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EDITORIAL COMMENTARY

Is the whole larger than the sum of the parts? Integrated PET/MRI as a tool for response prediction

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Several combinations of hybrid imaging have been evaluated in the last two decades [1]. From the beginning, it was clear that the combination of nuclear molecular imaging by means of PET or SPECT combined with contrast-enhanced computed tomography added a significant aspect on the sensitivity and specificity as well as the accuracy of the combined integrated methods compared to the side-by-side reading [2, 3].

About 40 years after [4–6] its introduction, radiolabeled fluoro-deoxyglucose still remains the most ubiquitously used radiopharmaceutical in PET imaging and its predictive value for different tumor entities as a response and outcome marker has been demonstrated. A dedicated response assessment protocol has been established [7]. Standard imaging protocols for the use hybrid PET/CT were published recently and the acquisition and post-processing of PET data has been standardized [8–12].

The use of non-invasive imaging as a predictive biomarker has already been in focus for a long time. Criteria to make images comparable or to standardize evaluation have been implemented (e.g., RECIST, EORTC, or PERCIST criteria). Among the PET-relevant parameters, the semiquantitative have especially gained importance due to their easy acquisition, access, and evaluation. Different thresholds of the standard uptake value to delineate tumor manifestations are the most common ones.

It has been shown that most primary breast cancers as well as the metastases display an increased glucose metabolism [13, 14]. The impact of FDG PET/CT on oncologic management decisions has also been presented [15]. Recently, the value of integrated PET/MRI on initial staging and therapy decision-making has been demonstrated [16, 17].

Several studies have evaluated the potential of prediction of response in breast cancer by means of FDG PET parameters [10, 18–20]. Already the first valuable study showed a very good correlation of two different PET parameters with the final pathological response in primary tumors receiving neoadjuvant chemotherapy [18]. Also, for dedicated breast MRI, different parameters (diffusion-weighted imaging, perfusion changes, or functional tumor volume) were evaluated and have been shown to be of value for response assessment in neoadjuvant chemotherapy [21–24].

In a randomized phase III study, defining response purely on tumor size reduction measured by means of ultrasound or clinically or response-guided adaptation of neoadjuvant chemotherapy, was shown to have a positive impact on survival in patients with early breast cancer [25]. It can be expected that by adding more sophisticated imaging biomarkers, even better decision-making will be made possible.

Combining multiple parameters of different imaging approaches is most likely the way to go to gain more accuracy in prediction. The implementation of several features in so-called "radiomics" approaches have been investigated for some tumor entities [26]. The impact of radiomics has also recently been further treated and discussed in a thorough review giving insight into the necessities of valuable big data sets as well as the processing of them [27]. Automatic structured reporting on conventional breast imaging has been investigated and promises to add a significant increase in user independent evaluation [28].

In this issue, a paper by Cho and coworkers reporting a prospective FDG PET/MRI study in breast cancer patients scheduled to receive neo-adjuvant chemotherapy is published [29]. In an earlier study, it was shown that simultaneous PET/MRI can enable illustration of close interactions between glucose metabolism and pharmacokinetic parameters in breast

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cancer patients and the potential of this for response assessment was discussed [30]. In the study by Cho and coworkers, subjects received PET/MRI scans before the start of NAC and after the first cycle of NAC [29]. In total, 26 patients were enrolled, of which 19 were classified as responders based on the histological classification of the surgery specimen and seven as non-responders. From a set of different quantitative and qualitative PET and MRI parameters, they describe an improved sensitivity and specificity in response prediction when combining the delta total lesion glycolysis (TLG30%) and the delta signal enhancement ratio (SER). These results, and also the knowledge of the potential of each method alone, supports definitely the notion that the integration of the information of these two methods will have the potential to provide a significant impact in therapy decision-making already in this very early phase. Recently, a review focused on the value of FDG PET/CT as a response prediction tool in breast cancer [31]. Although the current study does not present a head-to-head comparison to a pure PET/CT approach, the data suggest that PET/MRI will most likely be superior since the MRI increased significantly the sensitivity as well as the specificity of PET [29].

Further expanding this using the potential of data mining and deep-diving into imaging data in combination or in correlation with various tumors or patient-specific parameters will be the future of precision medicine. It will give a valuable hint for tailored chemotherapy approaches; in other words, early defined responders could benefit from a de-escalation of the chemotherapy regime. I assume that besides FDG, also more dedicated tracers like, e.g., HER-2 targeting [32] ones, will definitely benefit from the easy availability of the breast tissue for non-attenuated hybrid PET/MR imaging. In my opinion, PET/MRI definitely has the potential to become a state-of-the-art imaging modality for staging as well as response prediction of breast cancer.

Compliance with ethical standards

Conflict of interest The author Felix Mottaghy declares he has no conflicts of interest.

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