarker.

MRI radiomics features may become a convenient tool for phenotyping tumors and normal tissues and integrating spatially-driven parameters to guide therapy and outcome³⁸. In breast cancer, radiomics models have predicted tumor response to neoadjuvant and adjuvant therapy^{39,40}. Similarly in HNC radiomics models have predicted local control and survival^{41,42}. MRI has more acquisition parameters than CT (such as pulse sequence, echo time, relaxation time, etc.), which means that the task of standardizing reproducible features is even more challenging for MRI than CT⁴³. Different vendor sequences or perhaps different Tesla magnets could complicate the reproducibility of extracted features⁴⁴. Because MRI is more susceptible to motion artifact than CT, feature reproducibility may also depend on immobilization during acquisition. Effort is clearly needed to standardize different inconsistencies in MRI radiomics starting from imaging acquisition, imaging processing, model building, and model validation. This is a necessary step to integrate functional quantitative imaging data into clinical decision making tools toward personalized medicine.

2.3. PET Approaches

Utilization of PET for tumor response assessment has become a key component for monitoring disease progression and for restaging^{45,46}. PET visualizes metabolic activity within the body in ways that CT and MRI may be limited⁴⁷. The addition of this functional imaging modality presents a need for new standardized guidelines and criteria in tumor response assessment in order to provide patients with consistent quality care.

The first set of standardized tumor response guidelines for PET was defined by the European Organization for Research and Treatment of Cancer (EORTC) in 1999⁴⁸. These recommendations consider both clinical and subclinical measurements in treatment response interpretation. In 2009 the PET Response Criteria in Solid Tumors (PERCIST) criteria were introduced, which modifies the RECIST criteria to include metabolic activity with 18F-FDG-PET as an additional criterion to anatomical findings⁴⁹. PET standardized uptake values (SUV) are a quantitative metric for categorizing tumor response, progression, or stabilization of disease.

A review of the EORTC and PERCIST response criteria showed strong agreement between the two despite their different approaches⁵⁰. The review was limited by small patient cohorts, a heterogeneous patient populations, heterogeneous equipment, and other factors, so it is still necessary to investigate differences between the two on a larger, homogeneous patient population in order to validate possible interchangeability and use for practice.

PET/CT has become standard for response assessment in most lymphomas⁵¹. According to the Lugano Classification, a complete response is defined as complete metabolic response of initially FDG-avid lymphoma independent of residual masses, whereas progressive disease is considered in case of increased FDG uptake compared to baseline values or the appearance of new FDG-avid lesions consistent with lymphoma⁵¹.

To limit the incidence of false positive PET readings due to normal-tissue damage and immune response caused by radiation therapy, response assessment must be delayed for some period after treatment⁵². Local inflammation and radiotherapy changes will be FDG-avid and limit the positive predictive value for local residual tumor. However, PET remains a strong diagnostic tool for identifying distant metastatic disease and progression. A 16-week FDG PET reassessment in locally advanced HNC showed good diagnostic accuracy and can be used to guide management with the high negative probability of complete response⁵³. Although FDG is the most commonly used and studied radiotracer to monitor tumor response, others have shown some utility. 18F-fluorothymidine (18F-FLT), is promising as a more reliable tracer in measuring tumor proliferation than 18F-FDG, but is limited by its relatively low uptake in cells and is even more hindered by radiotherapy and cytotoxic chemotherapy⁵⁴.

Cancer cells have been noted to adapt metabolically to hypoxic environments despite functioning mitochondria and the presence of oxygen. This phenomenon, known as the Warburg Effect⁵⁵, contributes to therapy resistance and tumor progression⁵⁶. Measurement of hypoxia has historically been performed by assessing the oxygen partial pressure (pO₂) through a polarographic needle electrode which is invasive and limited to a small portion of the tumor⁵⁷. However, cellular hypoxia measurements can now be performed with PET/CT using radiotracers like 18F-fluoroazomycin arabinoside (FAZA) and 18F-fluoromisonidazole (FMISO). Both tracers fall under the nitroimidazole family, which work by the reduction of its NO₂-group in the hypoxic environment, leading to covalent binding with macromolecules in the cell⁵⁸. As a second-generation hypoxia PET radiotracer, FAZA has improved contrast when compared to the more widely used FMISO. The potential of both tracers to predict treatment outcome has been shown in several studies⁵⁹, but must be further examined before implementing into clinical use.

3. Imaging Applications for Organ at risk Assessment

3.1. CT Approaches

Advanced treatment options such as proton therapy^{60,61} and MR-guided radiation⁶² create new opportunities to spare normal tissues. As life expectancy for cancer survivors increases, so does demand for predicting the development of treatment-induced side effects. OAR morphologic changes may be informative for this goal^{63,64}, but so may other image parameters, such as intensity on CT^{65,66}.

Just as radiomics has been investigated for monitoring tumor response, it may also be serviceable for monitoring OARs^{16,67}. Aerts et al.⁶⁸ was the first to perform a large extraction of radiomics features from tumors – including intensity, morphological and texture features – to predict survival. Since then, a wealth of radiomics studies have investigated tumor features, yet radiomics is comparatively less utilized to investigate normal tissue response or toxicity. Van Dijk et al. showed that radiomics texture features were associated with radiation-induced side effects in addition to dosimetric parameters and could improve current normal tissue complication probability (NTCP) models⁶⁹. Radiomics features from images taken during treatment have been exploited to predict radiation-induced xerostomia^{63,65,70}, and Cunliffe et al.⁶⁶ showed that the change in lung texture

during treatment correlated with radiation-induced pneumonitis. Colen et al. showed in pilot study that radiomics analysis may also predict immunotherapy-induced toxicities⁷¹. As previously mentioned in the above discussion of radiomics for tumor response assessment, the development of radiomics for predicting or normal tissue toxicity is still in its early stages. Larger, more robust image validation sets and feature parameter standardization are needed. Nevertheless, current and past studies have highlighted the potential of radiomics to improve conventional toxicity modeling.

3.2. MRI Approaches

Like CT, MRI can be used to identify radiation-induced changes in size of the structures. For example, several studies have reported on a volume loss of the salivary glands during radiotherapy⁷². Muscles have likewise been described to shrink in a dose-dependent manner⁷³. Volumetric changes can be easily measured in standard anatomical T1 or T2 sequences. Functional MRI like DWI or intravoxel incoherent motion imaging (IVIM) can quantify free extracellular water as a biomarker for edema. DWI is one of the most reported functional sequences used for estimation of damage in OAR. Exemplarily, the ADC of the salivary glands increased during the course of radiotherapy and could be correlated with the degree of xerostomia⁷⁴. Another functional MR sequence commonly used is DCE imaging, which gives details about vasculature that can be affected in the case of radiation-induced inflammation, but more research is necessary to consistently report on the changes and correlate them with outcomes. A dedicated sequence to describe the fatty degeneration of tissue is DIXON, but this sequence has only rarely been used for OAR assessment so far⁷⁵. To better compare study results between different institutions, reporting percentage changes could be helpful. This could compensate for some inter-institutional variability caused by different MRI machines, radiofrequency coils and image acquisition parameters. Nevertheless, segmentation of OARs can also influence normal tissue complication probability outputs⁷⁶, as can post-processing methods⁷⁷.

MRI radiomics has been explored for predicting normal tissue toxicities as well. One study correlated fat content in parotid glands and xerostomia at 12 months post-therapy⁷⁸. Another study investigated femoral bone damage post-radiotherapy by exploring radiomics features extracted from different MRI sequences⁷⁹. As extensively discussed in the MRI for tumor response assessment section, standardization of radiomics acquisition and post-processing is crucial.

3.3. PET/SPECT Approaches

PET/CT and SPECT/CT are imaging modalities that are not currently used clinically for OAR toxicity assessment. However, there is potential for both modalities to quantify toxicity using the anatomical information from the CT and the functional information from the PET or SPECT to help clinicians ascertain the damage to normal tissue by providing metabolic⁸⁰ or perfusion⁸¹ information.

For example, 18F-FDG-PET has been used to investigate radiation-induced normal tissue toxicity to the parotid gland; a decrease in 18F-FDG-uptake post-radiotherapy correlated with the development of late xerostomia⁸².

⁶⁸Ga-PSMA is another radionuclide that can be used to quantify metabolic activity in prostate cancer and in salivary and lacrimal glands⁸³. PSMA-PET/CT further allows for visualization of seromucous glands in the soft palate, pharyngeal wall, nasal mucosa, and supraglottic larynx, which is not possible with other imaging modalities⁸³. This is a significant step along the path to quantifying radiation-induced metabolic activity changes in these minor glands.

Another possible application for PET/CT in OAR assessment was described for the prediction of radiation induced lung toxicity (RILT)⁸⁴. Petit et al. found that patients were more likely to develop RILT if the lung voxels with the highest ¹⁸F-FDG uptake in the pre-treatment scan received 2 Gy or more⁸⁴. In another study, SPECT/CT was used to evaluate the association between perfusion and radiation dose in patients who developed radiation pneumonitis post-treatment⁸¹.

Furthermore, PET/CT, using ¹⁵O-H₂O as tracer, can be utilized to detect perfusion changes in the heart after breast radiotherapy and thus also help to identify radiation-induced heart damage⁸⁵. Similarly, patients showed a significantly higher ¹⁸F-FDG uptake in myocardial regions within the radiation field as opposed to non-irradiated regions⁸⁶.

4. Conclusion

CT, MRI, PET or a combination of these modalities, is commonly used for response assessment after radiotherapy, depending on treatment site. With the recent technical advances, newer imaging methods and quantitative approaches have become increasingly available such as DE-CT, functional MRI and radiomics. Despite promising results regarding the prediction of tumor response and toxicity with newer techniques, larger studies are yet lacking to clinically validate them and thereafter scale them to the standard of care.

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Key Points

- CT, MRI and PET are the current state-of-the-art imaging methods in Radiation Oncology for treatment response assessment, depending on cancer site.
- New and promising imaging techniques like functional MRI and radiomics are currently investigated for prediction of treatment response in tumors and organs at risk.
- Still, more research needs to be conducted to implement these new imaging techniques into clinical routine.

Figure 1:

Example of a patient with a lung adenocarcinoma metastasis at the left skull base (red arrow). Left: 140 keV DE-CT (window level: -100 – 250 HU), middle: 60 keV DE-CT (window level: -100 – 250 HU), right: Iodine map of DE-CT (window level: -10 – 100 HU).

Figure 2:

Example of a patient with T2 base of tongue (BOT) tumor and ipsilateral neck lymph node. Left: Treatment plan with BOT tumor delineated in dark green, lymph node in light green and clinical target volume (CTV) in red; middle: PET/CT before treatment (window level for PET: 0.5 – 22 SUV); right: PET/CT 3 months after radiochemotherapy (window level for PET: 0.5 – 22 SUV).

Figure 3:
54-year old patient with bilateral tonsil cancer stage IVA. Parotid gland structures are highlighted in yellow and pink and were rigidly propagated from T2 image (left) to DIXON (middle) and ADC map (right side).