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Case Report

Successful Yttrium-90 Microsphere Radioembolization for Hepatic Metastases of Prostate Cancer

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Keywords
Radioembolization · Selective internal radiation therapy · Prostate cancer · Hepatic metastases

Abstract
Prostate cancer is the most common solid tumor malignancy worldwide with an estimated 180,000 new cases of prostate cancer and 26,000 deaths in the USA in 2016. Although significant advances in the treatment of prostate cancer have recently been made, the treatment of metastatic disease remains a challenge. With visceral metastases marking more advanced tumor stages, liver involvement is associated with the worst prognosis. So far, no locoregional treatment regimens for the management of liver metastases of prostatic cancer exist. Herein, we report for the first time a successful treatment of hepatic metastases of prostatic cancer using radioembolization with selective intra-arterial administration of Yttrium-90 resin microspheres.

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Introduction

Prostate cancer is the most common solid tumor in men worldwide with slightly varying incidence depending on region and ethnicity [1]. In Germany, about 60,000 men are diagnosed with prostate cancer each year, accounting for 10% of all cancer-related deaths in men which are around 13,400 men per year [2]. Prognosis is determined by genetic predisposition, tumor stage, histomorphology, and local tumor control [3, 4]. In the metastatic stage, prognosis heavily depends on the site of metastasis with the presence of liver metastases being an important adverse predictor of overall survival [5, 6].

Herein, we report on a 68-year-old male with advanced-stage prostatic cancer who developed multiple hepatic metastases. After numerous systemic therapies and sustained progression of liver metastases, radioembolization with selective intra-arterial administration of Yttrium-90 (Y-90) resin microspheres was performed.

Case Report

The 68-year-old patient was diagnosed with prostate cancer in early 2012 with a Gleason score of 4 + 3 = 7B and a G2/3 tumor grading. The initial TNM stage was pT2a N0 M0. At the time of diagnosis, the PSA level was 17 ng/ml. Initial treatment consisted of local combined radiotherapy (IGRT + HDR afterloading) of the prostatic gland and the pelvis, leading to partial remission and a decrease in the PSA level. In June 2013, an increase in the PSA level was observed, and bone metastases were detected on Ga-68-PSMA PET-CT necessitating radiation therapy of the cervical spine. Treatment with bisphosphonates and antihormonal therapy was initiated. In early 2014, therapy was escalated, and a complete androgen blockade was started due to PSA progression. Despite androgen blockade, PSA levels continuously increased accompanied by a steady progression of bone metastases fulfilling the criteria of castration-resistant disease [7]. In late 2014, there was diffuse bone involvement, and PSA level had increased to 180 ng/mL. On Ga-68-PSMA PET-CT, bone metastases remained predominantly PSMA negative, with only a small but increasing number of bone metastases being PSMA positive. On the same occasion, the contrast enhanced CT scan revealed the occurrence of initially PSMA-negative liver metastases, which was confirmed by liver biopsy. Liver biopsy showed androgen receptor-positive tumor cells. Despite treatment with abiraterone, liver metastases progressed, and new PSMA-positive liver metastases were observed on a Ga-68-PSMA PET-CT in June 2015. With clinically manifest castration-resistant prostate cancer, abiraterone treatment was terminated, and a therapy with enzalutamide was started in summer 2015. With sustained progression of hepatic metastases, eventually palliative chemotherapy with docetaxel and prednisone was initiated; from November 2015 to June 2016 a total of 10 cycles was given. Fortunately, a transient partial treatment response could be observed, and PSA level dropped from 197 to 35 ng/mL. In July 2016, radiation of the sacral bone was performed. In September 2016, a rise in PSA level to 242 ng/mL was seen, and PET-CT imaging confirmed further progression of hepatic tumor manifestation, while bone manifestations remained stable. Subsequently, the patient refused to take on another palliative chemotherapy with cabazitaxel and antihormonal therapy and decided to undergo systemic Lu-177-PSMA therapy. Despite the presence of PSMA-positive metastases, the treatment with a total of 3 cycles of Lu-177-PSMA therapy and a cumulative dose of 21,7 GBq Lu-177 PSMA resulted in only a transient treatment effect.

With a continued progression of liver metastases (more than 20 hepatic metastases) as confirmed by a MRI of the liver and otherwise stable disease manifestations at the end of 2016, the decision was made to proceed with radioembolization as a last-resort treatment. In early January 2017, the evaluation procedure was performed. On digital subtraction angiography, the arterial liver supply was assessed, showing a common hepatic artery branching off the celiac trunk and dividing into the gastroduodenal artery and the left hepatic artery. For protection from false embolization, the gastroduodenal artery was embolized using detachable coils. The right hepatic artery originated from the proximal superior mesenteric artery. In order to rule out any extrahepatic accumulation of radioisotopes including a significant pulmonary shunt, Technetium-99m-labelled macroaggregated albumin particles were injected into the left and right hepatic artery. Subsequent scintigraphy revealed no significant pulmonary shunting and no extrahepatic accumulation, confirming that proceeding with the definite treatment was safe. A week later, the selective internal radiation therapy (SIRT) treatment was performed with administration of 1.5 GBq yttrium-90 resin microspheres (SIR-Spheres®, Sirtex Medical Limited, Sydney, NSW, Australia) into the right and 1.0 GBq Y-90-SIR-Spheres® into the left hepatic lobe (Fig. 1). Overall treatment was well tolerated by the patient with no significant side effects. The patient was discharged 2 days after treatment. Six weeks later, a Ga-68-PSMA PET-CT (Fig. 2) and an MR scan (Fig. 3) were performed for assessment of early treatment response. PET-CT revealed a significant decrease in PSMA uptake of liver metastases. The MR scan confirmed a substantial treatment response with a considerable decrease in the size of the liver metastases. Systematic quantitative analysis using the RECIST 1.0 response criteria confirmed a decrease in liver target lesion sum by 43% (Fig. 4). PSA level dropped from to 377 to 90 ng/mL.

Discussion

While significant advances have been made in the understanding of the biology and the local and systemic treatment of prostatic cancer, adenocarcinoma of the prostate remains one of the most deadly cancers in men [2, 3, 8]. With more sufficient treatment options available, patients potentially live longer and subsequently are at a higher risk of developing visceral metastasis [9]. A recently published epidemiologic study revealed that the incidence of metastatic prostate cancer has significantly increased in the US between 2004 and 2013 [10]. The proportion of men diagnosed with aggressive cancer has also increased [11].

Throughout the course of the disease, initially hormone-dependent disease tends to become castration refractory, making treatment more challenging. Usually progression to castration-resistant prostate cancer (CRPC) occurs within 2–3 years of initiation of androgen deprivation therapy [12]. In patients with castration-resistant prostatic cancer, metastasis-free survival decreases from 79% after 1 year to 41% after 5 years [13].

The typical pattern of extraprostatic tumor spread comprises metastases to lymph nodes and bones. Visceral metastases to the liver, lung, or brain are less common, usually occur after prior hormone treatment or chemotherapy and mark more advanced-stage disease with poor outcome [9, 14]. In our patient, liver involvement occurred 1 year after complete androgen blockade, 1½ years after first detection of bone metastases, and nearly 3 years after initial diagnosis. In a recent meta-analysis, 20.8% of men with metastatic CRPC (mCRPC) had visceral disease, 41% of which had liver involvement [5]. After metastases to the bone and lung, the liver represents the third most common site of metastases affecting up to 8.6% of patients with mCRPC [9]. At the same time, tumor manifestation in the liver

usually determines the prognosis of the patient irrespective of additional sites of metastases. Compared to other sites of metastatic disease, liver metastases are associated with the worst median overall survival of about 13 months [5].

Despite advances in the treatment of metastatic CRPC, providing meaningful benefits to the patients, mCRPC continues to have an almost 100% mortality [8, 15]. Docetaxel has been shown to provide a survival benefit both in castration resistant disease as well as in castration-sensitive patients with high-volume disease [16]. In castration-sensitive patients, it prolongs time to the development of castration resistance when given at the time androgen deprivation therapy is initiated. In mCRPC patients, abiraterone and enzalutamide offer new means to interfere with androgenic stimulation further improving survival [8]. After initial good treatment response to palliative chemotherapy with docetaxel and prednisone with a significant fall in PSA levels, liver metastases eventually progressed further in our patient.

To date, no established locoregional treatment regimens specifically addressing hepatic involvement in prostatic cancer exist. Wang et al. [17] reported 1 case with isolated liver spread and successful surgical resection of a solitary liver metastasis. Due to the multitude of liver metastases in both lobes, liver surgery was no treatment option in our patient. In a recent publication, Wei et al. reported another case of a successful treatment of hepatic metastases of hormone-refractory prostate cancer using systemic radioligand therapy Lu-177-PSMA-617 [18]. In our patient, however, systemic radioligand therapy had no significant effect on tumor progression in the liver. A possible explanation might be that PET tracer avidity of liver metastases in our patient reflected PSMA expression in the neovasculature and not in the tumor cells. This could also explain, why PSMA positivity of liver metastases was observed in a fairly late stage in our patient. Unspecific PSMA expression in the neovasculature has been described in a variety of different malignant neoplasms [19].

Selective internal radiotherapy of the liver has been suggested for a number of radiosensitive tumor entities, including HCC, colorectal cancer, neuroendocrine tumor, and breast cancer [20]. Overall, radioembolization is tolerated well with only little side effects and results in a good quality of life in a palliative setting. So far, to our knowledge, no reports exist on the successful use of SIRT in patients with prostate cancer and hepatic metastases. With prostate cancer belonging to the group of radiosensitive tumors, radioembolization in the setting of hepatic metastases seems a self-evident treatment option.

In our patient, radioembolization led to an impressive treatment response with a significant reduction of hepatic tumor burden fulfilling the response criteria of a partial remission. With the current scarcity of effective treatment options in more advanced disease stages, radioembolization of the liver may provide a viable treatment option in prostate cancer patients with hepatic metastases.

Statement of Ethics

The authors have no ethical conflicts to disclose. Informed consent was obtained from the patient for publication of this case report.

Disclosure Statement

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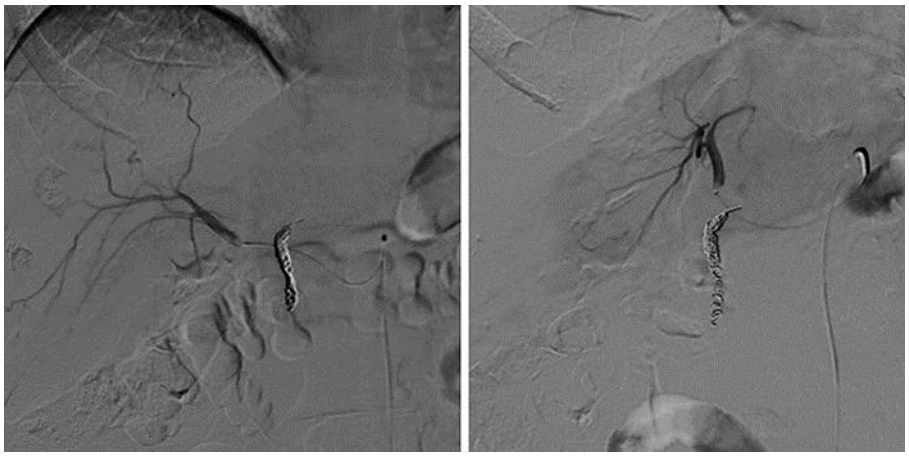

Fig. 1. Embolisation of the right and left hepatic artery with Y-90 SIR microsphere after protective coil embolization of the gastroduodenal artery.

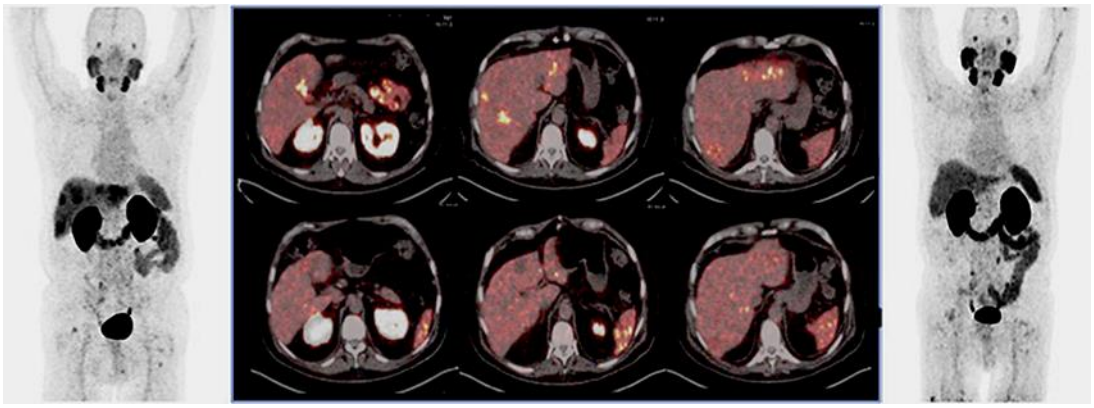

Fig. 2. Ga-68-PSMA PET/CT with multifocal liver metastases in castrate-resistant prostate cancer (top row) and after successful treatment with 2.5 GBq Y-90 microspheres (bottom row) demonstrating almost complete disappearance of PSMA-positive liver metastases

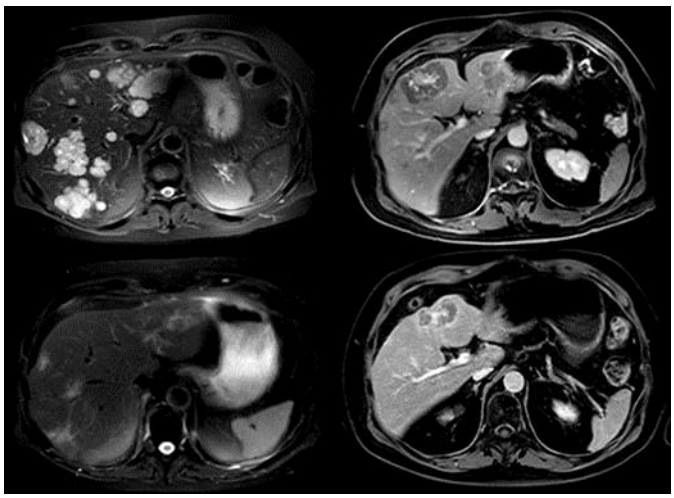

Fig. 3. Fat-saturated T2-weighted (left column) and gadolinium-enhanced (right column) MR imaging before (upper row) and 6 weeks after radioembolization (bottom row). Prior to radioembolization, multiple, multifocal, centrally hypervascularized metastases were found in both liver lobes. On follow-up, tumor burden significantly diminished.

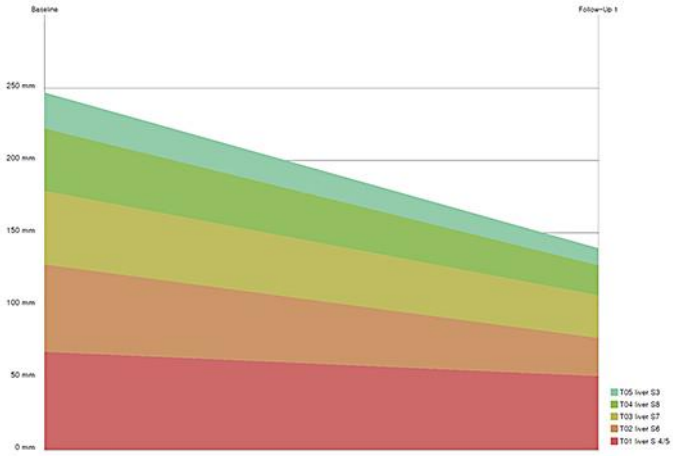

Fig. 4. Metastatic tumor burden in the liver according to Recist 1.0 (5 target lesion per organ) based on Gd-enhanced liver MRI before and after Y90-SIR-Sphere® radioembolization using dedicated tumor response evaluation software (mint Lesion™, Mint Medical Inc.).