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Review Article

Bone metastases from urothelial carcinoma. The dark side of the moon

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ABSTRACT

Bone metastases are common in genitourinary cancers, but they are underreported and not well researched.

Synchronous bone metastases occur in 1.39–5.5% of bladder cancer patients, while 30–40% of cases are metachronous.

Bone morphogenetic proteins (BMPs) play a key role in regulating proliferation, migration and invasion of tumor cells in bone microenvironment of bone metastases from metastatic urothelial carcinoma (mUC).

Bone metastases represent a poor prognostic factor due to high morbidity and mortality correlated to skeletal-related events (SREs). The incidence rate of SREs in bladder, renal pelvis, and ureteral cancer varies from 39 to 68%. Radiotherapy is the most frequent treatment for SREs. The early use of bone targeted therapies (BTT), zoledronic acid and denosumab, improves SREs incidence and morbidity and it seems to improve overall survival (OS).

To date, several new agents (immunotherapy and targeted drugs) demonstrated efficacy in mUC. However, subgroup analysis for bone metastases is often not available, due to difficulties in analysing bone samples, non-RECIST lesions and delay in systemic treatment due to SREs that limit the enrolment of bone mUC patients in clinical trials. Larger solid tumor studies that included UC patients are the main source of data for the management of mUC patients with bone metastases.

For these patients, multidisciplinary approach should be preferred, involving orthopaedics, radiotherapists and rehabilitation to improve outcome and quality of life. New prospective trials should characterize clinical and molecular features of patients with bone metastases and the impact of new drugs on this poor prognostic metastatic site.

Contents

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1. Introduction

Bladder cancer is the 12th most common cancer worldwide with a high morbidity and mortality rate [1,2]. Urothelial carcinoma (UC) is the most common type of bladder cancer. UC can involve also renal pelvis and ureters, namely upper tract urothelial carcinoma (UTUC), and urethra [3].

About 25% of patients present with metastatic disease, with limited therapeutic options [4,5]. The 5-year survival is 95.8% among those cases diagnosed in situ, 69.5% for localized disease, 36.3% for regional disease and only 4.6% for metastatic disease [6].

Conventionally, in mUC patients, the presence of bone metastases (BM) is defined as "visceral metastases". The most common sites of BM are pelvis (68%), spine (cervical 12%, thoracic 38% and lumbar 34%), ribs (24%) and femur (22%).

A model developed at the Memorial Sloan Kettering Cancer Center recognizes BM and Karnofsky performance status (PS) as negative prognostic factors in mUC patients receiving cisplatin-based chemotherapy [7]. Patients with BM from UC have worse outcome compared to patients with BM from other genitourinary cancers such as prostate cancer or renal cell carcinoma [8].

BM from UC remain a partially known field, difficult to manage due to the limited data available.

2. Epidemiology and clinical features of bone metastases in mUC

First reports of autopsies revealed presence of BM in 22–37% bladder UC cases [9]. In '70 s, Goldman et al. reported the presence of BM assessed radiographically in a group of 51 patients with bladder UC and demonstrated either an osteoblastic or a mixed osteolytic-osteoblastic pattern in 47% of the instances [10].

Nowadays, the incidence of BM in bladder cancer patients is between 1.39 and 5.5% as synchronous metastatic disease whereas 30–40% of metastatic patients will develop BM during the course of the disease [11] (Table 1).

Table 1
0444166300 Main feature of bone metastases from metastatic urothelial carcinoma. SRE: skeletal-related event; Hb: hemoglobin; T: tumor; N: nodes.

Bone metastases from urothelial carcinoma
Clinical features
Pain as the most common SRE
Poor prognosis
High rate of SRE
Mainly receive cisplatin chemotherapy
More often metacronous
Risk factors
Site of Primary tumor
High Alkaline Phosphatase
Low Hb
High Calcium
T stage
N stage
Grade 3-4
Histology type
Black race
41–60 yrs
Other Metastasis sites
Incidence
Overall incidence of bone recurrence of 35%
Most common sites are
- pelvis (68%),
- - spine (cervical 12%, thoracic 38% and lumbar 34%),
- - ribs (24%),
- - femur (22%)
Almost half of the patients with bone metastases have bone as the only site of recurrence

Risk factors for bone metastatic spread in bladder cancer include alkaline phosphatase, haemoglobin and calcium level, whereas advanced age, absence of surgery and presence of lung, liver, or brain metastases predict worse survival [12].

Fan et al. also evaluated risk factors for the onset of BM in bladder cancer. BM was associated in univariate and multivariate analyses with T stage, N stage, grade, histology type, race, primary site, age and site of other metastases. Authors developed a nomogram that can predict the onset of bone disease. Data excluded UTUC [13].

Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database defined age between 41 and 60, black race, married status, T stage, N stage, G3-G4, brain, lung and liver metastases to be risk factors for BM in bladder cancer. BM were associated to poor prognosis and authors suggested bone scan as routine exam in patients with the previous cited risk factors. The median OS in this cohort was 4 months for bone synchronous disease [11].

In SEER database, 799/1862 bladder cancer patients had BM, which configured as the most common site of disease. This cohort of patients with bone involvement had worse OS and cancer specific survival (CSS) compared to patients without BM. Multivariate analysis showed that BM was an independent prognostic factor for both OS and CSS, whereas distant node metastasis was not. Patients with liver metastases had the worst outcome though [14].

A study of 52 patients from Dana-Farber Cancer Institute reported that, in UTUC, lymph nodes (75% [39/52]), lung (65% [34/52]), liver (54% [28/52]), bone (39% [20/52]) and peritoneum (19% [10/52]) were the most common metastatic sites [12]. Cheaib et al. instead described, in 47 UTUC patients, metastases in multiple sites (30%, [14/47]), lungs (28%, [13/47]), bone (13%, [6/47]), liver (13%, [6/47]), lymph nodes (10%, [5/47]), muscle (4%, [2/47]), brain (2%, [1/47]), with both bone and liver metastases presenting quick onset and poor prognosis [15].

Analyses of SEER database of UTUC patients revealed that bone was a common site of relapse, as previously reported [18]. Liver metastases predicted unfavourable OS rather than CSS, whereas multivariate analysis showed that BM were not an independent prognostic factor for patients' survival [16].

Sengeløv, L. et al. described an incidence of bone recurrence of 35%, the third most common site after bladder and pelvic recurrence, in both bladder UC (194) and UTUC (18) patients. Authors reported that bone metastatic disease was more common in patients younger than 60 years old and with primary tumor of renal pelvis. Almost half of the patients (41%) with BM had bone as the only site of recurrence, and nearly a third had a single bone lesion [17].

Tsuda et al. analysed the features of BM in 48 mUC (31 bladder UC and 17 UTUC). Bone was the initial metastatic site for 25/48 patients (52.1%) and pain was the initial symptoms for 54.2% of patients. The most common locations were pelvis 64.6%, spine 58.3%, rib 20.8%, femur 12.5%, humerus 6.3% and clavicle 6.3%. BM were usually multiple (26/48, 54.2%) and osteolytic (66.7%) [18].

A retrospective trial of 203 mUC, including both UTUC (120 patients) and bladder UC (83 patients), reported similar outcome for patients with BM treated with chemotherapy agent such as MVAC and CG, with no statistical significance at univariate and multivariate analyses for overall survival. Patients with bone disease were 24/203 (16 bladder cancer and 8 UTUC) [19].

Data from the Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC) dataset provided a deeper understanding of BM from UC. Out of 1900 patients with bone disease (comprising 1586 bladder UC and 168 UTUC), 128 (6.7%, comprising 113 bladder UC and 5 UTUC) were found with exclusive bone disease. Patients in the latter group were more likely to have

poor ECOG PS, to be ineligible for chemotherapy (rather than cisplatin) and to have lower overall response rate (ORR) [20]. Despite receiving mainly cisplatin chemotherapy patients had poor prognosis, irrespective of additional sites of disease. 43% of patients received supportive and palliative treatment alone and had rapid decline of ECOG PS due to pain or other SREs. Nevertheless, patients who were able to receive additional therapies had the longest survival [20].

3. Biological concepts in bone metastases from mUC

Bone morphogenetic proteins (BMPs) belong to the transforming growth factor β (TGF-β) superfamily. These proteins bind to type I and type II serine-threonine kinase receptors and transduce signals through Smad and non-Smad signalling pathways [21]. Many studies have suggested that the BMPs are associated with BM in several cancers. BMPs receptors have been found in human urological cancer cell lines and BMPs are known to regulate the expression of their receptors [22]. In vitro studies demonstrated distinct effects of BMPs on proliferation, migration and invasion of tumor cells depending on the BMP type, the tumour cell line and the bone microenvironment [23].

Med19 is a mediator complex subunit that plays a key role in the activity of the mediator itself [24]. The mediator complex is a conserved interface between gene-specific regulatory proteins and the general transcription apparatus of eukaryotes at transcription initiation [25]. Wen et al. demonstrated the critical role of Med19 in bladder cancer and in promoting BM. BMPs are important in the adhesion of cancer cells to bone tissue, specifically BMP-2 is crucial in BM from mUC. When the cells gain access to lymph or vascular circulation, the elevated BMP-2 induced by Med19 may assist the seeding of bladder cancer cells in bone tissue [26]. In addition, the interaction of TNF-alpha with BPM-2 has a crucial role in bone colonization. Higher levels of both were found in metastatic bladder cancer with BM compared to nonmetastatic or noninvasively UC [22] (Fig. 1).

4. Bone targeted therapies

Larger solid tumor studies that included UC patients (Table 2) are the main source of data for the management of mUC patients with BM [27]. European Association of Urology (EAU) and AIOM (Italian Association of Medical Oncology) guidelines recommend the use of bone targeted therapy (BTT), zoledronic acid (ZOL AC) or denosumab, in this subset of patients [28,29].

ZOL AC has shown to prolong SRE-free interval in patients with solid tumors, including UC. A small, randomized, placebo-controlled trial investigated the impact of ZOL AC in 40 patients with BM from bladder UC previously treated with palliative radiotherapy. ZOL AC demonstrated to decrease SREs by 59% and to delay the onset of first SRE [30].

Phase 3 trials of denosumab in patients with solid tumors, including patients with renal cell carcinoma and bladder cancer, demonstrated that denosumab was superior to ZOL AC in preventing SRE. Patients with bladder cancer were only 28 though [31,32].

A study comparing denosumab or placebo with standard treatment in both bladder UC and UTUC patients with BM is nowadays ongoing (NCT03520231).

The incidence of SREs in mUC is reported to be 65–68%. Owari et al. reported 58% of SRE in mUC. In a cohort of 180 patients, 26 with mUC (13 bladder UC and 13 UTUC), multivariate analysis revealed that the type of primary cancer (UC vs prostate cancer and renal cell carcinoma vs prostate cancer), ECOG PS and bone pain at the diagnosis of bone metastases were independent predictors of SREs. Overall, the early use of BTT revealed to improve SRE [8].

Tsuda et al. reported in a court of 17 UTUC and 31 BC patients with BM that the first SRE collocated at pelvis (48.5%) or spine (45.5%) and resulted in radiation therapy (74.2%), spinal cord compression (12.9%) and pathological fracture (9.7%). After the first SRE 41.9% of patients experienced a second SRE. The median survival time (MST) was 6.2 months (IQR, 4.5–9.5) after the diagnosis of BM, and 5.6 months (IQR, 3.1–9.6) after SREs. On multivariate analysis, independent predictors of OS included PS $\geq$ 2 (HR 4.94; p 0.0003), liver metastases (HR 4.08; p 0.0018), chemotherapy after diagnosis of BM (HR 0.31; p 0.0018), and bone-modifying agents (HR 0.36; p 0.0147). 38 patients did not receive BTT. Median OS of patients treated whit BTT was 15.8 months (95% CI 4.5–26.9) vs 5.2 months, (95%CI 3.5–7.4; p 0.003). The median time from diagnosis of BM to development of first SRE was 0.9 months [18].

Yokomizo et al. reported that the rates of SRE in 41 bladder cancer patients and 25 renal pelvis and ureteral cancer patients were

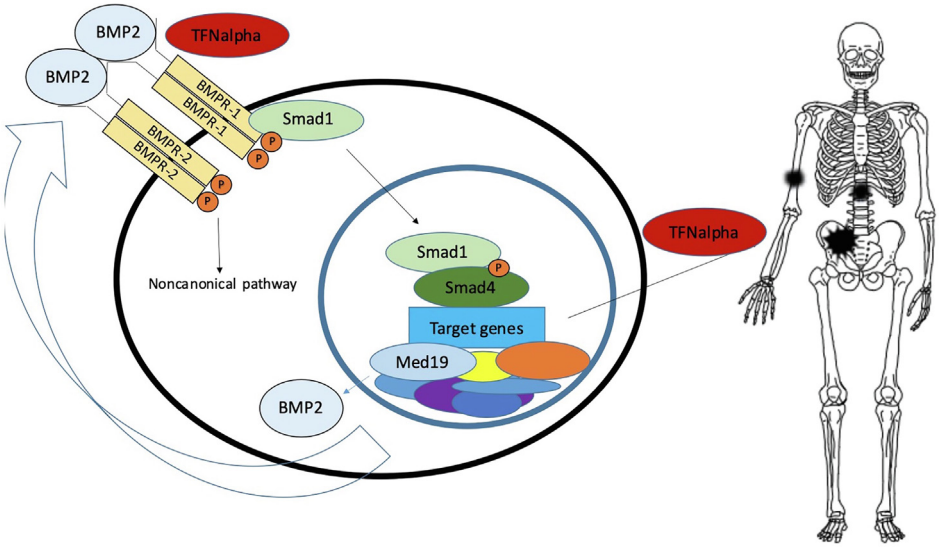

Fig. 1. Bone morphogenetic proteins and bone metastases from urothelial carcinoma. BMP2: bone morphogenetic proteins 2; BMPR: bone morphogenetic proteins receptor; TNF alpha: tumor necrosis factor alpha; Smad: small mother against decapentaplegic; Med19: mediator complex subunit 19; P: phosphoryl group.

Table 2
Bone target therapy in metastatic urothelial carcinoma. SRE: skeletal-related event; BTA: bone-targeted agent; BTT: bone-targeted therapy; mUC: metastatic urothelial carcinoma.

Authors	Bone Target Therapies in bone metastases from urothelial carcinoma			
	Year of publication	Type of study	Results	Number of patients
Zaghloul MS et al. [30]	2010	Prospective, placebo-controlled, randomized	Zoledronic acid demonstrated to decrease SRE by 59% and to prolong time to first SRE	40
Owari et al. [8]	2018	Retrospective	The early use of BTA revealed to improve SRE	180 (26 with mUC)
Tsuda Y et al. [18]	2017	Retrospective	Overall survival of patients receiving BTT was longer when compared to patients who did not receive BTA.	48

39–68%. Radiation therapy was the most frequent event. Authors confirmed the short SRE-free survival rate in UC after the diagnosis of BM in both upper tract and bladder UC. None of these patients received BTT [33].

5. Novel treatment for mUC and impact on bone disease

Several new agents demonstrated to improve outcome in mUC but patients with BM are underrepresented in all these trials.

Being mostly non-measurable lesions by RECIST criteria, it is difficult to fully assess the efficacy of treatments in BM, leading to exclusion from clinical trials. The bone response to treatments has not been evaluated in pivotal clinical trials [34,35].

Another limitation is that tumor tissue from BM is not evaluable for PD-L1 expression, preventing enrolment in many trials investigating the role of immunotherapy.

Symptomatic bone lesions susceptible to palliative radiotherapy should be treated prior to enrolment to avoid exclusion due to ongoing radiotherapy.

Furthermore, data about bone disease are often incomplete and they are reported together with other metastatic sites under the definition of "visceral metastases", due to the limited population in those studies [3,14].

In trials involving cisplatin ineligible patients treated with PD-1 or PD-L1 inhibitors as first line treatment, authors reported data about patients with visceral metastases. No patient had bone as single site of disease [36,37].

A real-world study of **vinflunine** in mUC reported that the 20/102 patients (comprising 84 bladder UC and 11 UTUC) with BM had a longer PFS and OS compared to patients with pulmonary or hepatic metastases [38].

Subgroup analysis for BM is not available in the pivotal trials of **avelumab** as maintenance treatment and **pembrolizumab** as second line treatment in mUC [36,39].

A retrospective trial recently reported that in patients treated with IO as first line therapy (cisplatin eligible and ineligible both), high burden of disease, liver and BM (HR 3.93*p* 0.02) were associated with shorter OS. In patients treated with IO as second line, bone metastases had negative prognostic effect on OS (HR 2.42), more than other site of disease, including liver. Furthermore, patients with BM were more likely to not receive further therapies after progressing to IO [40].

Results from TROPHY01 trial were reported at ESMO virtual congress 2020. **Sacituzumab Govitecan** (SG), an antibody-drug conjugate (ADC), demonstrated efficacy in terms of PFS and OS in mUC. 62% of patients had visceral metastases. The number of patients with BM is not reported. SG has received fast track designation and may have the potential to change clinical practice [41]. Recently, results from the trial have been published. SG demonstrated statistically significant ORR (27%) with manageable safety profile. Benefit from SG was seen across several subgroups but data about bone disease are not available [42].

Enfortumab vedotin is an ADC that targets Nectin-4, a transmembrane protein of the Nectin family of cell adhesion molecules involved in cellular processes associated with oncogenesis. 51/125 (41%) patients had bone disease. Enfortumab vedotin had consistent clinical activity across all subgroups analysed. Subgroup analysis for BM is not available [43].

In the phase II trial evaluating **Cabozantinib** as second line treatment for mUC, patients in cohort 2 (6/69) had bone-only disease assessed by PET scan whereas 15/69 had bone disease among different metastatic sites. From cohorts 1 and 2, 16/69 patients had a median OS of 7.2 months (95%CI 4.1–10.8) and a median PFS of 3.9 months (1.8–7.8) [44]. No difference in PFS and OS was reported based on number of bone lesions, alkaline phosphatase, and maximum SUV at baseline (Table 3). Patients with bone-only disease had an improvement in their BM, as assessed by sodium fluoride (NaF) fluorodeoxyglucose-PET.

Erdafitinib, a tyrosine kinase inhibitor of FGFR1-4, showed clinical activity in pretreated mUC patients. 10/21 patients with BM showed tumor response in the selected-regimen group, treated with a continue dose of 8 mg. Response rate (RR) was higher in patients with bone disease, 48% (95%CI 26–69), compared to other site of metastases such as liver (35% [95%CI 14–56]), lung (40% [95%CI 28–53]) and lymph nodes (33% [95%CI 7–60]). Even in the two other groups of patients treated with unselected intermittent regimen of 10 mg and 6 mg continuously, patients with BM had a satisfactory ORR of 17% (1/6) and 40% (6/15), respectively [45].

6. Discussion

Bone metastases from mUC represent a relevant problem for patients, physicians and health care systems. They are a poor prognostic factor and are related to high morbidity and mortality rates due to SRE.

Most common sites of BM are pelvis, spine, ribs and femur, as previously described, and patients usually present with pain and worse PS ECOG (Table 4). EAU and AIOM recommend BTT use in clinical practice, as ZOL AC and Denosumab improve SRE-free interval and OS. The impact of novel therapies on BM is mostly unknown due to the exclusion from clinical trials of this group of patients. Indeed, difficulties in analysing bone samples, non-RECIST lesions and delay of systemic treatments limit the evaluation of the efficacy of anticancer therapies, especially of novel drugs. Therefore, the treatment of BM from mUC represents an unmet clinical need.

The management of BM in genitourinary malignancies includes the spectrum of lifestyle modifications, therapies targeting the bone microenvironment and disease-targeting agents. Multidisciplinary approach should be preferred, involving orthopedics, radiotherapist and rehabilitators to improve outcome and quality of life.

Despite the mechanisms responsible for BM have been researched and partially reported, the molecular features of patients with bone disease from UC remain mostly unknown. Sev-

Table 3
Platinum-refractory patients with urothelial carcinoma and bone disease treated with cabozantinib in second line (n=22): no difference in OS and PFS was found in patients basing on number of bone lesions at baseline; max-SUV at baseline and alkaline phosphatase at baseline. OS: overall survival; PFS: progression free survival; HR: hazard ratio.

Lesion number	< or = 5 bone metastases N=11	>6 metastases N=11	HR (95%CI)	*p* value
Median OS (95%CI)	3.7 months (2.1-7.7)	4.7 months (3.4-9.7)	1.01 (0.41-2.4)	0.97
Median PFS (95%CI)	2.1 months (1.4-3.9)	1.9 months (1.3-6.0)	0.92 (0.38-2.2)	0.84
Max SUV	4–17 N=11	>17·1 N=11		
Median OS (95%CI)	3.7 (1.8-7.1)	6.7 (3.4-9.7)	0.57(0.24-1.35)	0.19
Median PFS (95%CI)	1.9 (1.3-3.6)	2.1 (1.8-5.3)	0.91(0.38-2.17)	0.83
Alkaline phosphatase (U/L)	< or = 103 N=11	>104 N=11		
Median OS (95%CI)	4.1(2.1-7.1)	6.7 (3.4-9.7)	0.66 (0.28-1.55)	0.33
Median PFS (95%CI)	1.9(1.4-3.6)	2.1 (1.3-5.3)	0.98 (0.41-2.34)	0.97

Table 4
Patients with bone metastases from mUC have dismal prognosis. This table resume the main evidences regarding clinical features of this subgroup of patients. BM: bone metastasis; mUC: metastatic urothelial carcinoma; GU: genitourinary; QOL: quality of life; SRE: skeletal related event; OS: overall survival; CSS: cancer-specific survival

Authors	Year of publication	Type of study	Results	Number of patients
Owari et al. [8]	2018	Retrospective	Patients with BM from UC have the worst outcome compared with patients with bone metastasis from other GU cancers and worse QOL due to SRE.	128 (26 with mUC)
Cheaib et al. [15]	2020	Retrospective	Hepatic and bone recurrences have relatively quicker onset and less favorable prognosis compared to other sites.	47
Zhang C. et al. [11]	2018	Retrospective	Patients with BM at diagnosis showed a marked decrease in survival rates compared with BC patients without BM occurrence	1223
Fan Dong et al. [14]	2017	Retrospective	BM was independent prognostic factors for both OS and CSS	1862
Gómez de Liaño Lista et al. [40]	2019	Retrospective	In patients treated with IO as first line therapy, high burden of disease, liver and bone metastases were associated with shorter OS	270

eral classifications into sets of molecular classes have been proposed for UC. Kamoun et al. on behalf of the Bladder Cancer Molecular Taxonomy Group, provided a consensus classification of muscle-invasive bladder cancer with clinical and histological correlations that suggests that the muscle-invasive bladder cancer is a molecularly heterogeneous disease [46].

Indirectly, aggressive features of bone metastatic disease suggest that these patients should be part of molecular classes with worse prognosis such as Basal/Squamous (Ba/Sq), Neuroendocrine-like (NE-like) or Luminal Unstable (LumU) tumors. Ba/Sq, furthermore, have higher clinical stages whereas Luminal Papillary (LumP) involve younger patients (<60yrs), feature described in patients with BM too. LumP tumors harbour more frequently *FGFR* mutations whereas Ba/Sq and NE-like tumors seems to respond to immunotherapy. Nevertheless, the missing data on bone response to novel and old therapies do not permit therapeutic correlations and make these suggestions speculative.

In conclusion, patients with bone metastasis from UC should be investigated more in depth and prospective trials should characterize clinical and molecular features of this population to explore and make the dark side of the moon less mysterious.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2019, CA. Cancer J. Clin. 69 (2019) 7–34.
[2] H. Sung et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 Countries, CA. Cancer J. Clin. 71 (2021) 209–249.
[3] R. Nadal, J. Bellmunt, Management of metastatic bladder cancer, Cancer Treat. Rev. 76 (2019) 10–21.
[4] A.B. Smith et al., Muscle-invasive bladder cancer: evaluating treatment and survival in the National Cancer Data Base, BJU Int. 114 (2014) 719–726.
[5] M. Burger et al., Epidemiology and risk factors of urothelial bladder cancer, Eur. Urol. 63 (2013) 234–241.
[6] K. Saginala, A. Barsouk, J.S. Aluru, P. Rawla, S.A. Padala, A. Barsouk, Epidemiology of bladder cancer, Med. Sci. (Basel, Switzerland) 8 (1) (2020) 15, https://doi.org/10.3390/medsci8010015.
[7] D.F. Bajorin et al., Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 17 (1999) 3173–3181.
[8] T. Owari, M. Miyake, Y. Nakai, Y. Morizawa, Y. Itami, S. Hori, S. Anai, N. Tanaka, K. Fujimoto, Clinical features and risk factors of skeletal-related events in genitourinary cancer patients with bone metastasis: a retrospective analysis of prostate cancer, renal cell carcinoma, and urothelial carcinoma, Oncology 95 (3) (2018) 170–178.
[9] R.J. Babaian, D.E. Johnson, L. Llamas, A.G. Ayala, Metastases from transitional cell carcinoma of urinary bladder, Urology 16 (2) (1980) 142–144.
[10] S.M. Goldman, A.A. Fajardo, R.C. Naraval, J.E. Madewell, Metastatic transitional cell carcinoma from the bladder: radiographic manifestions, AJR. Am. J. Roentgenol. 132 (1979) 419–425.
[11] C. Zhang, L. Liu, F. Tao, X.u. Guo, G. Feng, F. Chen, Y. Xu, L. Li, X. Han, V.P. Baklaushev, A.S. Bryukhovetskiy, X. Wang, G. Wang, Bone metastases pattern in newly diagnosed metastatic bladder cancer: a population-based study, J. Cancer 9 (24) (2018) 4706–4711.
[12] P. Huang, M. Lan, A.-F. Peng, Q.-F. Yu, W.-Z. Chen, Z.-L. Liu, J.-M. Liu, S.-H. Huang, A. Ahmad, Serum calcium, alkaline phosphotase and hemoglobin as risk factors for bone metastases in bladder cancer, PLoS ONE 12 (9) (2017) e0183835.
[13] Z. Fan, Z. Huang, C. Hu, Y. Tong, C. Zhao, Risk factors and nomogram for newly diagnosis of bone metastasis in bladder cancer: a SEER-based study, Medicine (Baltimore). 99 (2020) e22675.
[14] F. Dong et al., Prognostic value of site-specific metastases and therapeutic roles of surgery for patients with metastatic bladder cancer: a population-based study, Cancer Manage. Res. 9 (2017) 611–626.
[15] J.G. Cheaib, L.E. Claus, H.D. Patel, M.R. Kates, A. Matoso, N.M. Hahn, T.J. Bivalacqua, J.H. Hoffman-Censits, P.M. Pierorazio, Site of metastatic recurrence impacts prognosis in patients with high-grade upper tract urothelial carcinoma, Urol. Oncol. 39 (1) (2021) 74.e9–74.e16.
[16] F. Dong, H. Fu, X. Shi, Y. Shen, T. Xu, F. Gao, X. Wang, S. Zhong, Q. Ding, Z. Shen, S. Chen, How do organ-specific metastases affect prognosis and surgical treatment for patients with metastatic upper tract urothelial carcinoma: first evidence from population based data, Clin. & Exp. Metastasis 34 (8) (2017) 467–477.
[17] L. Sengeløv, C. Kamby, H. von der Maase, Pattern of metastases in relation to characteristics of primary tumor and treatment in patients with disseminated urothelial carcinoma, J. Urol. 155 (1996) 111–114.
[18] Y. Tsuda et al., Skeletal-related events and prognosis in urothelial cancer patients with bone metastasis, Int. J. Clin. Oncol. 22 (2017) 548–553.
[19] M.-C. Hsieh, P.-H. Chiang, K.-M. Rau, Y.-Y. Chen, Y.-L. Su, C.-H. Huang, The comparison of oncologic outcomes between metastatic upper tract urothelial carcinoma and urothelial carcinoma of the bladder after cisplatin-based chemotherapy, Urol. Oncol. 33 (11) (2015) 495.e9–495.e14.

[20] A. Necchi et al., Bone metastases as the only metastatic site in patients with urothelial carcinoma: focus on a special patient population, Clin. Genitourin. Cancer 16 (2018) e483–e490.
[21] K. Miyazono, Y. Kamiya, M. Morikawa, Bone morphogenetic protein receptors and signal transduction, J. Biochem. 147 (2010) 35–51.
[22] Z. Yang, F. Liu, Y. Yang, X. Yang, G. Zhu, Expression of bone-morphogenetic protein 2 and tumor necrosis factor α correlates with bone metastases in bladder urothelial carcinoma, Ann. Diagn. Pathol. 17 (2013) 51–53.
[23] J. Dai et al., Bone morphogenetic protein-6 promotes osteoblastic prostate cancer bone metastases through a dual mechanism, Cancer Res. 65 (2005) 8274–8285.
[24] S.M. Baidoobonso, B.W. Guidi, L.C. Myers, Med19(Rox3) regulates Intermodule interactions in the Saccharomyces cerevisiae mediator complex, J. Biol. Chem. 282 (2007) 5551–5559.
[25] Y.-J. Kim, S. Björklund, Y. Li, M.H. Sayre, R.D. Kornberg, A multiprotein mediator of transcriptional activation and its interaction with the C-terminal repeat domain of RNA polymerase II, Cell 77 (4) (1994) 599–608.
[26] H. Wen et al., Med19 promotes bone metastasis and invasiveness of bladder urothelial carcinoma via bone morphogenetic protein 2, Ann. Diagn. Pathol. 17 (2013) 259–264.
[27] S.H. Patel et al., Systemic treatment of bone disease in metastatic urinary malignancies, Eur. Urol. Focus 6 (2020) 17–25.
[28] D. Santini, A.C. Di, C. Ripamonti, Linee guida Aiom – Trattamento delle metastasi ossee, Assoc. Ital. di Oncol, Medica, 2018.
[29] EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07- 3.o Title, n.d.
[30] M.S. Zaghloul et al., A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer, Int. J. Clin. Oncol. 15 (2010) 382–389.
[31] D.H. Henry et al., Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 29 (2011) 1125–1132.
[32] A. Lipton et al., Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials, Eur. J. Cancer 48 (2012) 3082–3092.
[33] A. Yokomizo et al., Skeletal-related events in urological cancer patients with bone metastasis: a multicenter study in Japan, Int. J. Urol. 17 (2010) 332–336.
[34] S. Baleato-González, R. García-Figueiras, Specific criteria for tumor response., Radiologia. 60 Suppl 1 (2018) 64–81. https://doi.org/10.1016/j.rx.2018.01.005.
[35] F. Ruatta et al., Prognosis of renal cell carcinoma with bone metastases: experience from a large cancer centre, Eur. J. Cancer 107 (2019) 79–85.
[36] Y. Fradet et al., Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up, Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 30 (2019) 970–976.
[37] T. Powles, I. Durán, M.S. van der Heijden, Y. Loriot, N.J. Vogelzang, U. De Giorgi, S. Oudard, M.M. Retz, D. Castellano, A. Bamias, A. Fléchon, G. Gravis, S. Hussain, T. Takano, N. Leng, E.E. Kadel, R. Banchereau, P.S. Hegde, S. Mariathasan, N.a. Cui, X. Shen, C.L. Derleth, M.C. Green, A. Ravaud, Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): A multicentre, open-label, phase 3 randomised controlled trial, Lancet 391 (10122) (2018) 748–757, https://doi.org/10.1016/S0140-6736(17)33297-X.
[38] D. Castellano, J. Puente, G. de Velasco, I. Chirivella, P. López-Criado, N. Mohedano, O. Fernández, I. García-Carbonero, M.B. González, E. Grande, Safety and effectiveness of vinflunine in patients with metastatic transitional cell carcinoma of the urothelial tract after failure of one platinum-based systemic therapy in clinical practice, BMC Cancer 14 (1) (2014), https://doi.org/10.1186/1471-2407-14-779.
[39] T. Powles et al., Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, N. Engl. J. Med. 383 (2020) 1218–1230.
[40] G. de Liaño, A. Lista, et al., Clinical outcome after progressing to frontline and second-line Anti-PD-1/PD-L1 in advanced urothelial cancer.: european urology, Eur. Urol. 77 (2020) 269–276.
[41] S.T. Tagawa D.P. Petrylak P. Grivas N. Agarwal C.N. Sternberg C. Hernandez P. Siemon-Hryczyk T. Goswami Y. Loriot TROPHY-U-01: A phase II open-label study of sacituzumab govitecan (IMMU-132) in patients with advanced urothelial cancer after progression on platinum-based chemotherapy and/or anti-PD-1/PD-L1 checkpoint inhibitor therapy J. Clin. Oncol. 37 15_suppl 2019 TPS3153 TPS3153.
[42] S.T. Tagawa et al., TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 39 (2021) 2474–2485.
[43] T. Powles et al., Enfortumab vedotin in previously treated advanced urothelial carcinoma, N. Engl. J. Med. 384 (2021) 1125–1135.
[44] A.B. Apolo et al., Cabozantinib in patients with platinum-refractory metastatic urothelial carcinoma: an open-label, single-centre, phase 2 trial, Lancet. Oncol. 21 (2020) 1099–1109.
[45] Y. Loriot et al., Erdafitinib in locally advanced or metastatic urothelial carcinoma, N. Engl. J. Med. 381 (2019) 338–348.
[46] A. Kamoun et al., A consensus molecular classification of muscle-invasive bladder cancer[Formula presented], Eur. Urol. 77 (2020) 420–433.