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Review

Strategies and technical challenges for imaging oligometastatic disease: Recommendations from the European Organisation for Research and Treatment of Cancer imaging group

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Abstract Patients with oligometastatic disease (OMD) often have controllable symptoms, and cures are possible. Technical improvements in surgery and radiotherapy have introduced the option of metastasis-directed ablative therapies as an adjunct or alternative to standard-of-care systemic therapies. Several clinical trials and registries are investigating the benefit of these therapeutic approaches across several cancer sites. This requires that patients are correctly included and followed with appropriate imaging. This article discusses the evidence and offers recommendations for the implementation of standard-of-care (Response Evaluation Criteria in Solid Tumours measurements on computed tomography [CT], magnetic resonance imaging [MRI] and bone scintigraphy) and advanced imaging modalities (functional, metabolic and radionuclide targeted) for identifying and following up patients with OMD.

Imaging requirements for recognising OMD vary with tumour type, metastatic location, and timing of measurement in relation to previous treatment. At each point in the disease

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cycle (diagnosis, response assessment and follow-up), imaging must be tailored to the clinical question and the context of prior treatment. The differential use of whole-body approaches such as ^{18}F-FDG-positron emission tomography (PET)/CT, diffusion-weighted MRI, ^{18}F-Choline-PET/CT and ^{68}Ga-prostate specific membrane antigen–PET/CT require rationalisation depending on clinical risk assessment. Optimal standardised imaging approaches will enable OMD trials to document patterns of disease progression and outcomes of treatment. Quality assured and quality controlled imaging data included in databases such as the European Organisation for Research and Treatment of Cancer Imaging platform for the Oligocare trial (a prospective, large-scale observational basket study being set up to collect outcome data from patients with OMD treated with radiation therapy) will establish a large and high-quality imaging warehouse for future research.

1. Introduction

The recognition that a solitary or a 'few' metastases represent a better prognostic group than if metastases are numerous and widespread has led to the definition of an oligometastatic state [1]. Oligometastatic disease (OMD) has been defined as the presence of 1 and 5 distant metastases in <2 organs [2–4], although the exact number of metastases that should be considered remains debatable. Patients with OMD often have symptomatology that is easier to control, and cures are potentially obtainable particularly because of improved locally ablative surgical or radiation therapy [5–7]. Correct recognition of OMD and precise tumour delineation are therefore imperative to offer patients optimal management strategies based on their risk of further recurrence or progression.

Correct identification of OMD is not trivial. Although serum biomarkers such as prostate-specific antigen (PSA) or CA125 or cfDNA signal the likely presence of cancer and molecular techniques using micoRNAs have been shown to distinguish lung cancer metastases with high and low rates of progression [8], metastasis screening using whole-body *in vivo* imaging is the only real option for OMD detection. Limitations in the sensitivity of the selected imaging techniques mean that disease may be missed. Validation by biopsy of multiple visualised lesions is impractical and unacceptable to patients. Learning from prospective registries and clinical trials is the most pragmatic option, but it requires prospective data collection in a multinational, multivendor European registry. Clinical trials (within the European Organisation for Research and Treatment of Cancer [EORTC] network, such as Oligocare, as well as those outside it) are being set up to monitor OMD and address the benefit of metastasis-directed therapy [9–12] particularly with regard to radiation therapy [13,14]. Collection of meaningful imaging data in these trials would offer a unique opportunity to establish response patterns and outcomes of treating OMD. This article therefore describes the optimal strategies for imaging OMD based on the sensitivity of the imaging techniques and gives recommendations for their implementation in four cancer types with a known predilection for developing OMD (lung, breast, prostate and gastrointestinal) initially being studied in Oligocare.

2. Data collection

The recognition of OMD may require different imaging approaches at different points in the disease cycle: namely at initial diagnosis, at response assessment and at follow-up to identify metastatic recurrence. At each point, the type of imaging needs tailoring to the clinical question and to the therapeutic options that are available, especially in the context of prior treatment. At each point, the imaging needs to accurately determine the location, extent and ideally quantify the character of the metastases, so that treatment response can be assessed. An imaging working group enables specific common imaging requirements to be addressed across OMD trials and standard operating procedures for imaging to be proposed for implementation in a robust and reliable manner across multiple sites contributing to trial databases. Oligocare, a joint initiative between the European Society for Radiotherapy and Oncology (ESTRO) and the EORTC, is one such trial. It is a prospective, large-scale observational basket study being set up to collect outcome data from patients with OMD treated with radiation therapy. It seeks to address multiple unanswered questions around OMD. Those requiring imaging data include patterns of disease progression and characteristics of the tumour that influence both management and outcome.

Imaging modalities routinely used as standard-of-care may be inadequate. Several 'standard' imaging modalities have been superseded by more technologically 'advanced' imaging with better sensitivities and specificities. The utility of the advanced modalities depends not only on the modality itself but also is often

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