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Case Report

Transarterial Selective Internal Radiation Therapy with Yttrium-90 for Liver Metastatic Urothelial Carcinoma of the Ureter as a Bridging Therapy to Immunotherapy: A Case Report with a 10-Year Follow-Up

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Abstract
Primary transitional cell carcinoma of the ureter is a rare type of cancer with metastasis presented in approximately 25% at diagnosis. Due to its rarity and poor prognosis, the management of this neoplasm is still controversial, and the development of new therapies is of uttermost importance. Herein, we describe a case of a 54-year-old patient diagnosed with transitional cell carcinoma of the left ureter submitted to left nephroureterectomy (pT3N2M0) and methotrexate, vinblastine, doxorubicin, and cisplatin adjuvant chemotherapy. A single liver metastasis was detected and combination chemotherapy with gemcitabine and carboplatin was initiated along with stereotactic body radiation therapy. Despite these 2 previous chemotherapy regimens, the patient presented disease progression and transarterial selective internal radiation therapy (SIRT) with yttrium-90 was indicated. This locoregional treatment was performed with the administration of 1.2 GBq yttrium-90 resin microspheres (SIR-Spheres®, Sirtex Medical Limited, Sydney, NSW, Australia) into the right hepatic artery. Another systemic treatment was immunotherapy using nivolumab with excellent tolerability. After 10 years of follow-up, at the last clinical evaluation, the patient had no clinical symptoms and the last imaging follow-up

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using positron emission tomography-computed tomography scan showed complete response. This report introduces upper urinary tract urothelial carcinoma as a distinct type of malignancy in which SIRT can be safely implemented. As a transition method to nivolumab, it was successful. There might be a potential therapeutic synergism between these 2 treatment modalities.

Introduction

Primary transitional cell carcinoma of the ureter is a rare type of cancer with an estimated annual incidence of 1.8 cases per 100,000 person-years in the USA. It is a very aggressive disease with metastasis presented in approximately 25% at diagnosis with a median overall survival of 21 months for advanced-stage patients [1, 2].

Platinum-based combination chemotherapy is the first-line treatment in metastatic disease, but current regimens are toxic and lack a sustained response [3]. Due to its rarity and poor prognosis, the management of primary transitional cell carcinoma of the ureter is still controversial, and the development of new therapies is of the utmost importance.

Nivolumab is a fully human IgG4 programmed-death-1 immune checkpoint inhibitor antibody that represents one of these new treatments for metastatic urothelial carcinomas, showing promising results [3–9]. Another innovative approach in cancer control is transarterial selective internal radiation therapy with yttrium-90 (SIRT). It is based on the administration of microspheres loaded with the radioisotope yttrium-90, via selective arterial catheterization of tumor-feeding vessels [10].

This locoregional therapy was used from palliative care to neoadjuvant treatment in the treatment of several types of liver metastatic disease with encouraging outcomes [10–12]. Herein, we present a first-of-its-kind case where SIRT was successfully used in combination with other pre-established treatment options for metastatic upper urinary tract urothelial carcinoma.

Case Presentation

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531787) [13]. A 54-year-old Caucasian man with hypertension was diagnosed with transitional cell carcinoma of the left ureter in 2012. His physical examination showed no abnormal clinical findings. Initial treatment consisted of left nephroureterectomy (pT3N2M0) and methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC).

In March 2015, a single liver metastasis in segment VII (maximum diameter: 2.2 cm/SUV max: 7.8) was detected on magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET/CT) scanning and combination chemotherapy with gemcitabine and carboplatin was initiated along with stereotactic body radiation therapy. In December 2015, despite these 2 previous chemotherapy regimens, the patient presented disease progression according to the mRECIST criteria with the development of 2 new liver lesions (segment V: 3.7 cm and segment VI: 2 cm) revealed in MRI and PET/CT (SUV max: 11.8) [9, 14].

Hence, a multidisciplinary approach with oncologists, interventional radiologists, and urologists took place and the decision to proceed with SIRT was made. Therefore, in January 2016, the first step procedure with ^{99m}Technetium-macroaggregated albumin

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was performed to calculate the lung shunt fraction. No additional arteries that could lead to extrahepatic microsphere distribution were identified. The lung shunt fraction was 4.5%.

Two weeks later, SIRT was performed in the angiosuite of a tertiary care hospital and was headed by 3 highly experienced interventional radiologists (more than 15 years in practice) assisted by 2 interventional radiology fellows with the patient under conscious sedation in a supine position.

The target arterial tumoral supply was assessed, through a left femoral percutaneous approach with a 5-French Cobra 2 catheter (Cordis Corporation®, Miami lakes, FL, USA) and a 2.7-French microcatheter (Progreat®, Terumo, Shibuya-ku, Tokyo, Japan). Treatment was performed with the administration of 1.2 GBq yttrium-90 resin microspheres (SIR-Spheres®, Sirtex Medical Limited, Sydney, NSW, Australia) into the right hepatic artery (shown in Fig. 1).

Post-procedure imaging with single photon emission-computed tomography (SPECT/CT) confirmed adequate microsphere distribution and delivered dose. There were no complications, and the patient was subsequently discharged from the hospital 1 day after the procedure (shown in Fig. 2).

The commercial dosimetry software, MIM SurePlan LiverY90® (MIM Software Inc., Cleveland, OH) was used for absorbed dose calculation [10, 11, 15]. The tumors received 199 and 70 Gy at V70 (V70 = mean tumor dose to top 70% of tumor volume), respectively. The non-tumoral volume at V70 was 7 Gy.

After undergoing Y90 treatment, the patient was followed up at the interventional clinic for 5 years and received follow-up PET/CT scanning. Additional treatments included retroperitoneal lymph nodes robot-assisted resection in December 2017 and stereotactic body radiation therapy with a median dose of 50 Gy in 5 fractions for oligo-recurrent lymphnodal metastasis in September 2018.

Another systemic treatment was immunotherapy using nivolumab from July 2016 to July 2019 with excellent tolerability (no side effects were reported). The treatment was discontinued in November 2019 after successive imaging exams showing complete response and reimplemented once again for an increased SUV in a retroperitoneal lymph node from October 2020 to October 2021.

The complete therapeutic management is summarized in Figure 3 (shown in Fig. 3). Immunotherapy was discontinued in October 2021. At the last clinical evaluation in June 2022, the patient had no clinical symptoms, and the last imaging follow-up in April 2021 using PET/CT scan showed complete response (shown in Fig. 4).

Discussion

This report introduces upper urinary tract urothelial carcinoma as a new type of malignancy in which SIRT can be safely implemented. It was a successful method as bridging therapy to nivolumab with excellent tolerability.

It's an innovative finding that represents the first use of a new therapeutic option in the management of this challenging malignancy. Its minimally invasive approach and the possible synergisms with immunotherapy instigate further discussion.

SIRT was first introduced in the early 1960s for the treatment of hepatic malignancies [15]. With the development of glass and resin Y90 microspheres in the 1990s, several studies demonstrated its potential role for advanced-stage hepatocellular carcinoma [16]. Nowadays, its applications have evolved for several types of malignancies and for different situations in the treatment pathway for patients with cancer, not more restricted to the salvage setting for patients with chemorefractory disease [11, 12, 17–19].

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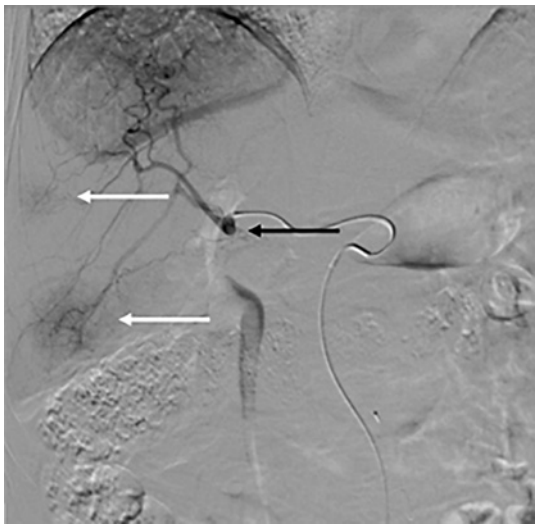

Fig. 1. The transarterial selective internal radiation therapy with yttrium-90 procedure: The angiography microcatheter positioned in the right hepatic artery (black arrow), showing its branches and the hypervascular lesions (white arrows).

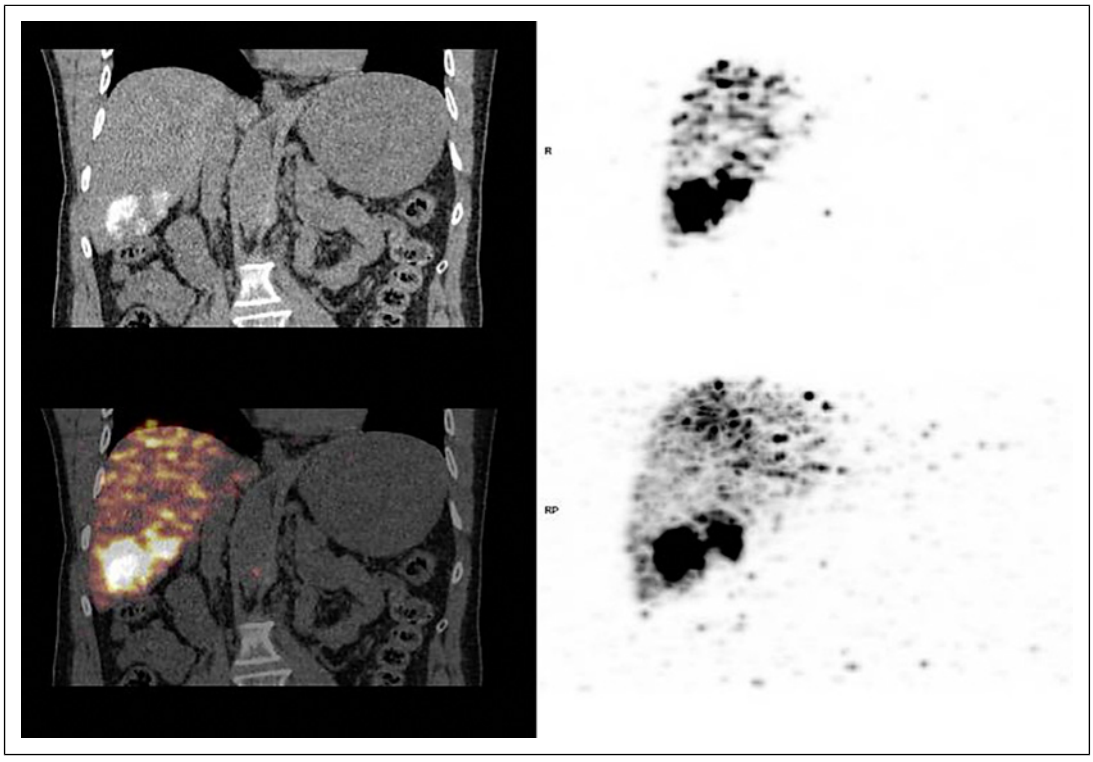

Fig. 2. The post-transarterial selective internal radiation therapy with yttrium-90 single photon emission-computed tomography (SPECT/CT) demonstrating an intense tracer uptake in the target lesions and little uptake in the normal liver.

One main reason for the development of SIRT in these several scenarios is the use of personalized dosimetry, based on macroaggregated albumin dosimetry, and software that enable a tailored therapy [15, 16, 20]. Its clinical impact on response and overall survival has been previously validated and was, once again, reaffirmed in this report [21, 22].

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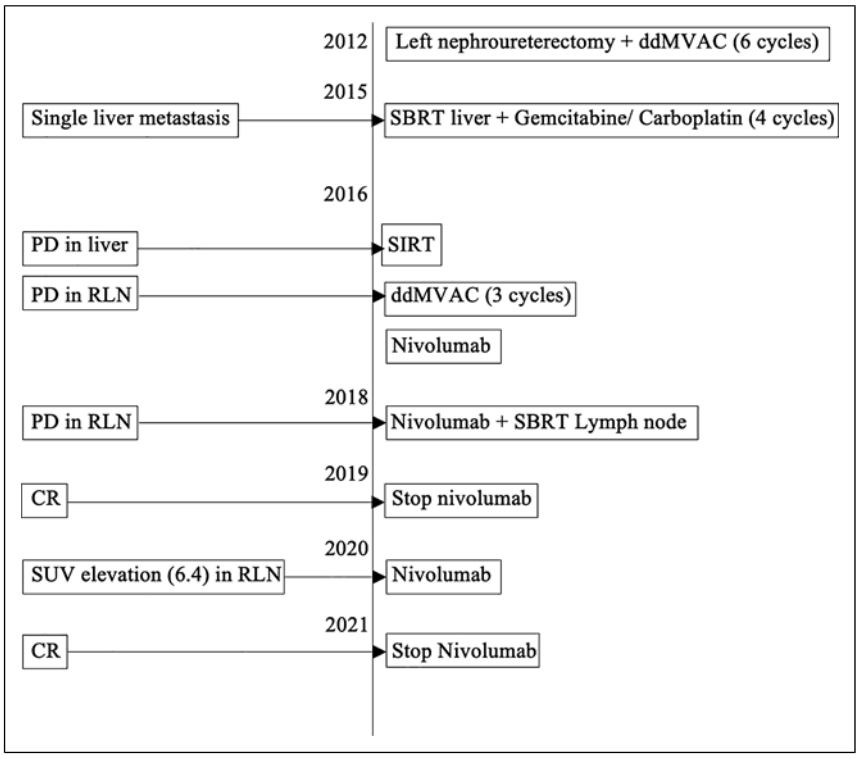

Fig. 3. The timeline of patient's therapies. CR, complete response; ddMVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; PD, progressive disease; RLN, retroperitoneal lymph node; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiation therapy; SUV, standardized uptake value.

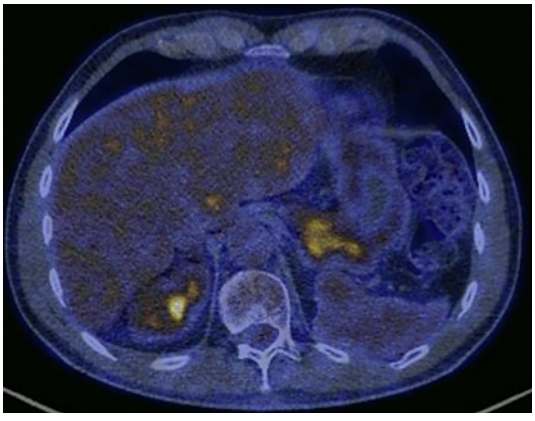

Fig. 4. The axial positron emission tomography-computed tomography with 18-fluorodeoxyglucose (18-FDG PET-CT) image performed in October 2021 showing regression of the hepatic lesions with complete resolution of FDG uptake.

Furthermore, some authors described the potential therapeutic synergism between SIRT and immune checkpoint blockade in patients with advanced hepatocellular carcinoma [23]. This study explores this treatment association strategy for a new type of malignancy (upper urinary tract urothelial carcinoma liver metastasis) with encouraging results.

The limitations of the Y90 utilization include the high-cost multistep process of the microsphere production [23]. Besides, 90Y is a pure therapeutic beta-energy emitter, which makes the evaluation of radiation dosimetry and microspheres distribution difficult to be analyzed during imaging follow-up [24].

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Thus, new microspheres labeled with new isotopes have been developed, such as the Samarium-153 (153Sm), a radionuclide with lower cost of production and more available worldwide, and the Holmium-166 (166Ho), suitable for SPECT and MRI [24]. Finally, the constant development of SIRT with profound knowledge regarding its interactions with immunotherapy, and the evolution of the technique with new endovascular devices and new isotopes are paramount expanding its use and further integrating interventional oncology into systemic treatment algorithms of upper urinary tract urothelial carcinoma.

Conclusion

SIRT is a promising technique as a bridging therapy to immunotherapy in the management of upper urinary tract urothelial carcinoma. There might be a potential therapeutic synergism between these 2 treatment modalities.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The Hospital Israelita Albert Einstein Ethics Committee approved the study protocol (reference number: 58642822100000071).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors contributed to the manuscript and review. Bruno Pagnin Schmid and Marcela Juliano Silva Cunha were responsible for the writing of the study, analysis design, and data collection. Leonardo Guedes Moreira Valle was a treating physician and revised the study critically for important intellectual content. Francisco Leonardo Galastri, Priscila Mina Falsarella, and Breno Boueri Affonso were a treating physician and revised the study critically for important intellectual content. Rafael Aliosha Kaliks Guendelmann was one of the treating physicians and leaded the tumor board. Rodrigo Gobbo Garcia was responsible for the analysis tools and revised the study critically for important intellectual content. Felipe Nasser was responsible for conception of the work, for the writing of the study, and was a treating physician.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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