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Short Communication

Magnetic resonance-guided stereotactic body radiation therapy for pancreatic oligometastases from renal cell carcinoma☆

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ABSTRACT

Stereotactic body radiation therapy (SBRT) may be a non-invasive strategy to treat patients with pancreatic oligometastases from renal cell carcinoma (RCC). We analyzed 11 patients treated with MR-guided SBRT to 31 pancreatic oligometastases. At a median follow-up of 31.6 months, 1-year and 2-year freedom from local progression was 100 % and 95 % (95 % CI 86–100 %), respectively. Moreover, 1-year and 2-year freedom from systemic therapy was 91 % (95 %CI 75–100 %) and 82 % (95 % CI 62–100 %), respectively. MR-guided SBRT may be a safe and effective treatment option for pancreatic oligometastases from RCC.

1. Introduction

Metastatic renal cell carcinoma (RCC) has been acknowledged as a heterogeneous condition, with behavior varying from widespread dissemination to an indolent course of disease with few metastases (i.e., oligometastatic disease) [1]. Among RCC metastases, pancreatic metastases are associated with the longest overall survival [2]. Local progression may result in obstruction of the pancreatic or bile ducts, with potential morbidity and impediment of starting systemic therapy as a consequence [3]. Hence, there is rationale for radical local treatment, to achieve definite or long-term local control. However, radical treatment by surgical procedures is extensive and accompanied by substantial complication and mortality rates [4,5]. Stereotactic body radiation therapy (SBRT) may be an effective, non-invasive, less-toxic, and lower-cost strategy. A *meta*-analysis [6] and 2 phase II trials [7,8] concluded SBRT to be feasible, safe and efficacious for extracranial RCC oligometastases in general, and to be a plausible strategy to delay systemic therapy. However, data for pancreatic metastases from RCC are scarce [7,8].

The pancreas has adjacent radiosensitive normal structures, such as duodenum, stomach and bowel. Conventional radiotherapy is therefore challenging, because of limited visualization on CT-based imaging and day-to-day anatomic variation [9]. Theoretically, MR-guided SBRT is appealing due to superior soft-tissue setup and potential daily plan adaptation [10]. Indeed, for locally advanced pancreatic cancer (LAPC), MR-guided SBRT has been safely delivered up to 40–50 Gy in five fractions [11–18]. For the presented clinical indication however, no data are available yet. Moreover, as patients with RCC frequently have multiple pancreatic metastases [19], treatment planning for SBRT in this patient group introduces an additional challenge. At the same time, online adaptive treatment could be crucial to resolve the complex anatomical situation and interfraction motion.

The aim of this paper is to illustrate the MR-guided SBRT technique used for treatment of pancreatic metastases from RCC and present toxicity and oncologic outcomes.

2. Materials and methods

2.1. Study population

All systemic therapy-naïve patients with pancreatic metastases from (clear cell) RCC who were treated with MR-guided SBRT till September 2022 at a single center were included. We identified 11 patients (age 65.6 years ± 6.8 SD, 73 % female), treated to 31 oligometastases (range 1–7 lesions per patient) (Supplementary table 1). In 7 patients, oligometastatic disease was diagnosed metachronously [20]. Informed

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consent for the prospective Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-linac (MOMENTUM) study was provided, which has been approved by the institutional review board (NCT04075305) [21].

2.2. Procedures

A full description of our workflow has been published [22]. In case of multiple lesions, patients were positioned on a vacuum mattress (BlueBAG, Elekta AB, Stockholm, Sweden). A custom-made abdominal corset was used to reduce breathing-induced tumor motion [23]. The planning target volume (PTV) was defined as gross tumor volume (GTV) with an isotropic 3-mm margin. Dose constraints and objectives were based on international consensus guidelines [24]. Coverage was reduced if dose constraints on organs at risk (OARs) were compromised. Reference treatment plans were generated with multiple (typically 9–14) intensity-modulated, using the Monaco treatment planning system (version 5.40.01, Elekta AB, Stockholm, Sweden).

SBRT was delivered in 5 fractions of 7–8 Gy over a period of 2 weeks. We used an online adaptive workflow on a 1.5 T MR-linac (Elekta Unity, Elekta AB, Stockholm, Sweden). Each fraction, a 3D T2w MRI-scan was acquired. Delineations were non-rigidly propagated and manually adapted to comply with the actual anatomy (i.e., adapt-to-shape workflow) and a new IMRT-plan was generated [22].

To assess technical feasibility, DVH parameters of all adaptive plans were scored. For DVH metrics on target coverage, this included the GTV V100%, the PTV V95%. For the most critical OARs, i.e. duodenum, small bowel, colon, and stomach, the D0.5 cc was extracted.

2.3. Outcome assessment

Clinical, tumor, and treatment characteristics were obtained from medical records. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria of Adverse Events V5.0. Patient follow-up was typically performed every 3–6 months using contrast-enhanced CT-scans. Freedom from local progression (FFLP) was defined as absence of local failure. Local failure was defined as 1) progressive enlargement over at least two consecutive follow-up scans ($\geq$20 % increase in size), 2) an increase of contrast enhancement (compared to nadir), confirmed at a second follow-up scan, or 3) in the absence of a second follow-up scan: clear progression on a single scan, at the radiologist's discretion. In the event of systemic therapy initiation or pancreatic resection without local failure, data were censored at the start date of systemic therapy/resection. Progression of disease outside the irradiated areas was defined in accordance with RECIST 1.1. Progression-free survival (PFS) was defined as interval to the first instance of progressive disease or death from any cause. Freedom from systemic therapy (FFST) was defined as interval to the start of systemic therapy or death. Overall survival (OS) was defined as death from any cause. All time-to-event endpoints were measured from the start date of SBRT and censored at the last available follow-up if no events occurred.

2.4. Statistical analysis

Descriptive statistics were used to summarize characteristics of the study population. Per patient, the maximum toxicity grade of each adverse event was collected. Swimmer plots were drawn to show the timing of SBRT, adverse events, progression and initiation of systemic therapy. The Kaplan-Meier method was used to describe the time-to-event endpoints. Since individual irradiated lesions have their own risk of local failure, FFLP was assessed per lesion, adding patient as a cluster effect. Analyses were performed using IBM SPSS Statistics™ (Version 25.0, IBM, Armonk, New York) and R (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Treatment characteristics

Median GTV volume of 31 irradiated lesions was 6.6 cm^3 (IQR1.7–10.4). Key DVH parameters from the individual fractions are presented in Supplementary table 2. Over all patients and fractions, the median (IQR) GTV V100% was 96.1 % (93.1–99.8 %), and the median (IQR) PTV V95% was 93.3 % (87.9–96.8 %), and OAR D0.5 cc remained well under the constraints. Pre-treatment imaging, online imaging, and the adapted treatment plan of an example case with three lesions is presented in Supplementary Fig. 1.

3.2. Toxicity

The most commonly reported (9 patients) adverse event was fatigue (Supplementary table 3). Overall, toxicity was mild, with no grade 4 or 5 events. Only one grade 3 event occurred, in a patient who was treated for one symptomatic periampullary lesion: 4 months after SBRT she developed a recurrent bleeding, which was successfully coiled. Because future bleeding risk was regarded to be considerable by the multidisciplinary board, she eventually underwent pancreatic surgery at 7 months post-radiotherapy.

3.3. Oncologic outcomes

At median follow-up of 31.6 months (IQR 26.0–37.8), one patient exhibited local failure of one (intraductal) pancreatic lesion, at 20 months post-SBRT. Consequently, 1-year FFLP was 100 % and 2-year FFLP was 95 % (95 % CI 86–100 %). During follow-up, the size of the irradiated lesions decreased by a median of 33 % (IQR 17–42 %). While tumor shrinkage was often limited and delayed, we frequently observed that a decrease in contrast enhancement and development of tumor necrosis was the predominant feature of response (Supplementary Fig. 2). Within the pancreas, one patient developed a new lesion at 22 months post-SBRT, which could be successfully treated with SBRT with little to no overlap with the previous irradiation field. As for distant recurrences, one patient developed a new metastasis in the gallbladder at 7 months post-SBRT, which was removed by a cholecystectomy. The same patient developed intrapulmonary and pancreatic metastases at 11 months post-SBRT and subsequently started a tyrosine kinase inhibitor. A second patient had a clinical deterioration and hypercalcemia at 20 months post-SBRT, considered to be caused by distant progression. A third patient had progression of a single metastatic lesion on a threatening location (left hilum), for which systemic therapy was initiated, 6 months after SBRT. A fourth patient developed slight progression of two metastases outside the irradiated area, 46 months after SBRT, for which surveillance was continued (no treatment was initiated). No other distant failures were observed, leading to a 1-year PFS of 81 % (95 % CI 60–100 % and 2-year PFS of 61 % (95 % CI 37–100 %). FFST at 1-year and 2-year were 91 % (95 % CI 75–100 %) and 82 % (95 % CI 62–100 %), respectively. Median PFS was 45.6 months. Median FFLP and FFST were not reached *(*Fig. 1 *and* Fig. 2*)*. One-year and two-year overall survival were 100 %.

4. Discussion

In this study of consecutive patients with pancreatic oligometastases from RCC, we observed that treatment with MR-guided SBRT was technically feasible, effective and showed a low frequency of grade 3 or worse adverse events. At the data cut-off, only one irradiated lesion showed local failure and for only 2 patients systemic therapy was initiated. Hence, SBRT could be a feasible strategy to defer systemic therapy.

Our results are in line with two phase II trials on definite radiotherapy for oligometastatic RCC, in which metastases were

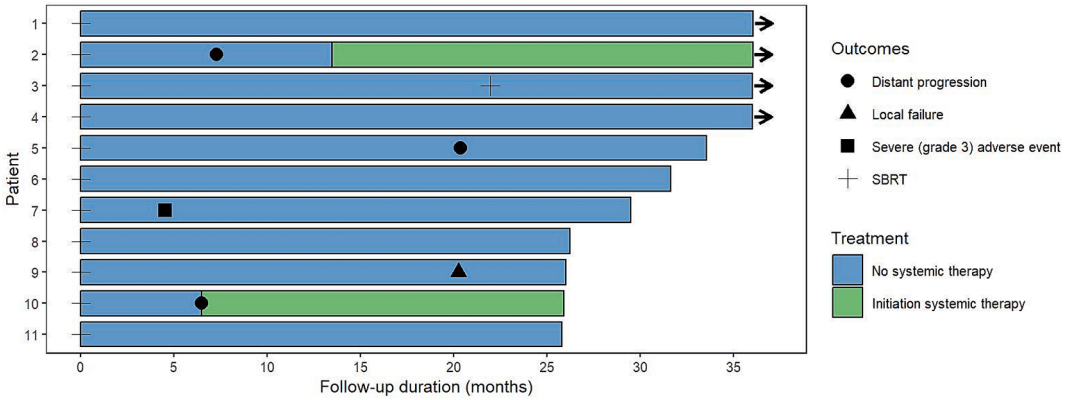

Fig. 1. Swimmer plot of patient treatment characteristics, toxicity, and outcomes. *Arrows indicate a follow-up of >24 months.*

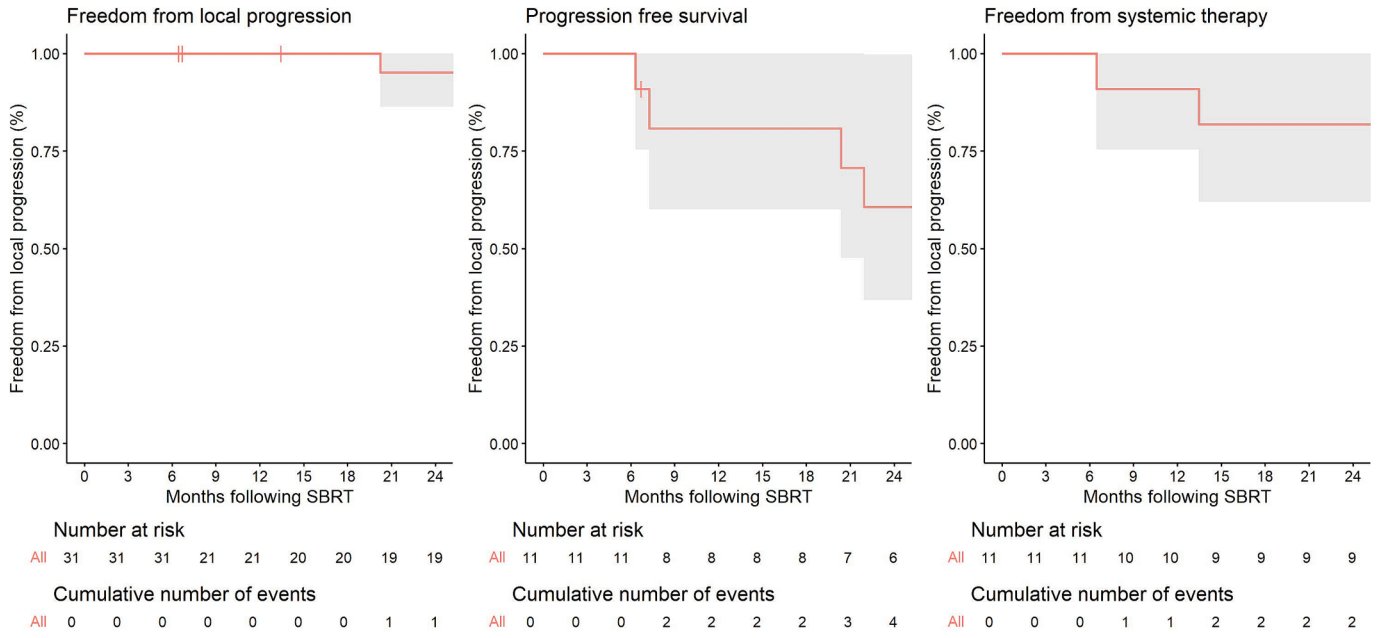

Fig. 2. Kaplan-Meier plots of freedom from local progression (per lesion), progression free survival and freedom from systemic therapy.

predominantly located in the lung, bone and lymph nodes [7,8]. In both trials, local control was ≥97 % and the start of systemic treatment could successfully be delayed for more than 1 year in 82–91 % of patients. Although pancreatic metastases are relatively uncommon, they form an interesting group because of their extremely favorable prognosis [2]. Local treatment may be prudent to decrease the risk of malignant biliary and pancreatic obstruction, and subsequent reduced possibilities for initiation of systemic therapy [25]. Especially in case of multiple pancreatic metastases (64 % in our group), proper visualization and adaptation to the daily anatomy are needed to safely and adequately administer an ablative radiotherapy dose. With an online adaptive workflow on a 1.5 T MR-linac, we were able to successfully irradiate up to seven pancreatic metastases per patient to a dose of 40 Gy in 5 fractions, with a favorable toxicity profile.

While assessing follow-up CT-scans of irradiated patients, we observed that tumor shrinkage was often minimal and delayed. Instead, a decrease in contrast enhancement and development of tumor necrosis was the predominant feature of response (Supplementary Fig. 2). This seems in line with observed responses after SBRT of primary RCC [26] and responses after initiation of anti-angiogenic agents for metastatic RCC, as a result of the induced devascularization in this hypervascular tumor [27]. Similarly, in case of local progression, an increase in contrast enhancement (compared to nadir) may be hypothesized. We, therefore, decided to incorporate both increase in tumor size and increase of contrast enhancement in our definition of local failure.

Treatment was deemed technically successful with high target coverages in the adapted treatment plans. The patient with seven simultaneously irradiated lesions had an average GTV V100% of 91.5 % over all fractions, indicating that even very challenging cases can be treated with an acceptable level of dosimetric coverage. To achieve this, online adaptive, MR-guided treatment is indispensable for precise delineation of targets and OARs. An obvious caveat is that delineation of multiple lesions and calculation of complex plans is even more labor intensive and time consuming than regular MR-linac treatments in the upper abdomen.

This study has inherent limitations relating to the non-comparative retrospective study design and small sample size. Consequently, no comparisons with other treatment modalities or active surveillance could be made, and our results should be considered explorative. Last, our study included only systemic therapy-naive patients, hence cannot provide information on SBRT for oligoprogressive disease, another novel area of interest for metastatic RCC [28,29]. Strengths include the complete follow-up for irradiated patients with a median duration of 31.6 months: all patients had regular follow-up visits with their physician and

were monitored by contrast-enhanced CT-scans approximately every three months.

In conclusion, exploration of MR-guided SBRT to pancreatic oligometastases from RCC suggests that it is an effective and safe treatment option. Moreover, this treatment approach might facilitate the deferral of systemic therapy initiation. With its high local control rates and favorable toxicity profile, it can be an effective and non-invasive alternative treatment strategy to surgery and systemic treatment, and should be considered as such in future updates of RCC treatment algorithms after prospective confirmation.

Author contributions

JKV and MPWI planned the project. JKV and MPWI collected the data. JKV, GG, GJM and MPWI were responsible for data handling, data analysis and interpretation. JKV wrote the first draft, and all authors contributed to and approved the final version of the manuscript for publication.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The MOMENTUM Study is financially supported by Elekta AB and through in-kind contributions from all participating institutions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2024.100683.

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