A PHASE 1B STUDY OF SAFETY AND PRELIMINARY EFFICACY OF EXTRACRANIAL STEREOTACTIC BODY RADIATION THERAPY IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA TREATED WITH SYSTEMIC THERAPY

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BACKGROUND

- Historically, renal cell carcinoma (RCC) has been considered one of the most radioresistant tumors with two main mechanisms of its insensitivity to conventional radiation doses: the intrinsic resistance of cancer cells and the tumor microenvironment related factors [1, 2].
- Tumors with low α/β ratio like RCC are not sensitive to low doses of radiotherapy (RT), as they are more efficient in repairing DNA sublethal damage, but more sensible to high RT doses per fraction.
- A genomic study showed that RCC does not demonstrate mutations of DNA repair genes [3]; this could explain RCC low sensibility not only to conventional doses of RT but also to standard chemotherapy.
- Stereotactic body radiotherapy (SBRT) has become an attractive treatment modality because of its ability to deliver highly conformal, large radiation doses to a well localized treatment volume (Figure 1)
- In a few studies SBRT demonstrated its effectiveness in cases of extracranial RCC metastases, mostly in bones and lungs, but for other metastatic sites, data are very limited, and no conclusions could be drawn

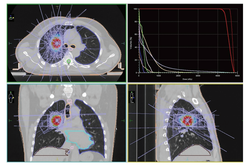

Figure 1. SBRT plan for upper right lobe lesion irradiation from 17 non-coplanar treatment fields

- Tyrosine kinase inhibitors (TKI) and checkpoint inhibitors (IO) have been established as effective treatment for mRCC, but only a minority of patients achieves complete response and additional strategies are necessary to improve the efficacy of these agents
- Combinations of TKIs or IO with radiation therapy could inhibit main growth pathways and enhance sensitivity of RCC cells to SBRT [4]. Abscopal effect – regression of tumors distant from the site of the irradiation - has been frequently observed with SBRT, and is believed to be mediated by immune mechanisms
- There is, however, a heightened concern over toxicity risks with combination of RT with these drugs, that is why we have designed a prospective phase 1b "Volga" study to determine the safety and efficacy of extracranial SBRT in combination with TKI and IO in patients with clear-cell mRCC

REFERENCES

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METHODS

- Patients were included if they had stable disease for at least 4 months on TKI or IO. SBRT was delivered to an organ with multiple comparable lesions, where one lesion was in the treatment target (target lesion) and the other lesion was intentionally left untreated (control lesion)
- Dose of radiation and number of fractions were determined based on target lesion localization and the proximity of organs at risk
- Response in both target and control lesions was scored using RECIST 1.1 criteria at least 2 months after completion of SBRT
- **Primary endpoint** was the rate of adverse events of SBRT and **secondary endpoints** included the rate of reduction in target lesion size and time to progression of the first (target) and the second (control) lesions

RESULTS (1)

- Between November 2016 and April 2018, 17 patients were enrolled
- **SBRT was delivered to:**
  - lungs (n=5)
  - bones (n=4)
  - lymph nodes (n=4)
  - liver (n=1)
  - primary RCC (n=1)
  - locally recurrent RCC (n=2)
- Equivalent Dose (EQD) with alpha/beta ratio of 2.6 was 114 Gy (range, 40-276 Gy)

Table 1. Baseline demographic and clinical characteristics

Age (years), mean (SD)	54,5 (±27,5)
Sex, N (%)	
Male	14 (82)
Female	3 (18)
Karnofsky performance status ≥80, N (%)	17 (100)
Metastatic sites, N (%)	
≤1	6 (35)
≥2	11 (65)
Site of metastasis, N (%)	
Lung	12 (71)
Lymph nodes	9 (53)
Liver	5 (29)
Bone	5 (29)
Locally recurrent RCC	3 (18)
Size of lesions (cm), median	
Target	3.0
Control	2.3
Differences (P)	0.67
Previous surgery, N (%)	
Radical nephrectomy	12 (71)
Cytoreductive nephrectomy	4 (24)
Systemic therapy, N (%)	
Sunitinib	6 (35)
Nivolumab	5 (29)
Everolimus	3 (18)
Lenvatinib + Everolimus	1 (6)
Temsirolimus	1 (6)
Sorafenib	1 (6)

RESULTS (2): TOXICITY

- With a median follow-up of 8 months (range, 3-18), cumulative rate of SBRT-related grade 1 toxicity was 12% (n=2), consisting of esophagitis (n=1) and skin erythema (n=1)
- No grade 2 or higher toxicity was detected

RESULTS (3): EFFICACY

- **Target lesion**

- Radiographic objective response was seen in 13 patients (76%), with complete response in 5 (29%) patients and partial response in 8 (47%) including abscopal effect in 1 (6%) patient

- Fraction size of equal to or greater than 10 Gy was associated with complete response in the target lesion

- **Control lesions**
- Stable disease was observed in 16 (94%) patients

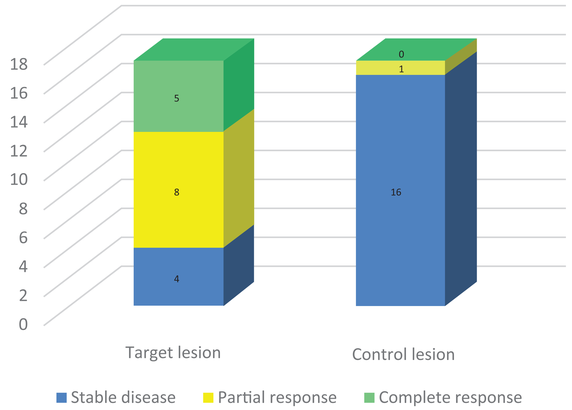

Figure 2. Radiographic response in target and control lesions

CASE REPORT #1

- Patient K., male, 48 y.o., was diagnosed with RCC stage III – T3aN0M0 in September 2013 when he underwent radical nephrectomy. In March 2014 multiple metastatic lesions in lungs, mediastinal lymph nodes and ribs were revealed; from May to August 2014 the patient received pazopanib, from September 2014 to January 2015 – sorafenib with further progression.
- Since March 2015 everolimus was administered with subsequent stabilization within 2,5 years. Patient K. was included into the study in October 2017; he received SBRT (50 Gy in 5 fractions) to the target lesion in S2 of the right lung with no acute toxicity registered.
- CT scan at 2 months (December 2017) showed that both target and control lesions were stable, however, next examination in March 2018 demonstrated partial regression in not only irradiated focus but in all lung and mediastinal metastases up to 50% from their initial size.
- This was assessed as an abscopal effect of previous irradiation.

CASE REPORT #2

- Patient B., male, 49 y.o., radical nephrectomy due to RCC stage II – T2N0M0 in 2004. In September 2005 he was diagnosed with multiple lung metastases, underwent right upper lobectomy, received immunotherapy and since March 2012 he started everolimus with durable stabilization in remaining lesions.
- The patient was included into the study in January 2017 to receive SBRT (5 subsequent fractions of 10 Gy) to the lesion in S10 of the right lung (Figure 3).
- CT scans at 2,5 months showed local fibrosis with no signs of tumor (Figure 4) while control lesion remained stable.

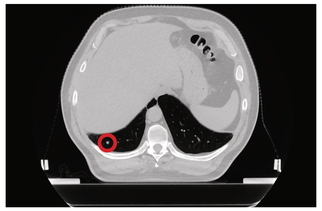

Figure 3. Patient B. before SBRT. Metastatic lesion in right lower lobe (red)

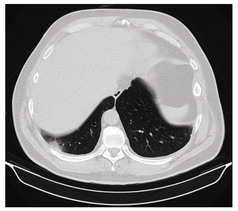

Figure 4. Patient B., 2,5 months after SBRT (50 Gy in 5 fractions). Localized fibrotic changes in lung tissue, lesion is not visualized

CONCLUSION

Extracranial SBRT in patients with mRCC treated with TKI or CI is well tolerated and could be effective. This approach will be studied in an expanded cohort of patients.