



Complete response after radiation-assisted immunotherapy for metastatic urothelial carcinoma: a case report and literature review

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Abstract: Immunotherapy is emerging to be a new effective option in patients with metastatic urothelial carcinoma (UC) who are cisplatin-ineligible. However the feasibility of combinatory strategy in this setting is unknown. We reported our experience of treating one case of metastatic UC with radiation-assisted immunotherapy (RAIT). A 69-year-old male patient with end stage renal disease is a case of metastatic UC. The tumor was microsatellite stable. He was treated with six doses of triweekly pembrolizumab in four months. Hypofractionated radiotherapy to all metastatic lymphadenopathies (LAPs) was delivered between the second and the third dose of pembrolizumab. Complete response was confirmed with positron emission tomography/computed tomography one month after treatment. Metachronous bladder cancer was noticed nine months later and was successfully treated with transurethral resection of bladder tumor followed by adjuvant Bacillus Calmette-Guerin intravesical instillation. Genetic profiling from next generation sequencing (NGS) revealed high mutational burden (65.2 mutations/megabase) and CDH1 mutation. He remains disease free and dialysis free one and half year after treatment. Furthermore, circulating tumor cells (CTCs) dynamics correlates with the disease course precisely. This is a case of exceptional response and treating metastatic UC with RAIT in cisplatin-ineligible patients may warrant further investigation.

Keywords: Hypofractionated radiotherapy; metastatic urothelial carcinoma; radiation-assisted immunotherapy (RAIT)

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Introduction

Cisplatin-based chemotherapy is the standard treatment for metastatic urothelial carcinoma (UC) with the progression-free survival (PFS) of 7.4 months and the overall survival (OS) of 14.0 months (1). However, approximately half of these patients are cisplatin-ineligible due to renal function impairment, poor performance status or other comorbidities.

Immune checkpoint blockades that target the programmed death-1 (PD-1)/programmed death-Ligand 1 (PD-L1) pathway have shown an inspiring result and were approved by Food and Drug Administration (FDA) for patients with locally advanced and metastatic UC. Radiotherapy to tumor cells can stimulate CD8⁺ T lymphocytes in tumor microenvironment and this may result in tumor response.

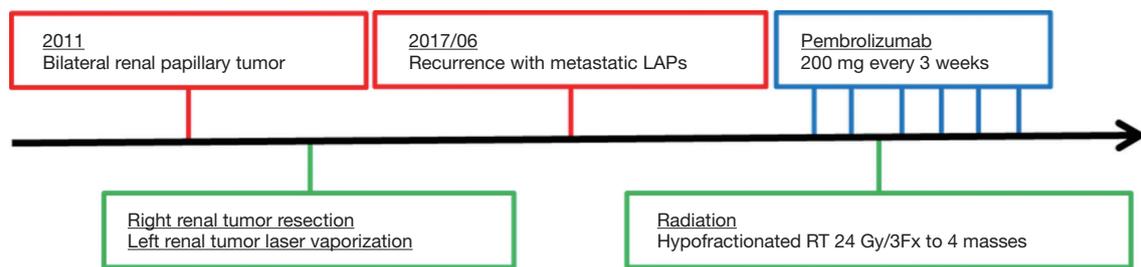


Figure 1 Treatment course of radiation-assisted immunotherapy. Pembrolizumab (200 mg) was administered every 3 weeks for 6 courses and hypofractionated radiotherapy to lymphadenopathies was delivered between the second and third dose of immunotherapy.

It has been reported that hypofractionated radiotherapy to oligometastatic tumor was associated with significantly improved 5-year OS from 28% to 41% (2). Therefore, it is a reasonable approach to combine radiotherapy with immunotherapy (radiation-assisted immunotherapy, RAIT) for cisplatin-ineligible patients with oligometastatic UC. Here, we reported our experience of treating one such case with RAIT. We present the following case in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/tro-20-30>).

Case presentation

A male patient with past medical history of chronic kidney disease, stage 5, and type 2 diabetes mellitus was diagnosed as bilateral ureteral papillary tumor in 2011 at 63 years of age. The patient refused bilateral nephroureterectomy and received right renal tumor resection and left renal tumor laser vaporization instead. There was no residual nor recurrent tumor at his upper urinary tract in the following studies.

He suffered from low back and left flank pain in June, 2017 and abdominal magnetic resonance imaging (MRI) showed lymphadenopathies (LAPs) up to 4 cm in left retrocrural & para-aortic regions. The para-aortic lymph node taken from computed tomography-guided percutaneous biopsy confirmed the diagnosis of metastatic carcinoma. Further immunohistochemistry studies revealed these tumor cells were positive for CK7, GATA3 and 34BE12 and negative for CK20. These results were consistent with a diagnosis of metastatic UC to para-aortic lymph node. Positron emission tomography/computed tomography (PET/CT) showed lymph node metastases in the left supra-clavicular fossa, left mediastinum and para-aortic areas without urinary tract lesions. His hemogram and serum biochemistry were anemic (hemoglobin: 9.8 g/dL)

with elevated creatinine level (creatinine: 8.0 mg/dL). Molecular pathology analysis revealed one of microsatellite markers (MONO-27) is altered, and the tumor was classified as microsatellite instability-low (MSI-L) but the sample was insufficient for further next generation sequencing (NGS). Count of EPCAM⁺CK⁺CD45⁻ nucleated cells (circulating tumor cells, CTCs) was enumerated with IsoFlux system (Fluxion, CA) and there were 40 CTCs per 7.5 mL venous blood sample before treatment.

The patient received pembrolizumab at a dose of 200 mg every 3 weeks, for six courses in four months (Figure 1). Hypofractionated radiotherapy (24 Gray in 3 fractions, via 6MV photons) to all metastatic LAPs was delivered between the second and third dose of pembrolizumab as cancer-directed treatment (Figure 2). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient. At the end of treatment, a PET/CT scan showed complete response (Figure 3). The CTCs count decreased to 16 per 7.5 mL venous blood sample (Figure 4). During the treatment, grade 1 side effects including fatigue and pruritus were noticed. Serum creatinine rose from 8.4 to 9.2 mg/dL without uremic symptoms (Figure 4).

The disease remained in complete response nine months after treatment when CTC count got increased to 22 per 7.5 mL venous blood sample. A new polypoid lesion at right posterior bladder wall was found during pelvic MRI two months later without upper urinary tract involvement. Transurethral resection of bladder tumor (TUR-BT) revealed a non-muscle invasive high grade bladder cancer. NGS finding suggested high mutation burden (65.2 mutations/MB) and incidentally found CDH1 mutation (Figure 5). He was treated with immediately intravesical mitomycin C and adjuvant intravesical Bacillus Calmette-Guerin (BCG). He

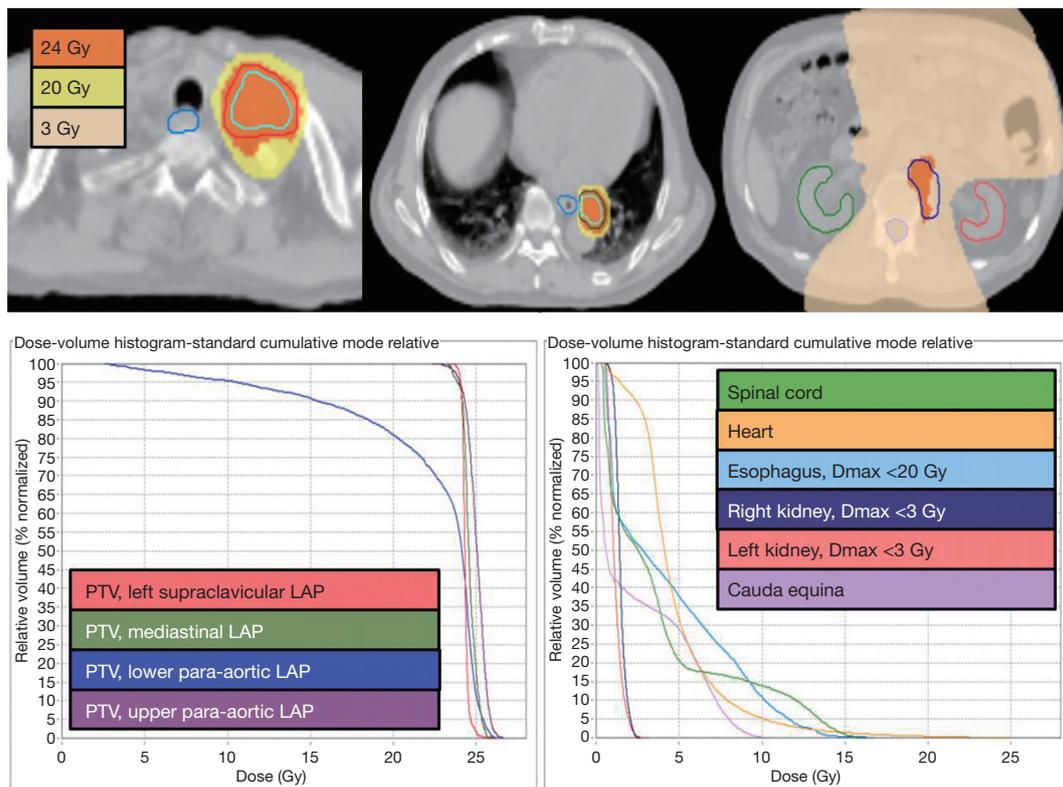


Figure 2 Irradiation was delivered to all metastatic lymphadenopathies (LAPs) over left supraclavicular area, left mediastinum, and para-aortic area. Radiation contour, dose distribution, dose volume histogram of treatment site and organs at risk. The sky blue line represented clinical target volume. The red, green, and blue lines represented plan target volume (PTV) of supraclavicular, mediastinal, para-aortic LAPs respectively. The volume receiving 97% or more prescribed dose, V97, of left supraclavicular, mediastinal, upper para-aortic LAP were more than 99%. The V97 of lower para-aortic LAP was 71.1% due to its proximity to left kidney. The organ at risk including esophagus and bilateral kidney in this plain received less than 20 Gy, and less than 3 Gy respectively.

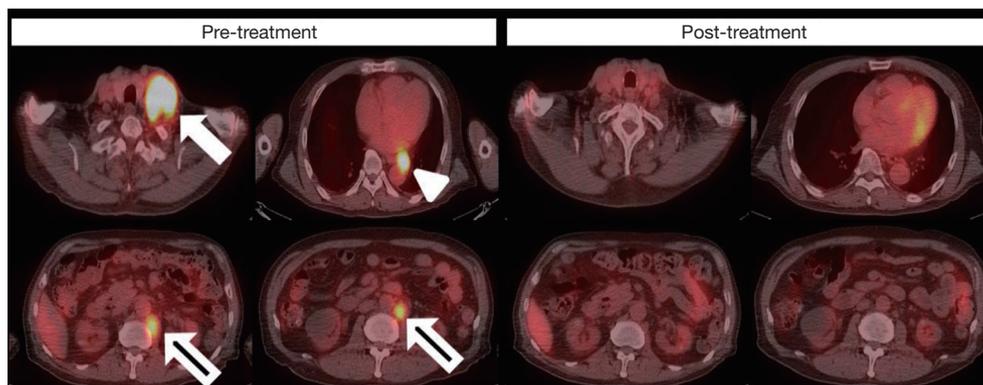


Figure 3 Pre-treatment and post-treatment PET/CT scan. Pre-treatment scan revealed metastatic lymphadenopathies in the left supraclavicular fossa (close arrow), and para-aortic areas in the left mediastinum (arrowhead) and abdomen (open arrow). One month post-treatment scan revealed complete response and no evidence of residual diseases in the whole body scan.

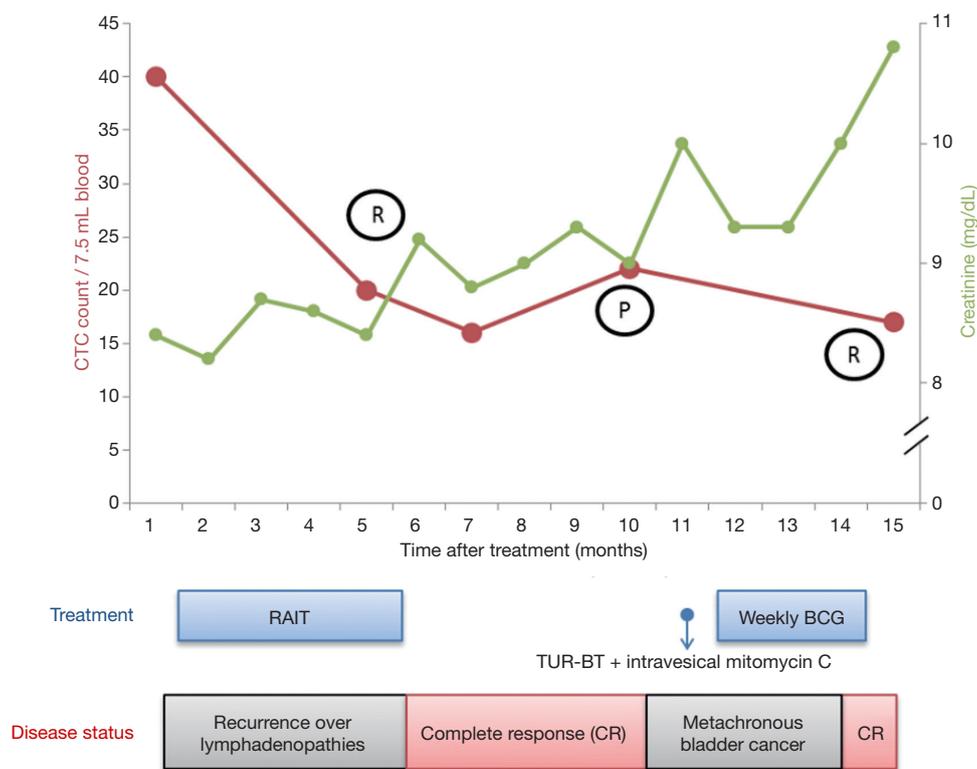


Figure 4 Serial monitoring CTCs, changes of serum creatinine, treatment history and clinical responses are noted in the plot. The red line indicated CTC counts in 7.5 venous blood sample which correlated with disease course. The green line indicated creatinine level (mg/dL) and there was Grade 1 creatinine elevation. P, disease progression; R, treatment response; CTCs, circulating tumor cells.

started peritoneal dialysis 17 months after RAIT.

Discussion

Cisplatin-based chemotherapy is the first-line treatment option for advanced UC. For patients who are cisplatin-ineligible, carboplatin-based chemotherapy, gemcitabine, and paclitaxel were alternative choices. However, toxicities and limited efficacy are still a major concern with these approaches. Erdafitinib, a tyrosine kinase inhibitor of fibroblast growth factor receptor (FGFR) 1–4, was recently approved by FDA and shows potent anti-tumor activity for previously treated locally advanced or metastatic UC with the response rate of 40% (3). A phase III investigation is now ongoing comparing the efficacy of erdafitinib, vinflunine or docetaxel or pembrolizumab in previously treated locally advanced and metastatic UC patients with FGFR gene aberrations.

PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are both immune-modulatory molecules which

act as immune checkpoint. The phase II study KEYNOTE 052 demonstrated that first-line pembrolizumab prolongs OS from 7.4 to 10.3 months for patients with metastatic UC who are cisplatin-ineligible (4). Atezolizumab, an anti-PD-L1 antagonist, also shows durable response in untreated, cisplatin-ineligible, metastatic UC (5). In addition, PD-L1 status and tumor mutation load are associated with higher frequency of treatment response. Both of the immune checkpoint blockade are well tolerated with the renal toxicity is mild as three of the 489 patients were reported to have treatment-related renal failure. Further clinical trial KEYNOTE 361 was designed to determine the efficacy and safety of pembrolizumab with or without chemotherapy as compared with chemotherapy alone in metastatic UC.

Tumor microenvironment plays an important role in treating cancers with immunotherapy. The interactions between T cells, dendritic cells, tumor cells regulate the activation of T-cells. Several studies demonstrated different biomarkers may predict the responses of immune

Variant(s) with clinical relevance			
Single nucleotide and small indel variants			
Gene	Amino acid change	Coverage	Allele frequency
CDKN2C	R68	1042	40.3%
CHEK2	K312	598	39.5%
HRAS	Q61L	620	38.5%
PTPRD	Splice donor	430	39.8%
Tumor mutational burden			
65.2 mutations/megabase (high)			
Microsatellite instability			
MSS			

Variant(s) of unknown significance							
Single nucleotide and small indel variants gene							
Gene	Amino acid change	Coverage	Allele frequency				
ADAMTS13	I110F	1247	37.4%	MUC16	W536R	2230	14.8%
ADAMTS16	Splice region	1312	37.5%	MUC16	L1684H	1965	13.1%
ARID1A	Q1552L	604	40.7%	MUC6	S2201T	1492	36.1%
ARID1B	Splice region	734	38.6%	NBN	I558L	998	61.8%
ASXL1	K586	582	33.0%	NFE2L2	P128S	470	49.4%
ATM	N485Y	628	35.8%	NOTCH1	Y358F	309	36.9%
BLM	Q1210L	445	39.8%	NTRK1	V99M	799	50.9%
CD19	M551L	684	34.6%	NTRK1	D306E	645	34.1%
CDH1	E864K	819	50.5%	NTRK2	YG400	947	41.2%
CDKN1B	K134M	874	35.8%	NTRK2	Splice acceptor	618	40.8%
CHEK2	K141E	307	35.5%	NTRK3	Q255L	927	38.5%
CREBBP	Splice acceptor	867	34.5%	NTRK3	K346M	932	35.9%
CYP2B6	P167A	119	49.6%	PAX5	Y388N	889	38.8%
DDR2	S449C	1164	38.0%	PDGFRA	S783T	714	42.0%
DTX1	D394E	613	37.2%	PIK3C2G	Y634	402	44.3%
E2F3	Q144L	892	40.0%	POLB	K230	1039	37.4%
E2F3	K133M	885	34.4%	PRKDC	R2529W	825	24.7%
EGFR	R252C	1740	43.4%	PTPRD	Y1897N	552	41.3%
EPHA7	E56V	709	35.3%	PTPRD	E118V	616	40.3%
EZH2	R33	202	38.6%	PTPRD	G1478R	981	38.6%
FANCD2	Q552L	1174	33.6%	RAD54L	Y121C	382	38.0%
FOXL2	S238C	238	50.4%	RET	K666	943	41.0%
GRIN2A	Splice acceptor	854	37.0%	ROS1	Y1021S	419	39.1%
HIST1H1C	A24V	381	48.8%	RUNX1T1	Splice region	979	22.0%
HNF1A	Q350H	690	38.3%	SMARCB1	Q244L	752	41.2%
INPP4B	Q857L	1031	36.4%	SMARCB1	Y313F	669	38.4%
KDM5A	K55M	1384	35.4%	SYNE1	V3890I	700	51.7%
KEAP1	Q62L	683	73.8%	SYNE1	T5957P	720	35.0%
KIT	Y259N	1045	38.7%	TAP2	G47R	1090	48.2%
KMT2D	E3078V	278	36.3%	TEK	Y1024F	1332	49.8%
LRP1B	E2499V	481	42.2%	TERT	Q770L	390	40.5%
MET	Y1177F	802	42.3%	TET1	Splice region	778	34.7%
MTOR	R2086W	956	36.9%	TGFBR2	Q306L	1451	53.5%
MUC16	L5485Q	2115	78.9%	TSHR	Y521F	767	41.1%
				USH2A	R2001C	607	50.9%
				USH2A	Y2179C	603	40.6%
				USH2A	Y3807N	1030	37.7%
				USH2A	F2353S	851	35.5%

Figure 5 Genetic profiles of the tumor samples from transurethral resection of bladder tumor. High mutation burden indicates the possibility of beneficial from immune checkpoint blockade. CDH1 variants with allele frequency around 50% may be related to the secondary gastric cancer diagnosed two years after the diagnosis of metastatic urothelial carcinoma.

Table 1 Reported four cases of upper urogenital tract cancer treated with radiation-assisted immunotherapy (RAIT)

Case	References	Age (y), sex	Cancer Histology	Radiotherapy (RT)	Immunotherapy (IO)	Time sequence of IO & RT	Response
1	Xie <i>et al.</i> (14)	54, M	RCC, clear cell	32 Gy/4 Fx	Pembrolizumab	Before & after	CR
2	van Gysen <i>et al.</i> (15)	66, F	RCC, clear cell	36 Gy/12 Fx	Nivolumab	Before	PR
3	LaPlant <i>et al.</i> (16)	24, M	RCC, clear cell	27 Gy/3 Fx	Nivolumab & Ipilimumab	Before & after	PR
4	Alexander <i>et al.</i> (17)	64, M	RCC, clear cell	20 Gy/5 Fx	Pembrolizumab	After	PD

RCC, renal cell carcinoma; CR, complete response; PR, partial response; PD, progressive disease.

checkpoint blockade. PD-L1 expression on tumor cells had been studied widely as a biomarker of response to immunotherapy. However, conflicting results were found between different studies (6,7). The other pathology information from tumor samples such as tumor infiltrative lymphocytes including cytotoxic and memory T cells, microsatellite instability, tumor mutation burden are associated with clinical outcomes (8-11). In addition, some of the serum biomarkers are associated with favorable treatment response of immunotherapy. These biomarkers include low lactate dehydrogenase level and high absolute or relative lymphocyte counts. However, there was no consensus about the cut-off value of each biomarker to predict clinical outcome. Furthermore, none of the above serum or pathology information could be used solely to predict treatment response after receiving immune checkpoint blockade. Hence, it is essential to establish robust biomarkers for treating cancer patients toward precision immune-oncology.

Traditionally, the role of radiotherapy for metastatic UC was to provide symptomatic palliation. However in the era of immuno-oncology, radiotherapy as an immune adjuvant may be considered to be an alternative curative approach. Irradiation to tumor cells can lead to the release of damage-associated molecular pattern (DAMP) molecules, such as high mobility group protein box 1 (HMGB1), adenosine triphosphate (ATP) and calreticulin (CRT). Also tumor irradiation will lead to intratumoral recruitment of tumor-reactive T cells as well as matured dendritic cells. The phenomenon is especially pronounced with a fraction size larger than 7.5 Gray. Together, these effects lead to in-situ vaccination and promote tumor control (12). RAIT is now under investigation towards a wide range of tumors in several early phase trials. In this report, we describe a case of exceptional response to RAIT in metastatic UC. While RAIT with a similar protocol has been reported in a phase I

study for treating 18 cases of metastatic bladder cancers, for upper urogenital tract cancers there were only 4 cases with renal cell carcinoma reports so far with satisfactory safety profiles (13-17) (*Table 1*). It is worth investigation if success experience of RAIT for bladder cancers and be extrapolated to metastatic upper genitourinary tract cancers that are cisplatin-ineligible.

In the era of precision medicine, genetic profiling from NGS sometimes provides possible treatment options and surveillance strategy. However, only FGFR genetic alteration was suggested while treating patients with locally advanced or metastatic UC. In our case, the pathology sample retrieved after TUR-BT was submitted for NGS. The absence of FGFR genetic alteration did not support consideration of erdafitinib use. High mutation burden indicates the possibility of response to immune checkpoint blockade (5). Therefore, it is reasonable to deliver pembrolizumab as adjuvant treatment for the patients with UC who are cisplatin-ineligible after maximal TUR-BT. On the other hand, NGS also provides information clinical relevant genetic alterations. It could be inferred that genetic alterations with allele frequency around 50% are possible germline mutation. *CDH1* gene, located at 16q22.1, encodes the cell-cell adhesion molecule protein called E-cadherin. It has been reported that *CDH1* mutation was associated with hereditary diffuse type gastric cancer and lobular breast cancer. Some of the studies had found the genetic alteration was associated with bladder cancer. These alterations include *CDH1* methylation, loss-of-function mutation, and single nucleotide polymorphism (18-20). The patient was diagnosed a secondary diffuse type gastric cancer two years after the diagnosis of metastatic UC. Apart from tumor samples, CTC from liquid biopsy can also be used for genetic profiling. Furthermore, there were no sensitive and specific serum tumor markers in UC and CTC may be a serum biomarker to detect recurrent UC. In our case, CTC dynamics correlated with the disease

course, and its elevation preceded image detection of bladder recurrence.

The reported case of metastatic UC was successfully treated with RAIT and therefore demonstrated the benefit of combining radiotherapy with immune checkpoint blockade. Although there were no prospective nor retrospective studies reported the toxicity profiles of RAIT. Our patients were well tolerated with RAIT with only grade 1 fatigue and pruritus noted. However, there were still some limitations in our study. Owing to lack of post-treatment sample after complete metabolic response, whether hypofractionated radiotherapy changed the tumor environment or not in our patient remains unclear.

In conclusion, this is a case of exceptional response and treating metastatic UC with RAIT in cisplatin-ineligible patients may warrant further investigation.

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Footnote

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accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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