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EVALUATING THE EFFICACY OF TARGET PXT IN METASTATIC LIVER TUMORS

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ABSTRACT: - The goal of assessing tumour response on imaging is to identify patients who are likely to benefit — or not — from anticancer treatment, especially in relation to survival. The World Health Organization was the first to develop assessment criteria. This early score, which assessed tumour burden by standardising lesion size measurements, laid the groundwork for many of the criteria that followed. This was then improved by the Response Evaluation Criteria in Solid Tumours (RECIST) which was quickly adopted by the oncology community. At the same time, many interventional oncology treatments were developed to target specific features of liver tumours that result in significant changes in tumours but have little effect on tumour size. New criteria focusing on the viable part of tumours were therefore designed to provide more appropriate feedback to guide patient management. Targeted therapy has resulted in a breakthrough that challenges conventional response criteria due to the non-linear relationship between response and tumour size, requiring the development of methods that emphasize the appearance of tumours. More recently, research into functional and quantitative imaging has created new opportunities in liver imaging. These results have suggested that certain parameters could serve as early predictors of response or could

predict later tumour response at baseline. These approaches have now been extended by machine learning and deep learning. This clinical review focuses on the progress made in the evaluation of liver tumours on imaging, discussing the rationale for this approach, addressing challenges and controversies in the field, and suggesting possible future developments.

KEYWORDS: Liver, Imaging, Tumours, Metastases, RECIST, mRECIST, LI-RADS, EASL.

INTRODUCTION

The main goal of anticancer treatment is to improve patient survival. Toxicity, adverse events, and changes in quality of life are considered to be ethically acceptable if patients benefit from treatment in the end. However, since not all patients actually do benefit, it is crucial to detect a lack of treatment response both from an oncological, ethical, and socio-economic point of view; although doing so is far from easy. A widely accepted assumption is that tumour burden — i.e. the size of the tumour — is strongly correlated with survival time. From this perspective, monitoring the progression of tumour burden over time can be considered a valid surrogate from the prediction of survival. More simply, tumour response has been assumed to be a strong and valid proxy for increased survival.

The World Health Organization (WHO) criteria for the assessment of tumour response were developed based on this assumption.1 These criteria were rapidly accepted by the oncological community and improvements were made to address their limitations. The Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 — updated as RECIST 1.1. — addresses most of the limitations of the WHO criteria and have become the most widely used and validated set of response criteria in solid tumours worldwide. They are particularly suited for patients treated with conventional cytotoxic chemotherapy, which mainly includes patients with colorectal metastases and cholangiocarcinoma in the liver.

Conventional chemotherapy regimens play a limited role in other liver tumours, especially hepatocellular carcinoma, and the RECIST criteria cannot reliably determine the oncological benefits of treatments. Indeed, liver tumours are almost exclusively fed by the hepatic artery and are characterized by a rich and a dense network of impaired vessels. This offers a strong rationale for locoregional intra-arterial therapies such as transarterial chemoembolisation (TACE) or radioembolisation. Moreover, numerous molecular treatments target specific biological pathways, such as angiogenesis, tumour metabolism, tumour proliferation, or immune response. All of these therapies, alone or combined, tend to induce necrosis or intratumoural changes that do not necessarily result in tumour shrinkage, leading to an underestimation of tumour response by RECIST.

New generations of imaging-based criteria have been proposed as surrogates for traditional survival-based endpoints that provide a more reliable quantitative assessment of treatment response. These approaches are based on the concept of the 'viable tumour', defined as the visualisation of any degree of enhancement after contrast injection. These criteria may be size-based (modified RECIST [mRECIST] and European Association for the Study of the Liver [EASL]

criteria) or include the quantification of inner changes in the tumour i (e.g. the Choi criteria) and have been shown to better identify responders. As a result, certain authors have suggested that some criteria could be used as valid surrogate endpoints for future trials.

Recently, studies have shown that all the aforementioned criteria fail to effectively take into consideration tumour heterogeneity because they are based on a 2D assessment. Thus, a 3D equivalent of size-based criteria has been proposed that assesses all viable tumour volumes and which seems to be more reliable than 2D criteria.

Quantitative and functional imaging is another stimulating field of research including several techniques that provide information about the physiological properties of tissue on a microscopic level. Diffusion-weighted imaging (DWI), perfusion imaging and metabolic imaging have been shown to successfully detect tumour response earlier than conventional morphological criteria. Studies have even suggested that baseline functional imaging parameters differ between future responders and non-responders, which could be valuable in adapting treatment, and in planning future management. Nevertheless, functional imaging is still only used for research purposes, due to problems with reproducibility. This quantitative approach has recently been extended by machine learning and deep learning technologies with promising preliminary results in the assessment of tumour response in the liver.

The aim of this review is to provide a critical overview of the most important imaging-based tumour response criteria in liver tumours. The article focuses on the 3 main hepatic tumours targeted by anticancer treatments, i.e. hepatocellular carcinoma (HCC), hepatic metastases and cholangiocarcinoma. We will follow the historical development from conventional size-based criteria to more recent criteria and discuss their main strengths and limitations.

Locoregional and systemic anticancer treatments are mainly evaluated by CT and MRI. Assessment is performed after contrast administration to assess tumour viability, with protocols including a combination of arterial, portal venous and delayed phases, depending on the tumour. Generally, the first evaluation is performed around 4 weeks after the initiation of treatment with follow-up every 3 to 6 months. Although conventional B-mode ultrasound plays an important role in tumour detection, it is marginal when evaluating response. While contrast-enhanced ultrasound (CEUS) is mainly performed for the characterisation of focal liver lesions, it has also been shown to be effective in quantifying tumour viability, and studies have suggested that it might be used to monitor patients after ablation, or targeted therapies. Of note, the performance of ultrasound and CEUS is usually poorer for deep or subdiaphragmatic lesions, especially in obese patients, and in patients with very heterogeneous liver parenchyma. Finally, metabolic imaging with positron emission tomography (PET) is not routinely performed for the assessment of liver tumour response. It may be performed in selected patients (e.g. isolated elevation of tumour markers, doubtful tumour progression, etc).

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