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 active 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 improvements in the systemic therapy 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 Radiotherapy
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Radiotherapy 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 tumor control or radiosensitization and, at the same time, limiting its cytotoxic effects on normal tissues or radioprotection.

Radiotherapy 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 immunotherapies. But, to be responsible of a 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 increasely 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 2009), 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.
in the mouse carcinoma after treatment with RT + CTLA-4 blockade. Significant changes in TCR repertoire were also seen in peripheral blood of responding patients, supporting the hypothesis that RT can convert the irradiated tumor into an in situ vaccine.

Immunogenic cell death is induced by radiation in a dose-dependent way, with higher ablative single doses being more effective in vitro (Golden et al., Oncoimmunology 2014). However, in vivo the interaction between the dying cancer cells and the pre-existing immune microenvironment determines the ability of RT to prime effective anti-tumor T cell responses. For instance, we have shown that the number of DCs available in the tumor and draining lymph nodes to uptake and present the antigens released by RT is a critical determinant of the magnitude of the immune response elicited (Pilones et al., J Immunother Cancer 2014). We have recently found that canonical pathways mediating the induction of type I interferon responses in epithelial cells during viral infection are induced by fractionated but not single dose RT. RT-induced cancer cell intrinsic interferon-I production enhanced DCs infiltration and was required for development of tumor-specific T cells capable of rejecting not only the irradiated tumor but also non-irradiated metastases (abscopal effect). This explains, at least in part, the synergy of fractionated RT regimens (8GyX3 or 6GyX5), but not a single ablative RT dose of 20 Gy, with anti-CTLA-4 in achieving abscopal responses against poorly immunogenic carcinomas (Dewan et al., Clin Cancer Res 2009). In addition, we have shown that immunosuppressive mediators such as TGF-beta, which is released in its active form by RT-generated ROS, need to be neutralized to improve DC maturation and activation of T cells capable of rejecting the tumor (Vanpouille-Box et al., Cancer Res 2015).

Overall, optimal RT regimens combined with targeting of dominant immune suppressive pathways enable RT use as a simple, widely available tool for patient and tumor-specific in situ vaccination. Supported by DOD BC100481P2, NIH RO1CA201246, Breast Cancer Research Foundation, and The Chemotherapy Foundation.

SP-0592
Combining immunotherapy and anticancer agents: the right path to achieve cancer cure?
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Recent clinical trials revealed the impressive efficacy of immunological checkpoint blockade in different types of metastatic cancers. Such data underscore that immunotherapy is one of the most promising strategies for cancer treatment. In addition, preclinical studies provide evidence that the chemotherapy and radiotherapy have the ability to stimulate the immune system, resulting in anti-tumor immune responses that contribute to clinical efficacy of these agents. These observations raise the hypothesis that the next step for cancer treatment is the combination of cytotoxic agents and immunotherapies. This presentation will discuss the immune-mediated effects of anticancer agents and their clinical relevance, the biological features of immune checkpoint blockers and finally, the rationale for novel therapeutic strategies combining anticancer agents and immune checkpoint blockers.

Joint Symposium: ESTRO-AAPM-EFOMP: Functional / biological imaging and radiotherapy physicists: new requests/challenges and the need for better and more specific training

SP-0593
The role of the medical physicist in integrating quantitative imaging in RT: practical and organisational issues
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The evolution of radiation oncology is based on the increasing integration of imaging data into the design of highly personalized cancer treatments. Technologically advanced image-guided delivery techniques have made modern radiotherapy treatment extremely flexible in terms of optimal sparing of the organs at risk and shaping different prescribed target doses to tumor volumes delineated on the basis of functional imaging information. In the last 10 years a remarkable development of more sensitive and specific signals (quantitative dynamic contrast-enhanced CT and MRI; diffusion MRI, specific PET tracers, multi-parametric MRI/PET, etc) have contributed to the prescription and design of radiation treatment plan.

The main contribution of new imaging modalities can be summarized:
- Improved delineation of target and normal structures (new hybrid imaging devices offer co-registration of anatomical, functional and molecular information); a further refinement of this approach is the possibility to shape the dose gradually according to the functional parameters (dose painting);
- Adaptation, the radiation technique defined at planning simulation can often require modification not only due to the changes in patient anatomy but because of early variations of certain imaging related parameters surrogates of treatment outcome.
- Predictive biomarkers, the use of more advanced image analysis methods (texture feature parameters) could be a surrogate of important tumor characteristics and have a higher predictive and prognostic power than simpler numeric approaches;
- Radiomics, the extraction of large amount from diagnostic medical images may be used to underlying molecular and genetic characteristics and this genetic profile may change over time because of therapy.

Despite the multiple benefits that the quantitative imaging can offer for radiation therapy improvement, there are a number of technical challenges and organisational issues that need to be solved before its fruitful integration into RT treatment planning process. The main aspects covered by this lecture will be:
- Standardized procedures for acquisition, reconstruction and elaboration of PET data set;
- Methods for delineation of the PET-related biological target volume (BTV);
- Data acquisition and processing techniques used to manage respiratory motion in PET/CT studies; the use of personalized motion information for target volume definition;
- A procedure to improve target volume definition when using contrast enhanced 4D-CT imaging in pancreatic carcinoma.

SP-0594
Individualised image-guided adaptive therapy in Michigan: lessons learned from clinical trial implementation
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SP-0595
Training in biological/functional imaging: lacks and opportunities
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Pubmed references, presentations and posters during a lot of Conferences (ESTRO, EFOMP, ESMRMB, EANM,...) are introducing a lot of biological and functional imaging for radiotherapy applications: MRI, PET, SPECT, functional CT are able to support radiation therapy for target and Organ of Risk definition. Looking at the EUROPEAN GUIDELINES ON MEDICAL PHYSICS EXPERT (RP 174) the competence on biological and functional imaging is not specific item into RT skill and competences. We can find the key activities of MEPs inside the following: Diag & Therap. NM Internal Dosimetry Measurements( K23: Explain methods for determining