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Commentary

The tumor dose sensitivity matrix and stem cells in head and neck cancer

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The Problem of Delivering Curative Doses of Radiation Therapy

Radiation therapy (RT) is one of the pillars of locally advanced head and neck cancer (HNSCC) treatment in combination with cisplatin or epidermal growth factor receptor inhibitors. Despite a very high local tumor control rate, approximately 50% of patients with locally advanced disease will develop a recurrence [1]. Although the human papilloma virus (HPV)-associated subtype of HNSCC generally have a better prognosis even they may recur even after standard chemoradiation. This has ramifications for the current trend to de-intensify therapy for HPV-associated oropharyngeal HNSCC with an aim of reducing treatment-associated morbidity and side effects [2]. However, outside of clinical trials patients with HPV-positive and negative tumors receive similar RT treatment uniformly prescribed to the whole tumor. Studying geographic patterns of failure after radiotherapy can aid in determining the optimal dose and distribution of RT in different patient subgroups [3] but even more attractive would be the ability to answer the fundamental question of how much radiation needs to be given to each individual patient and how much dose needs to be delivered to specific subregions of each tumor. It is well known that human tumors of the same or different histology, stage and site vary considerably in their radiation dose response. Thus, the ability to detect and predict inter- and intra-tumoral dose sensitivities would have significant impact on the clinical practice of radiotherapy [4].

The Tumor Dose Sensitivity Matrix: Does it Identify Cancer Stem Cells?

We have previously reported the development of a tumor dose sensitivity or response matrix (DRM) [5,[6] that was constructed at the positron emission tomography (PET) image voxel-level using multiple fluorodeoxyglucose (FDG)-PET/computed tomography (CT) images obtained before and during the early weeks of chemoradiation for HNSCC. The tumor voxel dose sensitivity, DRM, was derived based on the first order reaction law of cell killing from the linear regression of logarithmic ratio of tumor metabolic activity with treatment and is unique for each voxel. The tumor dose sensitivity matrix is highly individualized and has a strong capability to identify radioresistant tumor voxels during the early course of radiotherapy. Combining with the pre-treatment baseline PET standardized uptake vale (SUV), it results in a high capability to predict local tumor failure (**Figure 1**). Importantly, a tumor voxel control probability (TVCP) lookup table was created using the maximum likelihood estimation on these key tumor voxel parameters, the tumor voxel DRM and baseline SUV, which can be used as the objective function for adaptive dose painting by numbers (DPbN)-based inverse planning optimization [5,6]. In addition, considering the efficacy of hypofractionation for resistant tumor cells, early identification of distinct subpopulations derived from the intratumoral dose response could also be utilized to design dose fractionation painting by numbers (DFPbN) adaptively.

The response of tumors to radiation can be modified by many biological activities including tumor cell metabolism, hypoxia, reoxygenation, proliferation, vascular perfusion, immune cells, cancer associated fibroblasts and other components of the tumor microenvironment. All the major tumor biological hallmarks have been proposed to directly or indirectly connect to response to radiation [7]. The approach described above is unique in that it has the ability to describe an intra-tumoral dose

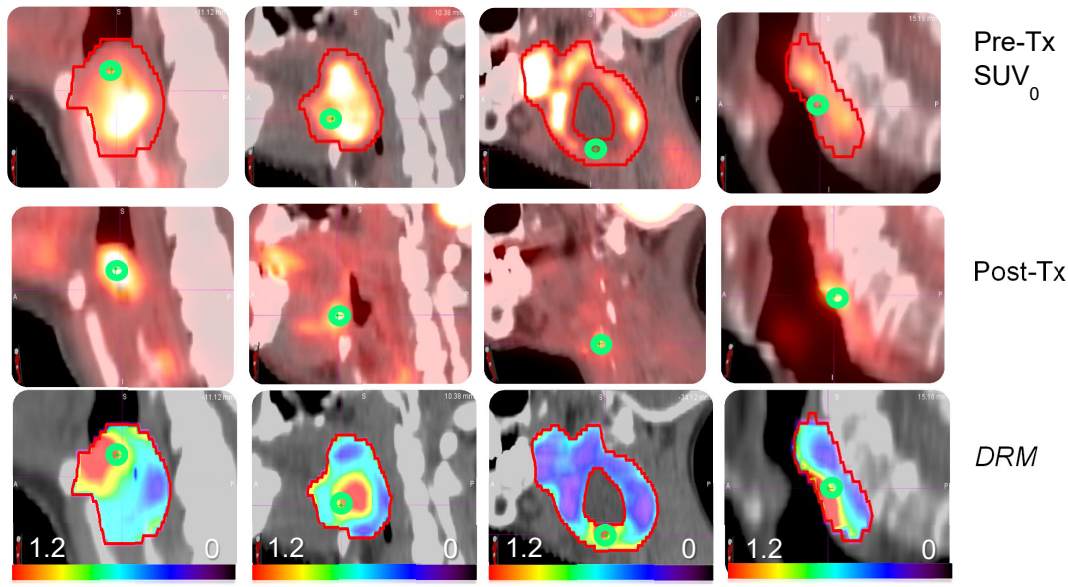

Figure 1. The vertical columns show the pre-treatment FDG-PET images (upper), post-treatment FDG-PET images at local recurrence (center) and DRM images during treatment after 40 Gy (lower) for the four patients that failed treatment locally. The green circle represents the same tumor voxels in each image.

sensitivity distribution using dynamic changes in the whole tumor *in situ* during treatment where many of the aforementioned features will be dynamically changing. This sets it apart from other studies that have developed a radiosensitivity index (RSI) based on biopsies [8]. The RSI has subsequently been validated in several independent clinical datasets [9-12]. Importantly, unlike many other studies where the identification of radioresistant tumors had no direct pathway to prescribe alternative treatment options, the RSI has been combined with linear quadratic modeling to develop the concept of the genomic-adjusted radiation dose (GARD) [13]. Similar to the gold standard clonogenic assay [14,15], this molecular assay provides only a single averaged parameter for each human tumor and does not take into account the microenvironment of the human tumor. Therefore, it cannot identify the intra-tumoral heterogeneity of dose response for individual human tumors.

Subsequently, we undertook a study on the pretreatment biopsies from the patients who had undergone the multiple imaging studies to see if there was any correlation with parameters derived from the tumor dose sensitivity matrix and some selected major biological indices. One of the most interesting findings of the study was the positive and highly significant correlation between CD44 expression and volume of tumor with a DRM greater than 0.8; this is indicative of a high degree of radioresistance. CD44-positive HNSCC cells have been previously shown to initiate tumor growth in immunocompromised animals much more efficiently than CD44-negative cells. This indicates that cancer stem cells (CSCs) are enriched in the CD44-positive subpopulation of HNSCC [16] and have been shown by [17,18] to predict local control after radiotherapy in HNSCC. Our data showed that specific foci of cells are responsible for tumor recurrence based on the imaging which is consistent with concept that CSCs may be randomly distributed in tumors in specific niches [19].

Cancer Stem Cells and Tumor Metabolism

In recent years evidence has accumulated showing that there are multiple genetically diverse clones that co-exist within various kinds of tumors and that CSCs are a distinct subpopulation within a tumor [20]. Not all cells within a tumor are equally sensitive to RT such that understanding the diverse radiosensitivity of different tumor cell subpopulations will be necessary to optimize RT. This challenges the common practice of employing macroscopic bulk tumor responses using medical imaging as the primary endpoint for determining the effectiveness of an anti-neoplastic treatment. Indeed, in our study, there was no correlation between the SUV obtained before and during treatment and the tumors that failed RT [5]. It would seem unlikely that the overall tumor response represents the response of all cells within the tumor, including the most resistant subpopulation within the tumor. The stem cell model of cancer may explain the existence of discrete subpopulations of cells with different genetic and phenotypical differences that set them apart from the bulk of the tumor and equip them to resist treatments and cause local recurrences.

It has been recognized that CSCs are able to self-renew and differentiate and possess a high capability to repair DNA damage, exhibit low levels of reactive oxygen species (ROS), and proliferate slowly. These features tend to render CSC resistant to various therapies, including radiation therapy (RT). More recently, it has been documented that CSCs have different metabolic phenotypes compared with differentiated cancer cells. CSCs can dynamically transform their metabolic state to favor glycolysis or oxidative metabolism whilst most cancer cells use the less efficient glycolysis to produce ATP and essential biomolecules [21-24]. The typical glycolytic pathway includes several enzyme reactions. The first is the phosphorylation of glucose to glucose-6-phosphate, a process

catalyzed by hexokinase (HK). The high expression and activity of hexokinase 2 (HK2) in cancer cells is the basis to detect and image tumors by FDG PET-CT. This feature of tumors has established an important role Indeed for FDG PET–CT in the staging and early detection of disease recurrence in number of solid tumors. It is thought that FDG PET–CT is a useful metabolic imaging modality that can measure glucose uptake and potentially reflect tumor aggressiveness [25]. However, the role of FDG PET-CT in predicting intra-tumoral dose response or local tumor niches that are resistant to radiation dose is not well-established [26-30].

Our data is consistent with heterogeneity and plasticity within the stem cell compartment. Those tumors that failed did not show any clear patterns on tumor voxel dose sensitivity distribution. Resistant tumor voxels were not correlated to the pre-treatment SUV and not at any special location within tumor. Based on the post-treatment PET-CT images, the recurrent tumor voxels were among the resistant voxels. However, large numbers of tumor voxels for these 4 failures were within the controlled region and some of them were very sensitive to the treatment dose. For these tumor voxels, a treatment dose, even lower than the standard prescription dose of 70Gy, could be appropriate. This highlights the variation in radiosensitivity and offers the possibility to escalate and de-escalate treatment plans based on individual voxel sensitivity.

In summary, the imaging method we have developed is a unique approach to study the response to radiation therapy of the whole tumor at the level of the individual voxel. The dynamic metabolic changes we have observed will be influenced by the tumor microenvironment and other heterogeneous physiological changes and biological variation that exist in the tumor before and during the early part of treatment. The relationship between the resistant tumor voxels and CSCs requires further study but the method already presents the opportunity to design dose and fractionation schedules that can deliver tailored treatment based on the expected radiosensitivity of the tumor voxel.

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