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PET/CT Biological Imaging of Irradiation-Treated Tumors: Which Studies may Lead to an Improvement in Curability?

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Introduction

The growing availability and development of PET/CT imaging has significantly improved the work of all professionals who deal with cancer care: radiologists, clinical oncologists, radiation oncologists and surgeons. The primary use of PET/CT is diagnosis. By using radiotracer-labeled agents that are able to specifically visualize tumor cells or even certain phenomena undergoing in them, significantly more information is delivered. ^{18}FDG is the earliest-introduced and thus the most used PET/CT radiotracer. It basically reflects the intensity of glucose metabolism, which is usually increased in tumors. It therefore reveals all tumor sites and helps differentiate benign and malignant nodules [1]. More tumor-specific radiotracers exist that bind to certain tumors, which demonstrate little ^{18}FDG avidity. These include ^{11}C-choline (prostate cancer), ^{68}Ga-DOTA octreotate (differentiated neuroendocrine tumors, meningiomas), ^{18}F-NaF (bone metastasis) [2]. ^{18}FET detects active DNA synthesis and is the tracer of choice for imaging of the brain tumors and differentiating vivid tumors from inflammatory and post-treatment lesions [3]. Aside from these diagnostic applications, numerous studies are emerging that attempt to derive information on tumor prognosis from PET/CT. Those that may eventually lead to selection of patient subgroups for treatment escalation are particularly important from radiation oncologist's point of view.

Tumors of Interest

One of the main principles of radiation oncology is to permanently arrest the growth of tumors that are not routinely resected. This particular role is associated with significant challenges. The availability of tumor specimen is limited as only biopsy is often performed. Therefore any insight into the biological tumor properties is practically limited to non-invasive methods. Furthermore, there is no standard second curative option for the patients in case of failure. Therefore, for a certain group of tumors PET/CT is a promising research strategy. Such tumors of radiation oncologists' interest should feature 1) a moderately high curability rate by standalone (chemo) irradiation while the primary surgery not being the modality of choice 2) the majority of failures being locoregional ones, 3) no unanimous gain for the general patient population in trials investigating escalated/intensified irradiation.

Basing on these criteria and current evidence-based medicine, optimal tumors for such research include but are not limited to: locally advanced squamous cell lung cancer [4], deep seated brain tumors [5], head and neck squamous cell cancers [6] and stage II&III cervical cancer [7].

Radiotracers of Interest

Quantitative parameters of ^{18}FDG uptake that can be measured for each tumor include the peak uptake, average uptake, volume, distribution homogeneity and their complex derivatives. Many studies have emerged attempting to identify the ^{18}FDGmetabolic quantifiers that best predict the treatment failure [8]. Some papers suggest that a comparison of PET/CT before and within/after the treatment predicts the outcome better than a single study [9]. However, the wide array of parameters and unsatisfactory repeatability across different centers [10] did not allow any PET/CT threshold-guided treatment escalation to be introduced so far. The high number of such studies in various tumors can make us expect certain guidelines in the near future. Their first implication may not be to alter the treatment options, but, for example, to select patients in whom to intensify the post-treatment surveillance.

^{18}F-misonidazole (^{18}F-MISO) is the most widely used PET/CT marker of hypoxia, a phenomenon that is proven to deteriorate the effectiveness of tumor irradiation. For hypoxic tumors, the application of particle therapy could overcome this limitation. The biological mechanism of action of protons and ions enables efficient tumor cell kill in hypoxic conditions, as opposed to the photons. Growing evidence shows an improved outcome of particle therapy in tumors that demonstrate mediocre curability by photons [11]. Therefore, an important role of 18F-MISO PET/CT and possibly other hypoxia-specific radiotracers [12] may be the identification of patient subgroups to be treated with particle therapy. Defining a unanimous definition of elevated radiotracer uptake would further help make optimal treatment decisions.

The concept that is least explored but may draw radiation oncologists' attention in the near future is the targeted radiotracers such as the single antigen-specific particles introduced for Her2 receptor [13]. For radiation oncology, the cells to selectively track by this approach and escalate the treatment applied would be the cancer stem cells of increased radioresistance [14]. These are likely responsible for the majority of local treatment failures and thus appear another important target for selective treatment escalation. The bottleneck of this concept seems to be the difficulty in identification of specific tumor stem cell antigens, as the data is scarce and only comes from in vitro experimental settings. However, single discoveries constantly emerge, such as the identification and characterization of CD133 in gliomas [15] or CD44 and BM1 in squamous head and neck cancers [16]. Modern radiotherapy seems to be ready for this approach as we can already greatly escalate the radiation dose to very small tumor sub-volumes using dose-painting techniques [17].

Conclusion

Studies of PET/CT prognostic factors have a deep clinical potential. This especially concerns tumors that rarely disseminate but the local curability rates are unsatisfactory. An optimal selection of patient subsets that would benefit from sophisticated irradiation modalities can improve the outcomes, while maintaining reasonable overall treatment toxicity and costs.

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