Molecular Imaging and Precision Medicine

PET/Computed Tomography and Therapy Response Assessment in Oncology

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KEYWORDS

• Molecular imaging • Precision medicine • PET/computed tomography • Therapy response • Oncology

KEY POINTS

- A variety of methods have been developed to assess the tumor response to therapy.
- Standardized qualitative criteria based on ^{18}F-fluoro-deoxyglucose PET/computed tomography have been proposed to evaluate the treatment effectiveness in specific cancers and these allow more accurate therapy response assessment and survival prognostication.
- Multiple studies have addressed the utility of the volumetric PET biomarkers, including metabolic tumor volume and total lesion glycolysis, as prognostic indicators in several malignancies; however, there is still no consensus about the preferred segmentation methodology for these metrics.
- Tumor heterogeneity (heterogeneous intratumoral uptake) was proposed as a novel PET metric for therapy response assessment.
- Advanced and novel PET imaging techniques will be used to study the specific biological behavior of cancer during therapy.

INTRODUCTION

Cancer is the second leading cause of death worldwide and has emerged as a major public health problem.[1] In 2013, there were 14.9 million new cancer cases and more than 8 million cancer-related deaths worldwide. The top 3 most commonly diagnosed cancers are breast, tracheobronchial-lung, and colorectal cancer, which accounted for 34.6% of all cancers in 2013.[1,2] Overall, the prognosis has improved for the most prevalent cancers in both developing and more developed countries, resulting in a steady decrease in mortalities (1% annually).[3] Recent advances in molecular biology, targeted

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therapies, and molecular imaging result in early diagnosis and improved survival of oncologic patients.[4] One of the most relevant advances was the introduction of ^{18}F-fluoro-deoxyglucose (FDG) PET combined with computed tomography (CT) in the diagnosis and management of oncologic patients. FDG-PET/CT has rapidly become an important imaging tool for the initial tumor staging and the assessment of cancer recurrence, and has also gained increased acceptance in the setting of tumor response assessment.[5]

The traditional approach to treatment monitoring through imaging has relied on anatomic changes assessing tumor size before and after therapy, using anatomic imaging modalities such as CT and MR imaging that mainly depend on tumor morphology and size, whereas FDG-PET has the ability to provide functional information by identifying metabolically active lesions and monitoring changes after therapy. Thus, FDG-PET/CT imaging has become a promising technique for monitoring therapy response and tumor heterogeneity, and for the early identification of patients who are likely to fail targeted or standard therapies. Furthermore, FDG-PET imaging has proved to be a successful tool with high diagnostic performance in the restaging of oncologic patients during and after completion of treatment, especially in lung cancer, head and neck cancer, breast cancer, and lymphoma, because of its ability to distinguish scar tissue and fibrosis from residual viable tumors.[6–9] To facilitate the assessment of treatment response using FDG-PET/CT imaging, several PET-based visual, semiquantitative, and absolute quantitative criteria have been developed.[4,7,8,10,11] Furthermore, the role of imaging as a determinant of therapeutic decisions in patients with cancer has become increasingly important in the era of genomic medicine, in which genomically defined subsets of patients are treated with anticancer therapy targeting. These targeted therapies vary significantly from the traditional cytotoxic effects of standard chemotherapy, thus response assessment should evolve in parallel with the advances in cancer treatment.

This article reviews and illustrates the commonly used PET/CT-based therapy assessment criteria and future directions for therapy response assessment in oncology.

QUANTITATIVE PET THERAPY RESPONSE ASSESSMENT CRITERIA

Postchemotherapy assessment is a necessary step in the overall treatment algorithm to determine the efficacy and the necessity of continuing treatment. Historically, a variety of methods were introduced and have been developed to assess tumor response to therapy.[4,10] Specifically, they were all designed to quantify therapy effectiveness by assessing tumor shrinkage, which has been shown to correlate with survival.[10]

The first anatomic tumor response criterion was the World Health Organization (WHO) method (1976), which was introduced before the widespread use of CT in the standard practice and the posttherapy follow-up of oncology patients.[10] The original WHO criteria included bidimensional measurements of the tumors, and tumor response was defined as a decrease of the product of these 2 perpendicular diameters of the tumor sites, in order to categorize the amount of shrinkage into 4 categories: complete response, partial response, no response, or progressive disease.[5,10] The WHO criteria did not fully standardize response assessment because of its limitation in specifying critical factors, such as the total number of tumor foci needed to be measured and the minimum measurable tumor size.[10]

With the growing use of CT as a standard for care, the WHO criteria were reevaluated by the National Cancer Institute (NCI) and the European Association for Research and Treatment of Cancer (EORTC) in order to enhance their sensitivity in the assessment of the posttherapy response. In 2000, following a series of clinical trials, the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) provided a new set of CT-based guidelines that assessed tumor response from unidimensional measurements made on CT along the tumor's longest axis, rendering the process more reproducible and applicable to the clinical practice.[12] RECIST 1.0 also defined parameters such as a maximum of 10 lesions, with a maximum of 5 per organ, and the minimum measurable lesion size of 1 cm. The RECIST 1.0 criteria divide intrinsically continuous data (tumor size) into 4 distinct outcome categories by defining the percentage reduction in target lesion size for each category (**Table 1**). RECIST 1.0 underwent further reevaluation and was modified as RECIST 1.1 in 2008.[10] The current RECIST 1.1 has a few key changes from the WHO criteria and the original RECIST that have contributed to its dominance in tumor response assessment. RECIST 1.1 simplifies the number of lesions required to assess the tumor burden, to a maximum of 5 tumors, and 2 per organ. It also specifies that the longest node diameter measurement is sufficient for assessing therapy response, rather than the product of the 2 longest perpendiculars.[5,10] In addition, the new criteria provided recalculated quantitative values for lymph node tumor response in which total response did not imply complete tumor shrinkage. The RECIST