DOES NEOADJUVANT RADIOTHERAPY MODIFIES TUMOR MICROENVIRONMENT AND PROMOTES TUMOR METASTASIS DURING SURGERY?

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Purpose: Colorectal cancer is the second leading cancer death and rectal tumors represent 30% of these cancers. Neoadjuvant Radiotherapy (RT) (i.e. applied before surgery) in Locally Advanced Rectal Cancer (LARC) decreases drastically local recurrences but has no impact on the overall survival and metastases occurrence. The best radiotherapy schedule and the right timing of surgery (ST) haven't been resolved, yet. We purpose to bring some scientific rationale and molecular basis to solve these questions. Therefore, we hypothesize that neoadjuvant RT schedules as well as the timing of the ST may influence tumor microenvironment and tumor dissemination.

Methods: For this study, we developed a unique model of neoadjuvant RT in mice. We injected subcutaneously, into the flank of the mice, mammary human tumor cells (MDA-MB231); irradiated precisely the tumor at a total dose of 10Gy based on clinical schedules (2X5Gy and 5X2Gy); removed the tumor at the 4th or the 11th day after the end of RT and then led the mice alive after the surgery for metastases growth. We quantified lung metastases by immunohistochemistry with human KI-67 labeling. Tumor expression of TIMP-1, PAI-1, MT1-MMP and HIF-1α were analyzed by RT-PCR.

Results: We observed two different metastatic profiles according to the RT schedule and the time of ST. The "RT schedule 2X5Gy" drastically decreased lung metastases compared to the unirradiated control mice. Surgery performed at the 11th day decreased by more than a half the number and the size of metastatic islets into the lungs compared to the group operated at the 4th day ($n=4-5$; $p<0,05$). Surprisingly, for "RT schedule 5X2Gy", the timing of ST had smaller impacts on lung metastases. We observed a significant reduction of lung metastases between groups (4th days *vs* 11th days) only for large metastatic islets (>50 and >100 cells) albeit we noted the same trend for small metastatic islets (<10 and >10 cells) ($n=13-19$). Moreover, in 5X2Gy, surgery performed at the 11th day appeared to favor lung metastases, mirroring the results obtained with RT 2X5Gy. We observed a significant increase of TIMP-1, PAI-1 and MT1-MMP mRNA into the tumor when ST was performed at the 11th compared to the 4th day in the 2X5Gy but not in the 5X2Gy group. Neither the tumor size nor the expression of HIF-1α was different between groups.

Conclusions: For the first time, we pointed here up that neoadjuvant RT schedules as well as the timing of the ST influence tumor dissemination and lung metastases. Underlying mechanisms are still not completely understood. They are probably dependent on the RT schedule. Further studies are needed for indentifying the best RT schedule and ST window for improving treatments and the development of new strategies for patients affected by LARC.

I agree to have the abstract released on the BACR website before the conference in February 2011