As a common deposit for tumor cells, the liver is second only to the lymph nodes as a site of metastatic disease. The liver is also the most common site of metastastic disease in cancers of the large intestine because it is the first major organ reached by venous blood draining from the intestinal tract.

Unfortunately, by the time some patients present with liver metastases there is usually evidence of the extensive systemic spread of the disease, and patients can no longer be considered as candidates for surgery or other local ablative treatments. However, there is a subset of patients with a few metastases (oligometastases) in which the role of a radical local treatment such as stereotactic body radiation therapy (SBRT) could change disease progression (1).

Most patients with liver metastases have a well-preserved liver function with absence of underlying diseases. Prediction of hepatic toxicity after SBRT in these patients have been primarily based on the assumption of a parallel architecture where subvolumes of the organ function relatively independently and a fraction of the organ can be damaged without clinical effect. A complication is only observed if more than a critical volume is damaged (2). A critical volume of 700 ml of healthy liver (liver-GTV) receiving a total dose of less than 15Gy in 3 fractions has been broadly adopted to avoid hepatic toxicity (3).

An accurate correlation between imaging and pathology is essential for target definition in SBRT. A good agreement between macroscopic pathology and MR imaging has been found for a group of colorectal liver metastases, suggesting that MR can be used for accurate tumor delineation (4). Pilot studies have reported positive integration of 4D PET-CT in the target delineation of liver metastases.

The liver moves with respiration, and can change position depending of filling in adjacent anatomical structures. Assessment of motion of tumor or tumor surrogates (fiducial markers) is mandatory for liver SBRT (5). Management of breathing motion during planning and/or treatment (abdominal compression, active breathing control, gating, tumor tracking) and image guided techniques for daily repositioning are required to increase treatment accuracy, and make possible to deliver very high doses to the tumor while protecting the surrounding organs at risk.

High local control rates after SBRT for liver metastases have been reported in several phase I-II and retrospective trials showing a local control between 80% and 100% at 2 years (6-8).

The American Association for Physics in Medicine has organized an SBRT working group (WGSBRT) to assess tumor control probability (TCP) and normal tissue control probability (NTCP) values for SBRT applied to different organs. In the case of liver metastases, the working liver TCP group investigated if outcomes were affected by the dose regimen. Local control outcomes were significantly better at 3 years for BED >100Gyip.

Toxicity reported after SBRT for liver metastases is in general limited. Quality of life has been assessed after liver SBRT showing no significant change between baseline and 1, 3, and 6 months after treatment (9).

Conclusion: High precision SBRT is an effective technique for treatment of liver oligometastases. Using the right dose, excellent local control rates can be achieved with limited toxicity and without impairment of quality of life.

References:


SP-0496
Disease specific evidence for the treatment of oligometastases: beyond colon cancer
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The treatment strategies for many metastatic cancers are undergoing a dramatic paradigm shift. Systemic therapies are increasingly tailored to unique characteristics of individual tumors. Routine testing for genetic mutations and rearrangements are identifying patients who can benefit from "targeted" therapies. Histology driven chemotherapy is commonly being used. The advent of highly active immune modulating therapies have altered treatment strategies for many diseases that once had few good systemic options.

Simultaneously, there is a growing belief that the number and location of metastases should also be considered in addition to molecular, histology, or immune related factors. Patients with metastases limited in number and destination organ, oligometastases, are often considered for surgery and/or radiation due to reports of long disease free intervals following treatment of all known metastases. Across many diseases, it is common to see 20-25% of patients treated for limited metastatic disease alive and disease free years later. Systemic therapies are often reserved for patients with more widespread or "polymetastases".

Breast cancer patients often present with limited metastases. Approximately 50% of patients treated on clinical trials had 2-4 sites of disease at enrollment. Additionally, breast cancer patients with limited metastases have improved survival compared to those with more extensive metastases. Following treatment of all known metastases median survivals are numerically higher than historic populations. Therefore, NRG BR002 is randomizing patients with 1-2 breast cancer metastases to ablative therapy (surgery or radiation) plus standard of care therapy vs standard of care therapy alone.

Oligometastases are also common in NSCLC. A prospective phase II study demonstrated long term survivors in patients treated with radiotherapy or surgery for oligometastatic disease. Multiple randomized studies have been attempted in this population to test consolidation with radiation following systemic therapy as well as radiation integrated into a systemic therapy treatment platform, however both have failed to accrue. An increasingly useful strategy in
NSCLC patients with known targetable molecular mutations is treatment of limited metastatic progression or oligoprogression. This is due to the fact that most patients with treatable mutations in NSCLC progress in a limited number of metastases. Ablation of these metastases has been shown to allow patients to remain on therapy longer thereby extending the time to the next line of therapy. Melanoma and Renal Cell Carcinoma, classically described “radioresistant” histologies, respond well to ablative radiation. Ablation of all known metastases has resulted in high (80-90%) rates of treated tumor control. Comparative analyses of metastatic melanoma patients treated with metastasectomy versus standard of care demonstrated improved survival for those treated with removal of metastases. However this was prior to the advent of improved immunomodulatory and targeted agents for metastatic melanoma. Furthermore, treatment of oligometastases with radiation has the potential to act as an immunosensitizer, stimulating the immune system and enhancing the response to immunomodulatory agents, perhaps inducing an abscopal effect.

Evidence also shows that oligometastases are common in prostate cancer. Ongoing studies are determining if ablative therapy to all known prostate oligometastases can delay the onset of androgen deprivation therapy, limiting the time, side effects and cost associated with treatment. There are other roles for treatment of oligometastases beyond improvements in survival vs standard therapies. Many patients are not candidates for standard therapies due to medical comorbidity. Other patients, intolerant of the side effects of “targeted therapies”, are left with few treatment options. Ablation of all metastases through surgery if feasible and possible or radiation can serve as another line of therapy to prolong disease free intervals.

SP-0497
Controversies and clinical trials in oligometastatic disease
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Although the term ‘oligometastasis’ was coined in the 1990’s, the first reports of treating limited metastatic disease with surgical resection originated six decades earlier. Several modalities are available to treat metastatic lesions, including surgical resection, stereotactic radiotherapy, conventional radiotherapy, and radiofrequency ablation. Numerous studies have reported ‘better than expected’ survival outcomes after ablative treatment of limited metastatic disease, encompassing patients with varied histologic subtypes and metastatic locations. However, significant controversies remain, as it is unclear as to the extent of which the ‘better than expected’ survival is due to the treatments themselves, or merely due to selection of very fit patients with indolent-behaving tumors. The goal of this presentation is to review the uncertainties associated with the oligometastatic state, the natural history of untreated oligometastatic disease, current and past clinical trials, and future areas of research.

Symposium with Proffered Papers: Immunotherapy and radiotherapy

SP-0498
Ablative radiation-mediated tumour control depends on DNA sensing and T cell responses
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It is thought that ablative radiotherapy (RT), used for rapid control tumor growth, induces genotoxic stress and mitosis crisis leading to prolonged dormancy of irradiated tumor at local and distal site in most patients. We have unexpectedly observed that initial reduction of tumor burden following ablative RT also depends largely on type I IFN for CTL. Targeting tumor with IFN can control tumor growth through initiating a coordinated innate and adaptive immune attack against tumor cells. However, the mechanism for radiation-mediated type I IFN induction remains unclear. Here, we demonstrated that STING, but not MYD88, was required for type I IFN-dependent antitumor effects of radiation. STING in dendritic cells (DCs) controlled radiation-mediated IFN-β induction and was activated by irradiated-tumor cells. The cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) mediated DCs sensing of irradiated-tumor cells. Moreover, STING was essential for radiation-induced adaptive immune responses, which relied on type I IFN signaling on DCs. Exogenous IFN-β treatment rescued cGAS/STING-deficient immune responses. Accordingly, enhancing STING signaling by cGAMP administration promoted antitumor efficacy of radiation. Our results reveal that the molecular mechanism of radiation-mediated antitumor immunity depends on a proper cytosolic DNA-sensing pathway, pointing towards a new understanding of radiation and host interactions. Furthermore, we uncover a new strategy to improve radiotherapy by cGAMP treatment. RT induced IFN can also upregulate PD-L1 that suppress T cell-mediated damage and develop radiation resistance for relapse over time. Anti-PD-L1 antibody can greatly reduce radiation resistance leading to complete tumor regression. Furthermore, our study challenges the rationale for current radio/chemotherapy strategies and highlights the importance of immune activation in preventing tumor relapse.

SP-0499
Understanding biological pathways mediating response to radioimmunotherapy
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Cells respond to radiation. The best known pathways involve DNA repair and anti-apoptotic activities. These have different effects on the cell, its environment and the resulting immune response. We will discuss a new mechanism of DNA repair control that makes cells less responsive to radiation and DNA damaging chemotherapies. In addition, local radiotherapy can boost antibody-based triggering of immune responses to tumors but also makes the cells and environment more susceptible for CTL based therapies. This has allowed us to perform genome-wide screens to identify new and unknown factors controlling DNA repair and susceptibility to DNA damaging regimes in cancer therapy. We will discuss how