Brief Report

Type I interferon signaling promotes radioresistance in head and neck cancer

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Abstract: Despite the promise of concurrent radiotherapy (RT) and immunotherapy in head and neck cancer (HNC), multiple randomized trials of this combination have had disappointing results. To evaluate potential immunologic mechanisms of RT resistance, we compared pre-treatment HNCs that developed RT resistance to a matched cohort that achieved curative status. Gene set enrichment analysis demonstrated that a pre-treatment pro-immunogenic tumor microenvironment (TME), including type II interferon [interferon gamma (IFNγ)] and tumor necrosis factor alpha (TNFα) signaling, predicted cure while type I interferon [interferon alpha (IFNα)] enrichment was associated with an immunosuppressive TME found in tumors that went on to recur. We then used immune deconvolution of RNA sequencing datasets to evaluate immunologic cell subset enrichment. This identified M2 macrophage signaling associated with type I IFN pathway expression in RT-recurrent disease. To further dissect mechanism, we then evaluated differential gene expression between pre-treatment and RT-resistant HNCs from sampled from the same patients at the same anatomical location in the oral cavity. Here, recurrent samples exhibited upregulation of type I IFN-stimulated genes (ISGs) including members of the IFN-induced protein with tetratricopeptide repeats (IFIT) and IFN-induced transmembrane (IFITM) gene families. While several ISGs were upregulated in each recurrent cancer, IFIT2 was significantly upregulated in all recurrent tumors when compared with the matched pre-RT specimens. Based on these observations, we hypothesized sustained type I IFN signaling through ISGs, such as IFIT2, may suppress the intra-tumoral immune response thereby promoting radiation resistance.

Keywords: Head and neck cancer (HNC); tumor microenvironment (TME); interferon (IFN); immuno-oncology; radiotherapy (RT)

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Introduction

Head and neck cancer (HNC), including squamous cell carcinomas of the oral cavity, pharynx, and larynx, has an annual incidence of 66,000 cases in the United States and results in over 14,000 deaths per year (1). Standard of care therapy includes major oral and pharyngeal surgery and/or high-dose chemoradiotherapy to the head and neck (2). Despite such aggressive treatments, long-term survival for patients with locoregionally advanced HNC remains below 50% (3). Further, surgical and non-surgical therapies may lead to profound detriments in survivors' long-term speech, swallowing, and quality of life (4). Novel approaches are needed for the management of HNC.

To improve outcomes, recent clinical trials have tested concurrent radiotherapy (RT) and programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1)-based immune checkpoint inhibition (ICI), based on the success of ICI in metastatic HNC (5,6). Unfortunately, the results of three clinical trials combining PD-1/PD-L1-targeted ICI with RT for HNC in the definitive setting [JAVELIN-100 (7), GORTEC 2017-01 (8) and PembroRad (9)] showed no benefit of combination therapy over standard of care. Given the independent efficacy of RT and ICI in HNC, and the expectation that ICI should augment the immunogenic response to RT (10), it is essential to identify the underlying etiology responsible for these unexpected trial results. By clarifying the mechanism, therapeutics may be developed to overcome treatment resistance to concurrent RT and ICI and thereby potentially improve HNC outcomes. To identify potential pathways that may lead to RT and ICI-resistance in HNC, we performed differential gene expression analyses comparing clinically recurrent HNCs to matched pre-RT biopsies. We identified upregulation of type I interferon (IFN) pathways in recurrent specimens associated with tumor microenvironment (TME) immunosuppression and M2 macrophage signaling. Although acute type I IFN exposure in the appropriate context may be beneficial, our results suggest chronic type I IFN signaling induced by RT constrains the immune response promoting RT resistance in HNC. We present this article in accordance with the MDAR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2104/rc).

Methods

Study design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All data and specimen acquisition were approved by the Medical College of Wisconsin (MCW) Institutional Review Board (No. PRO00040992) and individual consent for this retrospective analysis was waived. All patients included in the tumor bank provided written informed consent at the time of tumor banking. HNC specimens for ribonucleic acid (RNA) sequencing analysis were obtained from cryopreserved specimens in the MCW Tissue Bank. Patients who underwent surgery and post-operative RT for locoregionally advanced HNC were followed prospectively using our institutional tumor bank. Eight patients were included in this report, including three female and five male patients with a median follow-up 72 months. Demographic and tumor characteristics are listed in *Table 1*. Five patients developed local cancer recurrence, of which three underwent biopsy of the recurrent tumor. First, to identify pre-treatment factors that may predict RT resistance, we compared pre-treatment tumor samples from patients who developed HNC recurrence to those who achieved cure after management with surgery and post-operative RT (*Figure 1*, left). The groups were matched for similar age, tumor subsite, treatment, disease stage, and smoking status (*Table 1*). Next, to identify mechanisms of RT resistance, we compared pre-treatment tumor to a sample of the post-RT recurrence within the same patients biopsied from the same anatomical location in the oral cavity (*Figure 1*, right). All samples were analyzed per this pre-specified design and no samples or resulting data were excluded.

RNA sequencing and bioinformatics

Specimens were cryopreserved in optimal cutting temperature compound at the time of HNC surgery for each patient. HNC specimens were homogenized with TissueLyser LT (Qiagen, Germantown, MD, USA). RNA was extracted using the Qiagen RNeasy mini kit. RNA from tumor samples was analyzed at the MCW Mellowes Center Genomic Sciences and Precision Medicine Center (GSPMC). RNA was quantified and integrity assessed (RNA Integrity Number values from Agilent fragment analyzer). RNA libraries were prepared according to manufacturer's protocols utilizing Illumina's TruSeq stranded mRNA (messenger RNA) library kit. Sequencing was performed on the Illumina NovaSeq6000 with paired end 100 base pair reads generating >50 million reads per sample. Sequencing reads were processed through the Multiplexed Analysis of Projections by RNA sequencing (MAPR-Seq) Workflow (11) with differential expression analysis

Table 1 Demographics and treatment characteristics of included study patients

Characteristics	No recurrence (n=3)	Local recurrence (n=5)
Median age (years)	62	58
Tumor subsite	All oral cavity	All oral cavity
Pathological disease stage	All stage IV	All stage IV
Treatment	All surgery and post-operative radiotherapy	All surgery and post-operative radiotherapy
Smoking status	All former smokers	All former smokers

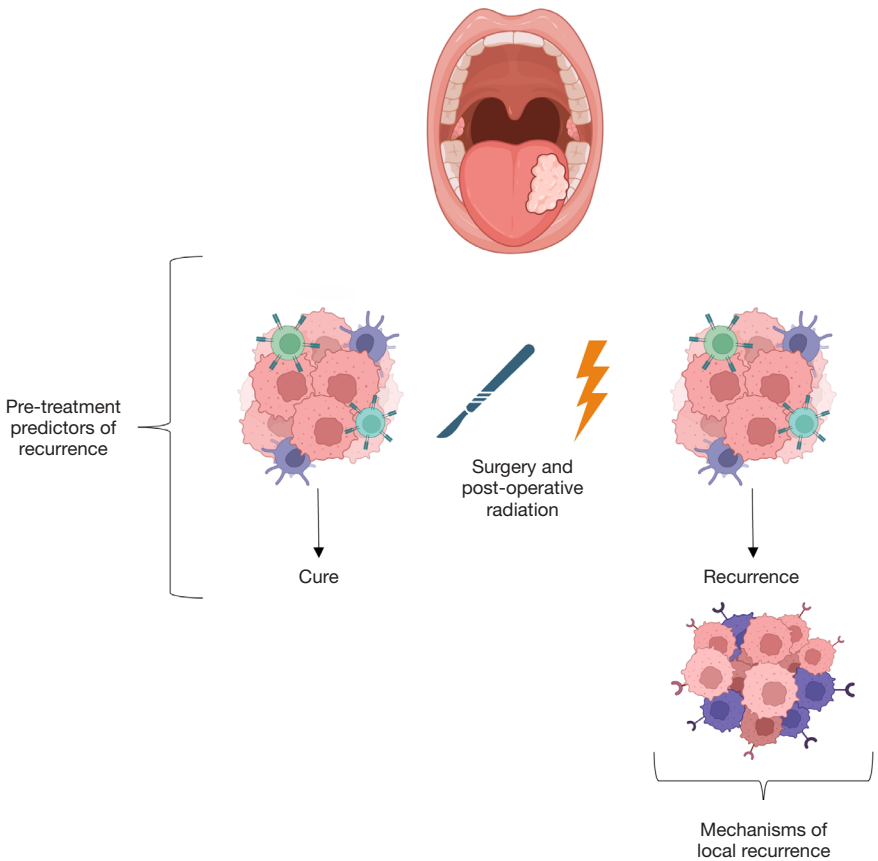

Figure 1 Study schematic demonstrating biospecimen groups, treatment, and analyzes.

completed in Bioconductor, edgeR v3.8.6 software (12). Genes with false discovery rate less than 5% and an absolute fold change ≥2 were considered differentially expressed. Ingenuity Pathway Analysis software (IPA, Qiagen) was used to evaluate for differential pathway enrichment and upstream regulators. Gene Set Enrichment Analysis (GSEA) used the Hallmark Gene Set Collection from the Molecular Signature Database (13). Intra-tumoral immune characterization was performed by quanTIseq deconvolution to estimate the absolute proportion of relevant immune cell types from bulk RNA sequencing profiles (14). The cell type fraction scores provided by this method allow comparisons of ten immune cell type fractions, elucidating differences in immune cell subsets including Tregs, cytotoxic T cells, helper T cells, M1 and M2 macrophages, and myeloid-derived suppressor cells. The quanTIseq method was applied through the R package Immunedeconv on differentially expressed genes (15).

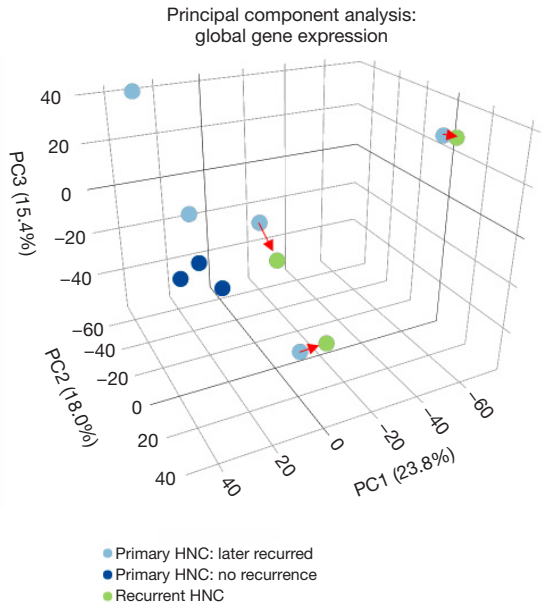

Figure 2 Principal component analysis of primary HNCs which achieved cure (dark blue, N=3) and those which went on to recur after treatment with surgery and radiotherapy (light blue, N=5). For three of the recurrent patients, matched recurrent tissue (green, N=3) was also analyzed. Matched recurrent tumors cluster most closely with their index primary tumors (red arrows). PC, principal component; HNCs, head and neck cancers.

Results

Pre-treatment HNCs achieving cure after treatment are enriched for pro-immunogenic pathways

We performed transcriptome sequencing with differential gene expression analyses to compare initial tumors from patients whose achieved cure with the patients who developed in-field local recurrence after RT. Principal component analysis showed that recurrent cancers clustered most closely with their matched primary tumor and that primary tumors from patients who achieve cure clustered separately from those which went on to relapse (*Figure 2*). This suggested that while certain mechanisms of recurrence are patient-specific, a pre-treatment gene signature may be associated with risk of recurrence. Of 16,355 genes evaluated, in patients who achieved cure 125 were significantly upregulated and 101 genes were downregulated compared with tumors that went on to recur. The differentially expressed genes (absolute fold change ≥2) were analyzed using GSEA and IPA. Top significantly enriched hallmark gene sets in HNCs which achieved cure included the pro-immunogenic tumor necrosis factor alpha (TNFα) and interferon gamma (IFNγ) signaling cascades [$-\log_{10}$(q-value) 13.6 and 7.5, respectively]. IPA analyses further confirmed the top upstream regulator associated with disease cure to be TNF signaling ($P=4.58\times10^{-31}$) with immune cell trafficking representing the top physiological system (P value range 2.19×10^{-59} to 2.04×10^{-19}).

To further understand how pre-treatment immune cell subsets and trafficking may predict disease control or recurrence, we then performed immune cell subset analysis using quanTIseq deconvolution of the transcriptome sequencing data (*Figure 3*) (14). With this technique, the fraction of cells within the bulk RNA sequencing sample representing specific immune cell populations can be approximated based on expression of known immune cell markers. HNCs which went on to recur demonstrated enrichment in M2 macrophage cell signaling, when compared with HNCs which achieved cure. These results further suggest that a pre-treatment pro-immunogenic TME predicts disease control while immunosuppressive influences pre-exist in tumors which go on to develop RT resistance.

Chronic type I IFN signaling is upregulated in RT recurrent HNCs

To better investigate mechanisms which lead to RT resistance, we next compared pre-treatment tumors to RT resistant tumors biopsied from the same patients in the same anatomical location. For the 3 of the 5 patients in our dataset who experienced local recurrence within the RT field, the recurrent tumor was biopsied. All three patients had human papillomavirus-negative oral squamous cell carcinomas and experienced local recurrence at the oral cavity site at a median of 13 months (range, 5–24 months) after completion of post-operative RT. Transcriptome sequencing was performed to compare gene expression profiles in the three recurrent HNC samples to matched pre-treatment tumor specimens which were cryopreserved at the time of each patient's initial surgery. A pairwise differential expression analysis was performed which demonstrated enrichment in type I IFN (IFNα/IFNβ) signaling in matched recurrent tumors. We identified upregulation of several type I IFN-stimulated genes (ISGs) in the recurrent specimens, including multiple IFN-induced protein with tetratricopeptide repeats (IFIT) and IFN-induced transmembrane (IFITM) gene family members

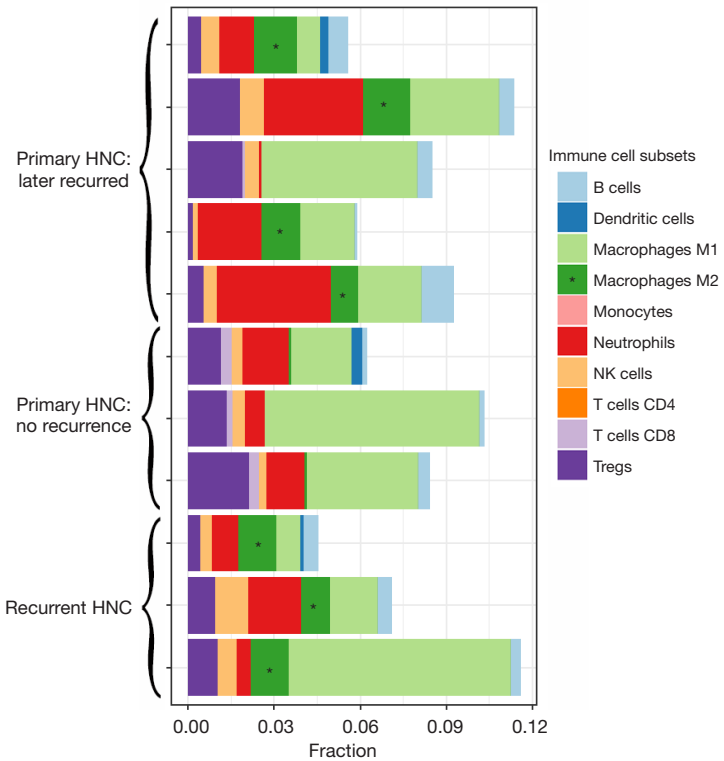

Figure 3 Immune deconvolution from RNA sequencing data of primary HNCs which went on to recur after treatment with surgery and radiotherapy (top 5 rows, N=5), primary HNCs which achieved cure (middle, N=3), and recurrent patients (bottom 3 rows, N=3). The fraction of M2 macrophages is represented for each patient sample as the starred (*) green segment. M2 macrophages were present in only the primary HNCs which later recurred or recurrent patient samples. HNCs, head and neck cancers.

(*Figure 4*). Specifically, IFIT2 was significantly upregulated in all three recurrent tumors, when compared with the matched pre-RT specimens. Pathway enrichment analysis was then performed to identify upstream regulators of differentially expressed genes in the dataset, comparing pre-treatment with matched locally recurrent tumors. Several predicted upstream regulators were identified, demonstrating overlap between expression of type I ISGs and multiple immunosuppressive pathways activated in RT-resistant HNCs (*Table 2*) (16). Apart from PD-L1 expression, multiple other immunoregulatory pathways were enriched in recurrent tumors including T cell exhaustion (CTLA-4, LAG3, TIGIT), anti-inflammatory (IL6, IL10), and immunosuppressive (IDO1) signaling pathways.

Discussion

The type I IFN pathway is a conserved anti-viral defense mechanism with important parallels to RT-induced DNA damage. Similar to a viral infection, RT induces the release of damaged DNA into the cytosol, activating this type I IFN pathway (17) resulting in one of two evolutionarily appropriate responses: (I) type I IFN signaling may induce pro-immunogenic and pro-apoptotic effects resulting in cell death to control viral spread, or (II) this signaling may seek to quell excess tissue damage from inflammation leading to cell survival and cessation of the immune response. As a result of this discordance, several studies have highlighted the importance of type I IFN signaling in anti-tumor immunity (17,18), while others have demonstrated that type I IFNs may lead to RT resistance, altered immunogenicity, and immunosuppression (19-23).

Our data support this context-dependent effect of type I IFN in mediating RT resistance. In pre-treatment tumors with pro-immunogenic features, RT-related type I IFN signaling did not predispose to recurrence. Conversely, in a pre-treatment immunosuppressive environment, chronic type I IFN signaling was associated with RT resistance. This observation is supported by a recent study performed

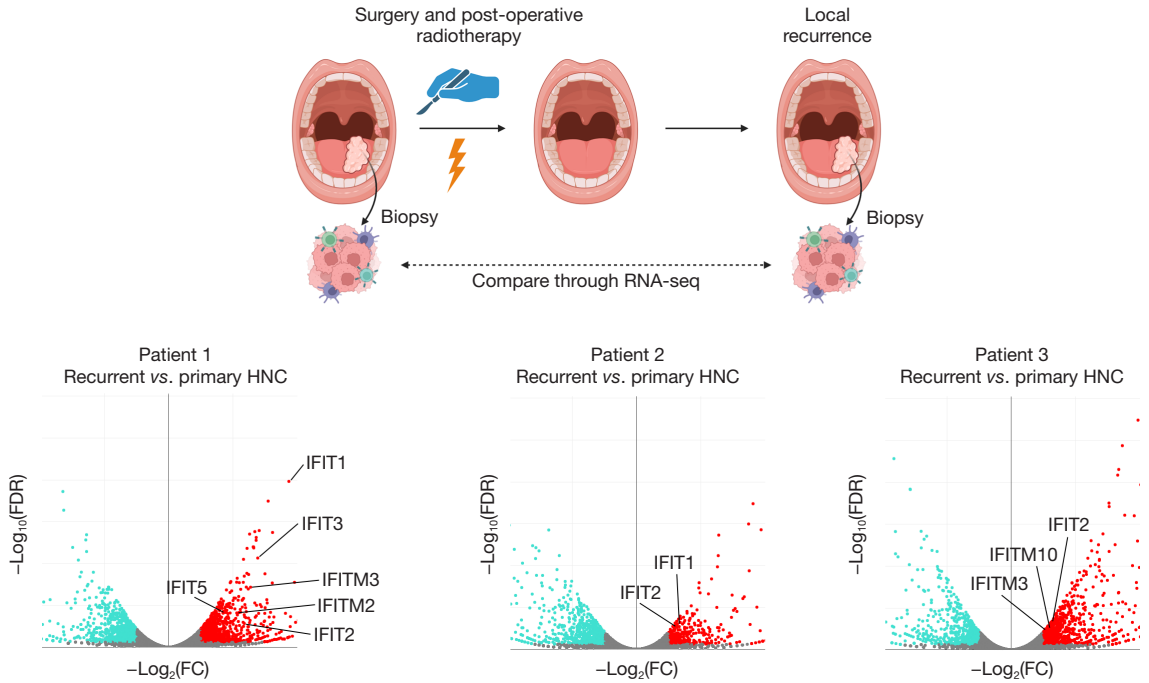

Figure 4 Study schematic illustrating the isolation of pre- and post-radiotherapy biopsies for the RNA-seq analysis is shown in the top panel. Individual volcano plots for patients 1, 2, and 3 were used to identify genes differentially expressed within a given patient (recurrent versus primary cancer) (bottom panel). Type I interferon mediators (IFIT and IFITM genes) were identified in each matched recurrent HNC patient. RNA-seq, RNA-sequencing; HNCs, head and neck cancer; FDR, false discovery rate; FC, fold change; IFIT, interferon-induced protein with tetratricopeptide repeats; IFITM, interferon-induced transmembrane.

Table 2 Ingenuity pathway analysis of differential gene expression between recurrent radiotherapy-resistant head and neck cancers and matched pre-radiotherapy biopsies. There is extensive overlap between type I IFN pathways and known immunosuppressive mediators

Upstream regulator	Molecule type	P value of overlap	Representative target molecules in dataset
STAT3	Transcription regulator	2E−30	PD-L1, CTLA-4, IFI27, IFI30, IFI35, IFI44, IFI6, IFIH1, IFIT1, IFIT2, IFIT3, IFIT5, IFITM1, IFITM2, IFITM3, IL10, IL6R, IL6ST, IRF4, IRF5, ISG15
IL10	Cytokine	7.89E−30	PD-L1, IFI30, IFIT2, IL10, IL6ST, LAG3
IFNα	Group	2.96E−23	PD-L1, IDO1, IFI27, IFI35, IFI44, IFI44L, IFI6, IFIH1, IFIT1, IFIT2, IFIT3, IFITM1, IFITM2, IFITM3, IL6R, IL6ST, IRF4, IRF5, IRF8, ISG15, TIGIT
IL6	Cytokine	1.05E−20	PD-L1, IDO1, IFIT1, IFIT2, IFITM3, IL10, IL6R, IL6ST, LAG3
IFNβ	Cytokine	7.65E−14	PD-L1, IDO1, IFI27, IFI35, IFI44, IFI6, IFIH1, IFIT1, IFIT2, IFIT3, IFITM1, IL10

IFN, interferon; PD-L1, programmed death ligand 1; IFIT, interferon-induced protein with tetratricopeptide repeats; IFITM, interferon-induced transmembrane; ISG, interferon-stimulated gene.

in patient-matched esophageal cancer biopsies where a panel of ISGs were increased in persistent tumors after chemoradiation compared to pre-treatment biopsies (24). Here, we performed additional GSEA and immune deconvolution to assess the changes in the TME in RT-resistance. In clinically recurrent HNCs after RT, type I IFN signaling was associated with immunologic changes in the TME including M2 macrophage infiltration and multiple PD-L1-independent mechanisms of immunosuppression.

Although ISG expression has been associated directly

with malignant cell RT resistance in previous reports (19,25,26), our results implicate an immunosuppressive response to chronic type I IFN signaling. In the chronic phase of viral infection, type I IFNs lead to increased expression of immunoregulatory factors, such as IL6, IL10, and PD-L1 (27,28). Similarly, long-term treatment with pegylated IFNα can result in intra-tumoral PD-1 expression and T cell exhaustion (21). Although, type I IFNs can be pro-immunogenic after acute exposure, long-term effects are largely immunosuppressive through chronic inflammatory pathways (29). Chronic inflammation has been implicated in both HNC progression and radioresistance (30,31).

This immunologic switch from acute pro-immunogenic inflammation to chronic immunosuppressive inflammation has been associated with alterations in type I IFN signaling. Specifically, this may involve transition from the pro-inflammatory STAT1 pathway to the more immunosuppressive STAT3 pathway with downstream production of immunoregulatory mediators (32). Our transcriptomic data support this context-dependent immunosuppressive effect of type I IFN as several predicted upstream regulators showed extensive overlap between type I IFN mediators and multiple immunosuppressive pathways. Notably, this effect was tumor-specific as demonstrated through GSEA. While all tumors treated with RT will have some measure of type I IFN exposure based on RT-induced cytosolic DNA leakage, tumors with a pre-treatment pro-immunogenic TME went on to achieve cure. Conversely, those tumors with a pre-treatment immunosuppressive signature developed chronic type IFN signaling associated with in-field disease recurrence.

These data suggesting the context-dependence of type I IFN-mediated RT resistance are reinforced by the failure of clinical trials combining type I IFN agonists with RT using a blanket approach to patient selection. Most recently, a phase II clinical trial in cervical squamous cell carcinoma demonstrated worse overall survival with systemic IFNα delivered concurrent with RT when compared to conventional chemoradiation (33). Similarly, in several prior phase III randomized clinical trials, the addition of type I IFN to standard of care RT-based therapies did not improve recurrence or survival in rectal cancer (34), non-small cell lung cancer (35), or glioma (36).

This study has several limitations including small sample size and reliance on bulk RNA sequencing data and interpretation. Improved resolution of type I IFN signaling in RT resistance may be achieved in future studies through single-cell sequencing and multiplex immunohistochemical approaches. Nonetheless, this study emphasizes the importance of context in the type I IFN response to RT which will be essential in developing improved treatment regimens. Precision approaches to patient selection will be needed to successfully combine therapeutics that target the type I IFN pathway with RT in HNC.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2104/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2104/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2104/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of Medical College of Wisconsin (MCW) Institutional Review Board (No. PRO00040992) and individual consent for this retrospective analysis was waived. All patients included in the tumor bank provided written informed consent at the time of tumor banking.

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