O11 Cytoreductive primary tumor removal slows down disease progression in an orthotopic xenograft model of prostate cancer

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Introduction & Objectives: In recent years, the concept of cytoreductive radical prostatectomy in oligometastatic prostate cancer (PCa) has been a matter of intense debates. Besides the avoidance of local complications, another rationale is to potentially slow down disease progression by inhibiting the interaction between primary tumor and metastases. In this project, which was funded by a Seeding Grant from the EAU Research Foundation, we aimed to examine the effect of cytoreductive primary tumor removal in a representative mouse model of metastatic PCa.

Materials & Methods: For our experiments we used an orthotopic xenograft model. $5x10^5$LuCaP136 cells were injected into the prostate of CB17-SCID mice. Thereafter, tumor burden was monitored by serum PSA-measurements and small animal imaging. In a first series of 15 mice, 5 mice underwent surgical removal of the primary tumor at 6, 8 and 10 weeks after tumor cell inoculation, respectively. At each time point 3 of 5 mice were sacrificed after primary tumor removal to examine them for the presence of metastases while 2 of 5 mice were kept alive and underwent further follow-up. This experiment was intended to define the time point at which metastases are already present and at which the primary tumor is still surgically removable. In a second series of 48 mice, animals were randomized 2:1 to primary tumor removal and sham operation at the time point defined in the first series and further followed up to examine if there was a different development of tumor burden in these two groups.

Results: Orthotopic tumors were surgically removable 6 and 8 but not 10 weeks after tumor cell inoculation (1^{st}series). Regional lymph node metastases were present in 60% of mice after 6 weeks and in 100% after 8 and 10 weeks. Hence, 8 weeks after tumor inoculation was defined as the optimal time point for primary tumor removal. In the 2^{nd}series, we observed an unexpectedly high mortality of the second surgical intervention at week 8 with only about 60% of mice showing long term survival (>2 weeks). However, further follow up of the surviving mice showed significantly slower PSA-progression ($p<0.01$) and longer survival ($p<0.01$) in the primary tumor removal compared to the sham operation group.

Conclusions: In this project, we used an orthotopic xenograft model of metastatic PCa to examine the effect of cytoreductive primary tumor removal on further disease progression. Tough we observed an unexpectedly high mortality after the second surgical intervention, mice who received primary tumor removal after 8 weeks had significantly slower PSA-progression and longer survival than mice who underwent sham operation. This model will further be used to unravel the molecular mechanisms of interaction between primary tumor and metastases and the preparation of premetastatic niches.