Measuring the response to selective internal radiation therapy

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1. Introduction

Measuring response to locoregional treatments such as selective internal radiation therapy (SIRT) with yttrium-90 (\( \text{Yttrium-90} \)) microspheres is difficult for a number of reasons. First, the response assessments in oncology are designed for systemic treatments, which in theory would have a similar effect on all metastases throughout the body. By contrast, locoregional treatments are usually staged approaches targeting different tumours sequentially over time. If a locoregional treatment is applied in a single cycle, a 10 cm diameter tumour may show a >50% reduction in volume; however, if during the same interval, a new liver lesion (measuring 1 cm in diameter) develops, the patient will be staged with disease progression despite the significant reduction in tumour load. Current staging systems do not take into account the possibility of repeat treatments (i.e. a staged approach). This limitation applies to all tumour response criteria, including the World Health Organization tumour response criteria \(^1\) and the Response Evaluation Criteria In Solid Tumours (RECIST 1.0) \(^2\) and RECIST 1.1 \(^3\) for solid tumours, and the European Association for the Study of the Liver (EASL) \(^4\) and modified RECIST \(^5\) for hepatocellular carcinomas (HCC).

In HCC, staging systems such as EASL and modified RECIST have been adopted by the American Association for the Study of Liver Diseases (AASLD) to measure the extent of viable tissue (defined as the contrast-enhancing proportion of a tumour in the arterial phase). \(^5\,^6\) Compared with RECIST, both the modified RECIST and EASL criteria are well correlated and have significantly improved the assessment of overall response to anti-angiogenic therapies (e.g. sorafenib) and locoregional treatments (e.g. transarterial chemoembolisation [TACE]) in HCC. \(^7\,^8\) However for locoregional therapies such as TACE, there is a poor correlation between progression rates overall compared with progression rates in target lesion, regardless of the assessment criteria used. \(^8\)

2. New concepts

Various concepts have been proposed to overcome the limitations of current staging systems for the assessment of the response to locoregional treatments, such as the primary index lesion \(^9\) or the time to untreatable progression. \(^10\) Riaz and colleagues, for example, have assessed the correlation between the imaging response in the primary index lesion and time to progression (TTP) and overall survival with TACE or SIRT in multifocal HCC (but not advanced extrahepatic disease). \(^9\) Overall, partial response using the EASL criteria was manifest at a much earlier time (1.6 months) compared with WHO/RECIST (7.7 months). The researchers also found that the response seen in the
primary index lesion following locoregional treatment was prognostic, even in the presence of multifocal disease. Hazard ratios using WHO and EASL were able to capture the significant TTP and survival benefit in responders compared with non-responders in patients with solitary and multifocal HCC. 9

Early data from the SPACE trial using time to untreatable progression show that confounding factors (such as tolerability) to systemic treatment when combined with locoregional treatments may impact on the results. 11 Neither the assessment of the primary index lesion nor time to untreatable progression have been validated sufficiently for adoption as a decision aid in routine practice or as a surrogate for prognosis in comparative clinical trials.

3. Focal effects of SIRT and targeted therapies

A second limitation of imaging is the effects of the locoregional treatment on adjacent tissue. Most locoregional or local ablation techniques cause damage to the adjacent tissue which may be indistinguishable from tumour necrosis and mimics tumour growth on post-interventional scans. Following SIRT for example, radiation-induced inflammatory reactions may provoke contrast enhancement adjacent to the necrotic or residual tumour and the border demarcation around the tumour may vanish. By contrast, with targeted drugs (anti-angiogenics) the lesion becomes sharply demarcated with the loss of perfusion or CM-enhancement.

4. The future

A variety of modalities may be used to assess local tumour response. However, as outlined previously, simple size measurements may fail to describe local tumours response. Thus, functional imaging such as diffusion-weighted MRI (in mCRC), 12 hepatobiliary MRI with gadolinium-ethoxybenzyl-diethylene-triamine pentaacetic acid (Gd-EOB-DTPA-MRI) 13 and positron emission tomography (PET)/computed tomography (CT) 14 in selected tumours are likely to be included in future guidelines although clinical data with these techniques are currently still lacking. Validation of new staging concepts and advanced imaging techniques with diffusion-weighted MRI in mCRC and Gd-EOB-DTPA-MRI in HCC are ongoing in clinical trials such as SIRFLOX and SORAMIC, respectively, which are evaluating the response to SIRT.

Conflict of interest statement

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References