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Overview

Role of Imaging in Response Assessment and Individualised Treatment for Sarcomas

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Abstract

The first systematic response evaluation criteria were established by WHO, based on the tumor size changes shortly after the computed tomography (CT) technique became available to the daily practice. RECIST, a simplified version of WHO criteria, and its newer version, RECIST1.1 are the currently available international response evaluation criteria in solid tumors and remains based on tumor size changes.

While the introduction of molecularly targeted drugs has significantly improved the survival in patient with sarcomas, the evaluation of tumor response has become more complicated. Increasing number of studies have reported the lack of shrinkage in responding tumors and raised concerns of significant underestimation of responses using RECIST. The first such observation was made on gastrointestinal stromal tumor (GIST) treated with imatinib. In GISTs responding to imatinib, the degree of contrast enhancement on CT typically decreases significantly compared with the baseline, and, regardless of whether tumors shrink, heterogeneous hyperattenuating tumors become homogeneous hypoattenuating tumors with a smaller enhancing solid component.

In current oncology practice, CT is a widely accepted method of evaluating tumor response. CT images are relatively simple to acquire and can be reasonably reproduced with no significant technical obstacles. FDG-PET is highly sensitive and specific in identifying responding sarcomas. It has mostly been used as a problem solver and for those with marginally resectable GIST. More recently, the utility of whole body MRI is undergoing exploration.

This article discusses the traditional size-based response evaluation criteria, and introduces new evidence based response evaluation based on changes in morphology in addition to changes in tumor size on CT images, and whole body imaging is introduced at the end.

Key words: Computed tomography; response evaluation; sarcoma

Statement of Search Strategies Used and Sources of Information

References for this overview were identified through searches of PubMed with the search terms sarcoma, response evaluation, imaging, computed tomography, PET, MRI, RECIST from 1 January 1990 to 15 January 2017. Only papers published in English were reviewed. The final reference list was generated on the basis of the relevance to the scope of this overview.

Introduction

The history of response evaluation of solid tumours goes back to 1960, when the evaluation was based on the physical examination. The response was then defined as a 50% decrease in tumour volume by physical examination [1]. A little after the cross-sectional imaging technique, computed tomography, became available, the first systematic response evaluation criteria were established based on tumour measurement by the World Health Organization (WHO). Since then, the size-based criteria, such as the WHO criteria and Response Evaluation Criteria in Solid Tumors (RECIST), have been well accepted and used routinely in clinical trials of new anticancer agents, from conventional cytotoxic chemotherapy to newly available molecularly targeted drugs. However, several studies have reported discrepancies between the response rates assessed with WHO

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criteria and those assessed with RECIST and the resulting impact on survival outcomes [1–4].

More importantly, it has been noted that the soft tissue sarcomas developing significant intratumoral necrosis after treatment with cytotoxic agents often do not shrink sufficiently to be considered therapy-responsive per traditional criteria ([AQ1]personal communication). Our recent study indicated that RECIST [5] significantly underestimated the initial response of metastatic gastrointestinal stromal tumours (GISTs) to imatinib [6]. Recently, similar changes have been observed with increasing frequency in different types of responding solid tumour treated with various molecularly targeted drugs (e.g. renal cell carcinoma treated with sunitinib, metastatic colon cancer treated with bevacizumab, hepatocellular carcinoma treated with sorafenib). The traditional size-based response evaluation criteria are no longer reliable for evaluating tumour response to treatment in these settings and there has been increasing concern about using WHO criteria or RECIST to assess treatment response in sarcomas treated with molecularly targeted drugs in particular [6–8].

Here we describe a novel approach to evaluating treatment response in sarcomas, based on our experience with GISTs at The University of Texas MD Anderson Cancer Center, together with the traditional size-based criteria. The role of whole body imaging in sarcoma is briefly discussed at the end.

Traditional Criteria for Evaluating Treatment Response

Traditionally, changes in tumour size have been the basis of criteria for evaluating the response of solid tumours to anticancer treatments. Size-based response evaluation criteria were first introduced in the late 1970s (WHO criteria) [9,10] and modified in 2000 (RECIST) [5]. The major difference between the two criteria sets is that RECIST uses the sum of unidimensional measurements of tumour size, whereas WHO criteria use the product of bidimensional measurements to assess the progression of a target lesion. The definitions of objective responses were modified accordingly (Table 1): partial response is defined as a decrease in tumour size of ≥50% by WHO criteria and a decrease in tumour size of ≥30% by RECIST; progressive disease is defined as an increase in tumour size of ≥25% by WHO criteria and an increase in tumour size of ≥20% by RECIST. RECIST also provides guidelines for measuring the baseline overall tumour burden (up to 10 target lesions per patient) and defines target, non-target and measurable lesions. Since its creation almost a decade ago, RECIST has been used almost exclusively in numerous clinical trials.

Many investigators have confirmed the validity of transitioning from using WHO criteria (bidimensional measurements) to using RECIST (undimensional measurements) to assess treatment response in solid tumours. However, some concerns were raised about the discrepancy in the response rates obtained using the two criteria sets and the ways in which this discrepancy potentially affects survival data [4,12]. One comparison study found that 17 of 234 patients (7.3%) had earlier disease progression by WHO criteria than by RECIST [5,12]. Julka *et al.* [3] reported an overall discordance rate of 10% among responses evaluated using WHO criteria and RECIST in 80 patients with different types of solid tumour. The discordance rates Julka *et al.* [3] reported are relatively small but worrisome nonetheless because the cytotoxic drugs that produce 10–20% regression in phase II trial are expected to have a reasonable chance of improving overall survival rates or other time-to-event measures in randomised trials [11].

More importantly, several investigators have reported the inappropriateness of using RECIST to assess the treatment response of some solid tumours that were treated with molecularly targeted drugs [6–8]. In our own study, metastatic or recurrent GISTs that responded to treatment showed dramatic changes in their computed tomography enhancement characteristics and significant decreases in 2-fluoro-2-deoxy-D-glucose (FDG) uptake on positron emission tomography (PET) images at 8 weeks; however, the

Table 1
Traditional response evaluation criteria for solid tumours

Response	WHO criteria [7]	RECIST [7]	RECIST 1.1 [11]
CR	Disappearance of all known lesions	Disappearance of all target and non-target lesions (confirm at 4 weeks)	Disappearance of all target and non-target lesions*
PR	≥50% decrease in the sum of the products of the longest diameters of all lesions (confirm at 4 weeks); no new lesions and no progression of any lesions	≥30% decrease from baseline of the sum of the maximum diameters of ≤10 lesions (confirm at 4 weeks); no new lesions and no progression	≥30% decrease from the baseline of the sum of the maximum diameters of ≤5 lesions; no new lesions and no progression*
SD	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD
PD	≥25% increase of a single lesion over the smallest measurement; any new lesions	≥20% increase over the smallest sum of the maximum diameters observed; any new lesions	≥20% increase over the smallest sum of the maximum diameters observed and an increase of ≥5 mm or any new lesions

WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

* Confirmation at 4 weeks required only for non-randomised trials with the primary end point of response.

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