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Stereotactic radiotherapy in oligoprogressive and oligorecurrent urothelial cancer patients: A retrospective experience.

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ABSTRACT

Urothelial cancer is one of the most common malignancies; after relapse or disease progression available therapeutic options are limited. We analyze efficacy and toxicity of local treatment on metastases using stereotactic body radiation therapy (SBRT) in selected patients with oligometastatic disease from urothelial cancer. A significant percentage of treated lesions achieved local control, with a promising overall response rate.

Objectives: to analyze efficacy and toxicity of local treatment on metastases using stereotactic body radiation therapy (SBRT) in selected patients with oligometastatic disease from urothelial cancer.

Materials and methods: Data from clinical records of 19 patients treated in our institution since May 2011 to October 2017 with SBRT for oligometastatic/oligoprogressive urothelial carcinoma were retrospectively collected. Clinical outcomes in terms of local control (LC), response rate, symptoms control, progression free and overall survival (PFS and OS), and adverse events were analyzed and reported.

Results: Nineteen patients were treated on 25 metastatic lesions; 5 of them received treatment on multiple sites. After an average follow up of 11.5 months, LC was achieved in 17 lesions (68%) and there was no local recurrence in lesions with complete or partial response. OS was 13.8 months. Adverse events were reported only in 3 patients (5 overall events). No late toxicity was reported.

Conclusions: An approach consisting in SBRT for local treatment of oligometastatic or persistent disease can be effective and safe in selected patients. Prospective studies are needed, to find correct selection criteria and optimal dose and fractionation.

1. Introduction

Urothelial cancer is one of the most common malignancies, and the bladder represents its usual site of occurrence. Urothelial bladder cancer occurs mainly in elderly patients, with an incidence of 12% and 4% in females and males over 70 years, respectively. [1]. Metastatic disease will be detected at diagnosis in up to 4% of cases, and 50% of patients will eventually recur after local surgery, with distant metastases representing 70–90% of all relapses [2]. After relapse, available therapeutic options are limited, principally relying on first line systemic therapies based on platinum and gemcitabine doublets [3], with a median overall survival of 9–15 months [3, 4]. After disease progression, data from literature show further deterioration of clinical outcome, with a decreased overall survival of 5–7 months in patients treated with vinflunine [5]. Another therapeutic option in patients progressed after a first- line chemotherapy regimen is immunotherapy with immune checkpoint inhibitors. Recently, Food and Drug Administration (FDA) approved treatment of these patients with Pembrolizumab, Atezolizumab, Nivolumab, Durvalumab and Avelumab [6–13]. However, only Pembrolizumab showed significant improvement in survival in this setting [6], while no difference in terms of overall survival (OS) have been shown in a direct comparison between Atezolizumab and conventional chemotherapy [7]. Furthermore, despite the promising results of Nivolumab [8,9], Durvalumab [10,11]

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and Avelumab [12,13] in this setting, a direct comparison between these agents and conventional chemotherapy is currently lacking. Thus, overall results of systemic therapy in these patients are poor, and therapeutic options are often further reduced in this population due to older age or coexisting comorbidities. However, highly selected patients with low burden of disease (e.g. Oligometastatic disease) and without evidence of a rapid progression may benefit from local treatment of metastatic disease. For example, several retrospective data showed survival advantage after surgical metastasectomy [14–17]. Moreover, stereotactic-body radiation therapy (SBRT) for oligometastases showed to be safe and effective in many non-randomized studies, with excellent results in terms of local control [18]. The aim of this treatment strategy in these patients is to delay disease progression and the need for subsequent line of systemic therapies. In the current paper, we retrospectively reviewed data from patients affected by urothelial cancer, treated with SBRT in our institution for nodal, bone or visceral metastases. The aim of this study is to analyse clinical outcomes and toxicity in this series.

2. Materials and methods

Data from clinical records of 19 patients affected by metastatic urothelial cancer consecutively treated with SBRT were retrospectively collected and reported. Patients underwent SBRT treatment with either Cyberknife^{R} robotic radiosurgery system (Accuray Inc., USA) or Volumetric Modulated Arc Therapy (VMAT) radiotherapy at our institute since May 2011 to September 2017 (See Fig.1). Prescription doses ranged from 18 to 60 Gy and were delivered in 1–8 fractions for all patients. For patients treated with the Cyberknife^{R} System, a planning CT was acquired with 1.25 mm slice thickness. Contrast enhanced planning CT scan was obtained for nodal, visceral of brain lesions. During treatment delivery the tumor position, detected by two orthogonal diagnostic kV X-ray images acquired at regular intervals (60–80 s), was tracked with submillimetric accuracy by the robotic system. [19] Tumor tracking modalities were based on Xsight^{R} spine tracking system for lesions solidal to vertebral bodies [20], 6D Skull Tracking System for brain lesions [21], Xsight^{R} lung tracking system for lung lesions [22]. Fiducial tracking using golden markers implanted in close proximity to the tumor was necessary for liver or nodal lesions far from vertebral bodies [19]. Synchrony respiratory tracking system was used for all tumors moving with respiration [19]. For patients undergoing VMAT, a planning CT was acquired with 3 mm slice thickness. Contrast enhanced planning CT scan was obtained for nodal, visceral of brain lesions. For lung lesions, a 4D CT scan was acquired and an internal target volume (ITV) was delineated to account for respiratory organ motion [23]. All patients were treated with an ELEKTA Synergy^{R} system, patients positioning was verified through daily cone-beam CTs. Patients were treated with SBRT for oligometastatic recurrence after local surgery or oligoprogression during first or subsequent lines of systemic therapy. Patients were defined oligometastatic or oligoprogressive if ≤ 3 metastatic lesions, amenable with SBRT, were detected during follow up after surgery or systemic therapy for metastatic disease. Simple descriptive statistic were used to analyze local control (LC), response rate, symptoms control, progression free and overall survival (PFS and OS), measured from the start of treatment to progression or death from any cause). Acute and late adverse events were reported according to Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. [24]. Local control (LC) was defined as absence of either volumetric growth or increase in metabolic activity of the irradiated lesion. LC and survival rates were calculated from the date of the first fraction of SBRT. Follow-up imaging and toxicity evaluation were assessed every three months. Treatment response was evaluated with computed tomography (CT), magnetic resonance imaging (MRI), and/or Positron emission tomography-computed tomography (PET-CT) imaging. All images were re-evaluated for LC by an experienced radiologist, nuclear medicine physician and radiation oncologist. Appearance of new lesions outside the treatment volume during follow up was considered as distant progression.

3. Results

Nineteen consecutive patients were treated on 25 metastatic lesions between May 2011 and October 2017. Five patients received treatment on multiple metastatic sites (four patients on 2 lesions and one patient on 3 lesions, respectively). Median age at treatment time was 70 years (range 45–86), and primary tumor sites were bladder, kidney pelvis or urethra. Overall, treated lesions were mostly located in lymph nodes (8, 32%) followed by lung (5, 20%) and bones (5, 20%). Two cases of local recurrence were also treated (one bladder and one urethra recurrence). Baseline population characteristics are summarized in Table 1. All patients received radical surgery as primary treatment with the exception of one patient affected by intra-prostatic urethral cancer who underwent a debulking-only surgery. Average follow up was 11.5 months (range 1, 44); Local control was achieved in 17 treated lesions (68%); of

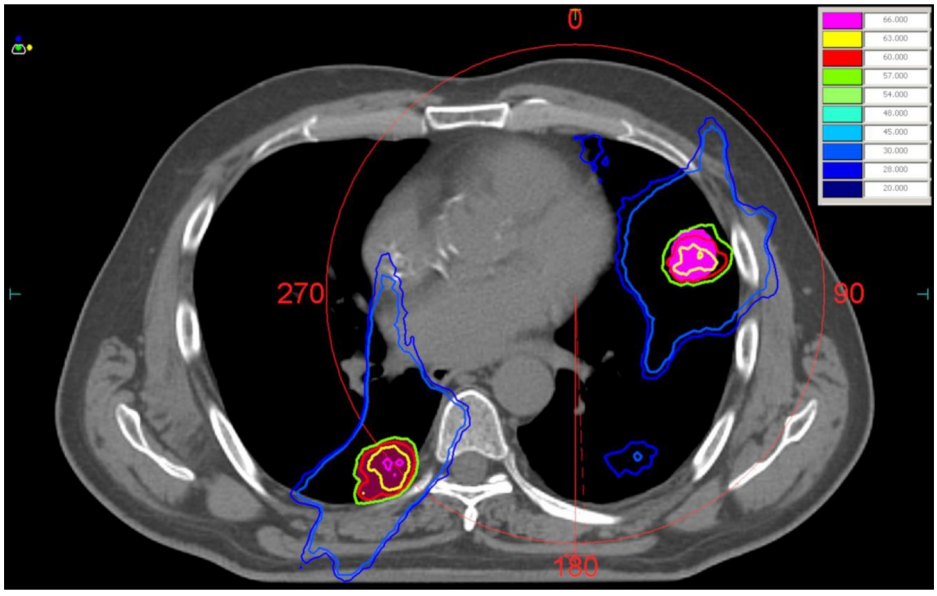

Fig. 1. Example of a VMAT stereotactic body radiation treatment on 2 lung lesions.

Table 1
Patients characteristics.

Mean age *(years)*	70.2
Gender (%)	Male: 15 (78.95%)
Female: 4 (21.05%)	PS0: 68% PS1: 22%
PS (%)	
Primary tumor sites (%)	Bladder: 15 (78,9%) kidney pelvis: 3 (15,8%) urethra: 1 (5.3%)
Chemotherapy (%)	No Chemotherapy: 9 (47,4%) CDDP/CBCDA plus Gemcitabine: 10 (52,6%)
Lesions localization (%)	Bone: 5 (20%) Lymph nodes: 8 (32%) Local recurrence: 2 (8%) Brain: 3 (12%) Liver: 2 (8%) Lung: 5 (20%)

Note: CDDP: cisplatin; CBCDA: carboplatin; Gem: gemcitabine; RT: radiotherapy; VMAT: Volumetric Modulated Arc Therapy; PS: performance status.

Table 2
Radiation treatment characteristics.

Lesions localization (%)	Radiation dose (Gy)	Fractions (*n*)	RT technique
Bone: 5 (20%)	25	5	Cyberknife
	24	3	Cyberknife
	25	5	Cyberknife
	25	5	Cyberknife
	36	3	VMAT
Lymph nodes: 8 (32%)	35	5	Cyberknife
	30	5	Cyberknife
	30	5	Cyberknife
	25	5	Cyberknife
	30	5	Cyberknife
	30	3	Cyberknife
	21	3	VMAT
	30	3	VMAT
Local recurrence: 2 (8%)	25	5	Cyberknife
	35	5	Cyberknife
Brain: 3 (12%)	24	1	Cyberknife
	18	1	Cyberknife
	25	1	Cyberknife
Liver: 2 (8%)	35	5	Cyberknife
	36	3	VMAT
Lung: 5 (20%)	26	1	Cyberknife
	54	12	VMAT
	54	3	VMAT
	55	5	VMAT
	60	8	VMAT

Note: RT: radiotherapy; VMAT: Volumetric Modulated Arc Therapy, IDL: isodose line.

Table 3
Main outcome summary.

Average follow up *(months)*	11.5 (1–44)
Median time to metastatic recurrence *(months)*	5.6 (0–16)
OS *(months)*	13.8 (4–26)
Overall response rate *(%)*	40
Local control *(%)*	68
Acute toxicities *(n = 5)*	Asthenia: 1 G1, 1 G2 Nausea: 2 G1 Dysphagia: 1 G1

these, complete response, partial response and stable disease was reported in two (8%), eight (32%) and seven (28%) treated lesions, with an overall response rate of 40%. Due to the short length of follow up, response could not be assessed in four treated lesions. Data about survival showed that mean overall survival (OS), was 13.8 months. Of note, no local recurrence or progression was noticed in lesions with complete or partial response, while three lesions (42.9%) with stable disease as best response had local recurrence or progression after a median time of nine months. Acute toxicities occurred only in three patients: overall two Grade 1 nausea, two Grade 1–2 asthenia and one Grade 1 dysphagia were reported. Late adverse events did not occur in this series. Of note, 12 out of 19 patients were receiving systemic treatment during radiotherapy, six patients had received at least one previous line of systemic therapy before radiotherapy. In those patients currently receiving a systemic treatment, SBRT was performed after a washout period of one week. See Tables 2 and 3 for SBRT characteristics and main outcomes summary.

4. Discussion

Data from the current analysis showed that a significant percentage of treated lesions (68%) achieved local control, with a promising overall response rate. This data is particularly interesting, considering the potential impact that local progression could have on symptoms development and overall Health related quality of life in metastatic patients. Furthermore, in patients who responded to therapy, no local progression was noticed during the follow-up, underlining the excellent duration of response. Data show that median overall survival after treatment was 13.8 months. Considering the mixed cohort analyzed, including patients who received at least one previous line of systemic therapy before radiation, this data seems really promising. Outcome after SBRT in patients undergoing systemic therapy could potentially have been influenced by synergistic effect between concomitant treatment administered. However, due to the limited sample size, no differences have been observed between different subgroups in the present cohort.

Another factor potentially influencing patients outcome is the time between diagnosis and SBRT; However, considering the retrospective nature of the present paper and the small sample size, many confounding factors (e.g. time of recurrence, duration of response to chemotherapy) must be taken into account. Therefore, no significant impact of this parameter was noticed. As previously stated, survival for patients treated in first-line metastatic setting is comparable with our results, ranging between 9 and 15 months [25, 4], while survival in second-line setting ranges from 5–7 months for patients treated with Vinflunine [5], and 10–11 months for more recent trials testing Pembrolizumab and Atezolizumab after progression under a platinum chemotherapy regimen [6,7]. Another retrospective experience from literature explored the role of consolidative radiotherapy in patients with relapsing urothelial cancer after surgery. Authors reported a median overall and progression-free survival of 29 and 13 months, respectively. However, survival was measured from the beginning of chemotherapy, and analyzed population included only patients treated in first-line setting [26]; these differences could explain the survival outcomes variability in comparison with our data. The current analysis underlines the need for prospective trials exploring treatment strategies integrating systemic therapies with local radiation treatment of metastatic foci. This could be more interesting considering the potential synergistic effect of immune therapies, an emerging treatment option for metastatic urothelial carcinoma, and radiotherapy to metastatic foci. Biological rationale for this kind of interaction has been shown in several preclinical experiences, showing that stereotactic body radiation treatment could modulate immune response [27,28], increase activity of antigen presenting dendritic cells [29] and promote infiltration of lymphocytes in tumor tissues [30,31].

Currently, association of immune checkpoint inhibitors and SBRT is investigational and it has been the object of a recent Phase I trial [32], showing an overall response rate up to 44% and no concerns regarding toxicity. Other case series investigating use of SBRT in this setting have

Limited sample size, retrospective series and heterogeneity of population are the principal weaknesses of the current study. However,

literature exploring this clinical scenario is lacking, and data presented in this study underline the promising outcomes of stereotactic treatment in urothelial cancer patients with oligometastatic or persistent metastatic disease after systemic therapy.

In conclusion, excellent local control in the current series highlights the benefit of an aggressive local approach on oligometastatic or persistent disease after systemic therapies. However, prospective data exploring integration between systemic treatment and radiotherapy are needed, focusing on correct selection criteria and optimal dose and fractionation for radiotherapy in this setting. Another promising area of research is the association between stereotactic radiotherapy and new systemic agents available in this clinical setting.

Example of a VMAT stereotactic body radiation treatment on two lung lesions. Isodose curves are indicated with different colors.

Clinical practice points

Overall results of systemic therapies after relapse or progression of disease in urothelial cancer are poor and therapeutic options are often further reduced in this population due to older age or coexisting comorbidities. However, highly selected patients with low burden of disease may benefit from local treatment of metastatic disease. For example, several retrospective data showed survival advantage after surgical metastasectomy. Moreover, stereotactic-body radiation therapy (SBRT) for oligometastases showed to be safe and effective in many non-randomized studies, with excellent results in terms of local control. Data from the current analysis showed that a significant percentage of treated lesions achieved local control, with a promising overall response rate. This data is particularly interesting, considering the potential impact that local progression could have on symptoms development and overall Health related quality of life in metastatic patients. Furthermore, in patients who responded to therapy, no local progression were noticed during the follow-up, underlining the excellent duration of response. However, prospective data exploring integration between systemic treatment and radiotherapy are needed, focusing on correct selection criteria and optimal dose and fractionation for radiotherapy in this setting.

Conflict of interest

Authors of this manuscript have no conflict of interest to declare.

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