This practice is based on reported experience from single institutions. In the first decade of the 21st century, local control using stereotactic radiotherapy or surgical resection of individual brain metastases has emerged as a clinically beneficial modality for highly selected patients. Whole brain radiotherapy is increasingly seen as a treatment provided in addition to this local control, or is held in reserve for salvage management should new or recurrent brain metastases develop at a later date - without RCT evidence supporting this approach (4,5,6). The majority of patients with brain metastases, however, are not suitable for stereotactic or surgical approaches and WBRT continues to be seen as the standard of care for this group, particularly if they are perceived to have a durable prognosis (5). Until the MRC QUARTZ trial was undertaken in non-small cell lung cancer (NSCLC) (Mulvenna et al 2016-in press), there were no sufficiently powered randomised controlled trials specifically addressing the utility of WBRT compared to supportive care (7). Although prophylactic cranial irradiation has enhanced overall survival and reduced incidence of brain metastases for patients with the exquisitely radiosensitive small cell variant of lung cancer, trials addressing this issue in NSCLC and Breast cancer have failed to address this. This lack of high quality evidence added to the fear of neurocognitive decline remains a potential barrier to applying this technique to other solid tumours with a propensity for metastasising to the brain.

Questions to address:

Can we apply prognostic indices reliably to all solid tumour types?

Do we really know which patients will benefit from WBRT, whether used as a sole palliative modality or as an adjunct to local (stereotactic or surgical) modalities?

If so, how can we best use Image Guided radiotherapy to minimise long term neurocognitive impact?

References:

Median survival of patients with brain dissemination in the course of solid tumors typically ranges between 3 and 6 months, depending on several prognostic factors. In order to select patients for most appropriate treatment or best supportive care, several prognostic indices were proposed, of which recursive partitioning analysis (RPA) score and graded prognostic assessment (GPA) are most widely used. In patients with good prognosis and limited number of metastatic lesions, aggressive local treatment, including surgery and radiosurgery is common, with median survival approaching 12 months. Patients in the intermediate group are typically managed with whole brain radiotherapy (WBRT), whereas patients with poor prognosis are typically offered best supportive care. Advances in the systemic therapy of several malignancies have changed this picture, particularly in subsets of patients with driving molecular aberrations, such as ALK rearranged non-small cell lung cancer or BRAF mutant melanoma. In these patients, long-term responses in the brain and other tumor locations are documented, with series of patients being alive and well for several years after treatment commencement. Penetration of novel targeted agents to CNS becomes its critical feature, as demonstrated by relatively poor intracranial control for ALK inhibitor crizotinib vs. new generation ALK inhibitors such as alectinib. The activity of immunotherapy (anti-CTLA4 and checkpoint inhibitors) in patients with brain metastases is less well documented, but also appears substantial in patients who do not require steroids. Paradoxically, at some point of time, aggressive local treatment strategies and WBRT remain important options in patients with prolonged intracranial control or to improve treatment results even further. The optimal management of these patients remains challenging due to limited evidence-based data and requires multidisciplinary approach.

Symposium: Radiotherapy “autovaccination” with systemic immune modulators for modern immunotherapy

SP-0590
Should the combined treatment be part of our field of knowledge? The “5th R”, (Immune-mediated) Rejection of Radiobiology
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Radiation therapy is an important part of oncological treatment for advanced and metastatic patients and is widely employed, usually in combination with other treatment modalities. Several strategies have been developed to increase the therapeutic index of radiation therapy, in order to maximize the antitumor effect of radiotherapy to improve treatment results even further, limiting its cytotoxic effects on normal tissues or radioprotection. Radiation therapy includes new, high precision, low toxicity, treatments as SRS and SBRT. The paradigm of a systemic treatment alone for systemic disease, has been clearly changed over the last decade, as SRS/SBRT achieved unexpectedly (90%) high rates of local control for metastasis and different tumor primary locations. High doses of radiotherapy can now be delivered with high precision and very limited toxicity, therefore increasing the opportunities for treating patients in combination with systemic treatments without compromising tolerance. Such excellent responses do not completely fit the standard radiobiology models, based on well-known classical DNA damage and tumor cell kill, described by the “4 Rs” of radiobiology (Reassortment, Reoxygenation, Repair, and Repopulation). Some non-targeted effects seem to be involved and preclinical radiobiological studies have suggested that they may be immune-mediated. Either local bystander or distant abscopal effects could explain part of the unexpected results of radiotherapy. In fact, local radiotherapy appears to be a powerful tool for autovaccinating the patient by modifying the highly immunosuppressive microenvironment of established cancers. These pro-immunogenic effects of ionizing radiation on the tumor microenvironment, include potentiated innate and adaptive immune responses through release of pro-inflammatory molecules and modifications in MHC and adhesion molecules in cancer cells, stroma and endothelium. Therefore radiation therapy elicits immune responses as part of its role for killing cancer cells. Unfortunately the abscopal effect is uncommonly observed in clinical practice with radiotherapy alone. Although there is a clear contribution of the immune system to eradication of tumors by novel systemic immunotherapy, only a subset of patients benefit from these therapeutic approaches. The preexisting immune microenvironment seems to be an important predictor of response to such treatments. The increase of productive immune synapses induced by radiation, could be required for the local therapeutic responses to immune agents. In that scenario, changes induced by radiotherapy could modify the immune microenvironment of the tumour, improving response to systemic immune treatments. On the other hand, novel systemic immune treatments could increase the rate of abscopal responses observed after radiotherapy. Radioimmunotherapy seems to be an excellent approach for cancer. In fact, responses and improved outcomes are continuously reported in highly resistant tumours and could be hypothetized to provide a “broad spectrum” treatment for advanced cancer. In that case, modern systemic immunotherapy could represent the most recent form of radiosensitizing tumour cells and increase the radiation induced abscopal effect. We could anticipate that in the next few years radiation-driven immunotherapy will be systematically used in combinations with other agents. But, to be responsible of a standard treatment, we must be aware of the potential acute and late toxicity issues. As for other radiosensitizing treatments, we should also know the best supportive treatment to manage such adverse events. At present anti-CTLA-4 and anti-PD-1/PD-L1 antibodies are becoming increasingly used in clinical practice and clinical trials. Although several reports showed no increase expected toxicity in combination with radiotherapy, these drugs are associated with immune-related adverse events (irAEs). irAEs are believed to arise from general immunologic enhancement and affect the dermatologic, gastrointestinal, hepatic, endocrine, and other organ systems. Temporary immunosuppression with corticosteroids, tumor necrosis factor-alpha antagonists or other agents can be effective treatment. As oncologists, radioimmunotherapy should be part of our field of knowledge and must be rapidly incorporated to our clinical practice.

SP-0591
Radiotherapy for immunotherapy: optimizing the doses and fractionation
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Elimination of virally-infected epithelial cells is mediated by CD8+ T cells and results in life-long protective immunity against reinfection. Similarly, clinical data have shown that CD8+ T cells mediate the rejection of solid tumors and can confer long-term protection from disease recurrence when their activity is unleashed by immune checkpoint inhibitors. Like viral proteins, mutated proteins expressed by an individual tumor are a source of powerful tumor-specific T cell epitopes. However, most of the cancer patients do not develop a sufficient number and repertoire of tumor-reactive T cells and are unresponsive to currently available immunotherapies. We have pioneered studies to explore the use of local tumor radiotherapy (RT) as a means to release tumor antigens in an immunogenic context. We demonstrated that RT converted an insensitive mouse carcinoma into one responsive to CTLA-4 blockade (Demaria et al., Clin Cancer Res 2005), and have recently shown that this combination is effective in lung cancer patients (NCT02221739), a carcinoma unresponsive to anti-CTLA-4 monotherapy. Unique changes in T cell receptor (TCR) repertoire of intra-tumoral CD8+ T cells were observed.