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Original Research

Tumour radiosensitivity is associated with immune activation in solid tumours

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Abstract ***Purpose:*** Our goal was to determine whether tumour radiosensitivity is associated with activation of the immune system across all tumour types as measured by two gene expression signatures (GESs).
Methods: We identified 10,240 genomically profiled distinct solid primary tumours with gene expression analysis available from an institutional de-identified database. Two separate GESs were included in the analysis, the radiosensitivity index (RSI) GES (a 10-gene GES as a measure of radiosensitivity) and the 12-chemokine (12-CK) signature (a 12-gene GES as a measure of immune activation). We tested whether the RSI and 12-CK were associated with each other across all tumour samples and, in an exploratory analysis, their prognostic significance in predicting distant metastasis-free survival (DMFS) among a well-characterised, independent cohort of 282 early-stage breast cancer cases treated with surgery and post-operative radiation

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alone without systemic therapy. The lower the RSI score, the higher the tumour radiosensitivity; whereas, the higher the 12-CK score the higher the immune activation.
Results: Using an RSI cut-point of ≤0.3745, RSI-low tumours (n = 4,291, 41.9%) had a significantly higher median 12-CK GES value (0.54 [−0.136, 1.095]) compared with RSI-high tumours (−0.17 [−0.82, 0.42]; $p < 0.001$) across all tumour samples, indicating that radiosensitivity is associated with immune activation. In an exploratory analysis of early-stage breast cancer cases, a multivariable model with patient age, RSI and 12-CK provided a strong composite model for DMFS ($p = 0.02$), with RSI (hazard ratio [HR] 0.63 [95% confidence interval 0.36, 1.09]) and 12-CK (HR 0.66 [0.41, 1.04]) each providing comparable contributions.
Conclusions: Tumour radiosensitivity is associated with immune activation as measured by the two GESs.
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1. Introduction

Over the past few decades, it has been well established that specific cancers are exquisitely radiosensitive, resulting in high loco-regional control rates following treatment. Human Papilloma Virus (HPV)-positive oropharyngeal squamous-cell carcinoma is a radiosensitive tumour, which exhibits a high cure rate following radiotherapy (RT) with or without concurrent chemotherapy [1,2]. Using daily or weekly 3D image guidance, HPV-positive oropharyngeal tumours often demonstrate a complete radiologic response shortly after completing definitive radiation therapy [3]. However, the pre-treatment identification of radiosensitive tumours and host factors associated with radiosensitivity remains a fragmented story for other tumour types.

The tumour microenvironment, including the immune system and function of the host, has been shown to play an important role in mediating both tumour growth and responses to radiation therapy [4]. Tumours frequently down-regulate the host's adaptive immune system to avoid cell-mediated death and, in response, immune modulators have become a promising tool to combat this effect. Radiation therapy has been shown to have both enhancing and inhibitory effects on host-immune function depending largely on the radiation dose and target [5]. A large radiation field targeting multiple vertebral bodies as palliative therapy for spinal metastases, for instance, can reduce a patient's white blood cell count and potentially act as an immunosuppressive agent [5,6]. However, when radiation is highly conformal, with the use of modern treatment planning and delivery, and when it is delivered in higher doses per fraction, radiation has the potential to act as an immune-stimulatory agent [5].

Additionally, when combined with immune modulators, pre-clinical studies and case reports have shown a potential synergy between the radiation and immunotherapy via the abscopal effect [7–9]. How often the abscopal effect occurs and whether it can be triggered by a pre-defined strategy via combining RT and immunotherapy remains a critical clinical question [9]. Radiation has been shown to have a mixed response on programmed death-ligand 1 (PD-L1) expression on the surface of tumour cells, by upregulating or even downregulating PD-L1 expression [10,11], with differing responses possibly driven by tumour site, histology and/or radiation dose per fraction [5]. Thus the identification of biomarker-based approaches is central to the development of clinical strategies to combine radiation therapy and immunotherapy.

To address this, our group recently developed two gene expression signatures (GESs) of radiosensitivity and immune activation. The radiosensitivity index (RSI) is a 10-gene based signature developed as a marker of cellular radiosensitivity that has been independently validated as pan-tissue biomarker of radiosensitivity in multiple disease sites [12–16]. The 12-chemokine (12-CK) GES is based on 12 chemokine genes (*CCL2*, *CCL3*, *CCL4*, *CCL5*, *CCL8*, *CCL18*, *CCL19*, *CCL21*, *CXCL9*, *CXCL10*, *CXCL11* and *CXCL13*) chosen from a metagene grouping of immune-related and inflammation-related genes [17]. The 12-CK GES has been shown to be associated with the presence of tumour-localised ectopic lymph node–like structures (TL-ELNs) in both colorectal cancer and metastatic melanoma patients and was associated with improved survival outcomes in both patient populations [17–19].

In the present study, we hypothesise that RSI and 12-CK are associated and, when combined, will provide an improved prognostic tool for patient outcomes. Combining RSI and 12-CK also serves as a possible clinical strategy to explore the relationship between tumour radiosensitivity and patient immune activation across many unique tumour types.

2. Methods

2.1. Gene profile analysis of archived tumours—Total Cancer Care (TCC) database

We identified 10,240 genomically profiled distinct solid, primary, non-metastatic tumours from the TCC

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