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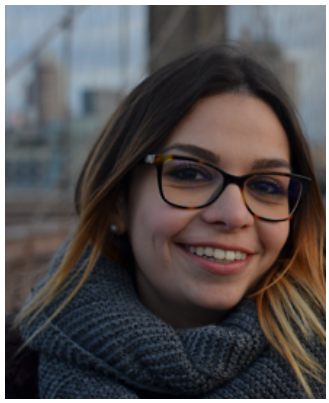
https://www.physiol.uzh.ch/en/research/integration/grpruschy.html



KEYWORDS – preclinical radiotherapy research, radiotherapy treatment volume, radiobiology, radioimmunotherapy, cancer immunology

RADIOTHERAPY TREATMENT VOLUME AND ITS ROLE FOR THE TUMOR-ORIENTED IMMUNE RESPONSE

Despite continuous multidisciplinary efforts, the prospect to transform advanced tumors into a state of "chronic disease" is still limited. Tumor immune evasion and associated failure of immunotherapy are contributing reasons for this and are based on insufficient infiltration or effectiveness of immune competent cells in the tumor. Radiotherapy has been demonstrated to overcome the immunosuppressive tumor microenvironment and anecdotal reports suggest that local tumor irradiation may even exert systemic or abscopal anti-tumor effects by immune-response modification with subsequent response of non-irradiated tumor metastases.

Radiotherapy acts cytotoxic against the tumor and the co-irradiated tumor (micro)environment. Thus, radiotherapy has detrimental effects not only on tumor infiltrating lymphocytes but also on co-irradiated circulating lymphocytes in the bloodstream during radiotherapy, as these cells are particularly radiosensitive. Prolonged lymphopenia during or after the tumor treatment has been shown to be a prognostic factor for the overall survival in many cancer types and the role of radiotherapy in this respect may be suspected. Thereby, larger radiotherapy treatment volumes may lead to a decreased immunogenic effect of a combined radioimmunotherapy and might also suppress abscopal effects, which are indeed only rarely observed in the clinic.

In this project, we investigate the impact of the radiotherapy treatment volume on the efficacy and the immune response alone and in combination with immune checkpoint inhibitors against the irradiated primary tumor and abscopal tumor burdens. Smaller treatment volumes may decrease the number of co-irradiated (circulating) lymphocytes substantially, which may lead to a significantly increased immune response towards the primary, but also the non-irradiated secondary tumor. Larger treatment volumes may diminish immune responses below a critical threshold for an effective immune response. In extremis, even just partial primary tumor irradiation might elicit a sufficiently strong immune response.

Large elective target volumes (e.g. elective lymph node irradiation) are often included into the radiotherapy treatment plan to eradicate potential microscopic tumor cells. In the setting of abscopal or systemic immune responses, this may be unnecessary or even harmful regarding irradiated immune cells. This research project will therefore contribute to a better understanding and potential treatment optimization of patients in this scenario.

SPECIAL TECHNIQUES AND EQUIPMENT

murine tumor models, small animal image guided radiation therapy research platform (X-RAD SmART), immunohistochemistry, flow cytometry