

## REVIEW

# Interaction between Immunotherapy and Radiotherapy

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### ABSTRACT

In recent years, treatment methods on immune checkpoints have emerged as promising novel therapeutic modalities against cancer as a result of studies focusing on elucidation of immune micro-environment. Immunotherapy has now become an established treatment in some cancers. [1-2] This has led the need for investigation of biomarkers which allow determining effectiveness of immunotherapies and patient groups which will most benefit from these therapies. In previous studies, it was suggested that programmed death receptor-1 (PD-1) and programmed death ligand-1 (PD-L1) expressions could be predictive biomarkers in cancers. PD-1 is a transmembrane protein present in macrophages, myeloid dendritic cells, B cells, epithelial cells and vascular endothelial cells, which limits and inhibits immunological activation in activated T cells. Blocking PD-1/PD-L1 interaction promises hope in the cancer treatment. In clinical studies, it was shown that targeted PD-1/PD-L1 therapy alone or in combination with other modalities is beneficial in advanced cancers with aggressive behavior. It was shown that overexpression of PD-1 present in tumoral micro-environment is associated to poor prognosis in gastric cancer, breast cancer, ovarian cancer, kidney, pancreas and lung cancers and in melanoma. [1-5]

## 1. Introduction

**R**adiotherapy exerts its effect by enhancing death in irradiated tumor cells and elimination inflammation at tumor micro-environment. In other words, it exerts its effect by inducing antigen expression on tumor cells and activating lymphocytes. <sup>1,2</sup> Radiation can induce either inflammatory or anti-inflammatory reactions depending on dose and fractionation. In a study, Patel et al. assessed activated and enhancing T cell infiltration in high-dose (15-20 Gy; 1-3 fractions) and low-dose (3-5

Gy; 4-5 fractions) radiotherapy regimens. Authors emphasized that T cell infiltration was higher resulting in delay in tumor growth in high-dose regimens. <sup>4</sup> Dewan et al. investigated different dose and schemes (20 Gy/one fraction; 24 Gy/3 fractions; 30 Gy/5 fractions) on two poorly immunogenic tumors. Authors found that anti-tumor activity was higher in those received 24 Gy in 3 fractions. <sup>[5]</sup>

## 2. Study and Test

The success of blockade of PD-1/PD-L1 pathway in combination with radiotherapy in killing tumors in

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preclinical studies has encouraged researchers for testing these agents in some tumors. In preclinical studies, it was shown that concomitant use of immunotherapy with radiotherapy was more effective than sequential administration. Currently, phase 1 and 2 clinical trials investigating combination of targeted PD-1 and PD-L1 blockage with chemotherapy (NCT02305186) and radiotherapy (NCT02303990, NCT02311361, NCT02298946) are ongoing. In published series, controversial outcomes have been reported regarding timing of immunotherapy in accurate dose and fractionation of radiotherapy. Radiation necrosis is most common adverse effect of radiotherapy and immunotherapy, which is difficult to manage<sup>2,4</sup>

### 3. Conclusion

In conclusion, programmed death pathway is an important immune control step that functions in late phases of inflammation. Targeted PD-1/PD-L1 therapy in combination with radiotherapy may enable promising results in cancer patients. It is now unclear which radiotherapy technique or regiment will be effective together with immunotherapy. It seems very important to produce a synergism between radiation dose and immune system. Further prospective, randomized studies with large sample size are needed for this purpose.

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