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Review

Review: Brain Metastases in Bladder Cancer

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Abstract. Nearly 50% of bladder cancer patients either present with metastatic disease or relapse distantly following initial local therapy. Prior to platinum-based chemotherapy, the incidence of bladder cancer central nervous system metastases was approximately 1%; however, their incidence has increased to 3–16% following definitive treatment as platinum-based regimens have changed the natural history of the disease. Bladder cancer brain metastases are generally managed similarly to those from more common malignancies such as non-small cell lung cancer, with surgery +/– adjuvant radiotherapy, or radiotherapy alone using stereotactic radiosurgery or whole brain radiotherapy. Limited data suggest that patients with inoperable urothelial carcinoma brain metastases who are not candidates for stereotactic radiosurgery may benefit from shorter whole brain radiation therapy courses compared to other histologies, but data is hypothesis-generating. Given improvements in the efficacy of systemic therapy and supportive care strategies for metastatic urothelial carcinoma translating in improved survival, the incidence of intracranial failures may increase. Immune checkpoint blockade therapy may benefit cisplatin-ineligible metastatic urothelial carcinoma patients as first-line therapy; however, the effectiveness of immune checkpoint blockade to treat central nervous system disease has not been established. In this review, we discuss the incidence and management of bladder cancer brain metastases and considerations regarding variations in management relative to more commonly encountered non-urothelial histologies.

Keywords: Urothelial carcinoma, urinary bladder neoplasms, radiotherapy, neoplasm metastasis, immune checkpoint blockade

ABBREVIATIONS

BC	Bladder Cancer
CNS	Central Nervous System
CT	Computerized Tomography
CTLA-4	Cytotoxic T Lymphocyte Antigen-4
ICB	Immune Checkpoint Blockade
IMRT	Intensity-Modulated Radiation Therapy
KPS	Karnofsky Performance Status
LC	Local Control
MRI	Magnetic Resonance Imaging
mUC	Metastatic Urothelial Cancer
MVAC	Methotrexate/Vinblastine/Adriamycin/Cisplatin
mAb	Monoclonal antibody/antibodies
MIBC	Muscle Invasive Bladder Cancer
NMIBC	Non-Muscle Invasive Bladder Cancer
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival

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PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PCI	Prophylactic Cranial Irradiation
RC	Radical Cystectomy
RTOG	Radiation Therapy Oncology Group
RT	Radiotherapy/Radiation Therapy
RPA	Recursive Partitioning Analysis
SCCB	Small Cell Carcinoma of the Bladder
SCLC	Small Cell Lung Cancer
SRS	Stereotactic Radiosurgery
UC	Urothelial Carcinoma
WBRT	Whole-Brain Radiation Therapy

INTRODUCTION

In 2020, an estimated 81,400 patients in the United States will be diagnosed with bladder cancer (BC), including all stages from non-muscle invasive BC (NMIBC) to metastatic muscle-invasive bladder cancer (MIBC), and 17,980 will succumb to this disease, representing 4.5% of all new cancer cases, and nearly 3% of cancer deaths [1]. Over 90% of BCs in Western countries are urothelial carcinomas (UC) arising from the urothelial lining of the upper and lower urinary tract, and are grouped with BC in some series [2]. Less common histological BC variants include adenocarcinoma (AC), squamous cell carcinoma (SCCa), and small cell carcinoma of the bladder (SCCB); upfront management of rarer histologies can vary significantly from UC, such as the choice of upfront systemic therapy for SCCB [3–6]. Nearly three-quarters of BC patients present with NMIBC, while the remaining 25% having either MIBC or distant metastases [7–9]. Most BC deaths are attributable to metastatic disease, present in 10–15% at diagnosis and in ∼50% after definitive treatment for MIBC. The most common sites of metastatic disease include distant lymph nodes, liver, lung, and bone [10–15]. Survival for metastatic BC patients prior to the use of immune checkpoint blockade (ICB) immunotherapy was poor, with 5-year overall survival (OS) of ∼5% [16]. Brain metastases are uncommon, though incidence is higher following first-line platinum-based systemic therapy, which improves extracranial disease control and OS [17]. Responding BC patients live longer and are at higher risk for developing intracranial failure, likely secondary to reduced penetration of systemic agents across the blood-brain barrier [18–20]. Recent approval of ICB monoclonal antibodies (mAbs) as first- or second-line therapy for metastatic urothelial carcinoma (mUC) may offer alternatives to treat or prevent intracranial failures; however, their efficacy for prophylaxis or treatment of BC brain metastases is currently unknown [21, 22]. Thus, the potential for central nervous system (CNS) involvement in patients with advanced BC is an important topic for consideration given limited data on optimal treatment approaches for BC brain metastases, clinical implementation of alternatives to platinum-based systemic therapy, and rapidly improving methods for palliative CNS radiotherapy.

INCIDENCE OF BLADDER CANCER BRAIN METASTASES

Incidence of BC brain metastases in the pre-cisplatin era was low, ranging from <1% to 7% based on autopsy series and radiotherapy trials on treatment of brain metastases, with most series closer to 1–3% [23–29]. Clinical series in the pre-cisplatin era likely underestimated the incidence of BC brain metastases due to limitations in diagnostic imaging prior to the widespread use of high-quality computerized tomography (CT) and magnetic resonance imaging (MRI) scans and because patients were not scanned unless they developed symptoms. It is also difficult to assess the true incidence of BC brain metastases in the cisplatin-era as routine brain imaging, whether for initial staging or for follow-up scans, is not performed and patients are typically diagnosed only if symptomatic. To our knowledge, only two reports testing systemic therapy for metastatic BC documented inclusion of brain metastases as reporter lesions for assessing response and both were relatively small studies [30, 31]. More data is available on CNS relapse after initial systemic therapy. Sternberg et al. observed responses of metastatic reporter lesions to combinatorial chemotherapy (MVAC: methotrexate, vinblastine, Adriamycin, cisplatin) in >70% of patients, with a median survival of 13 months [20]. In their initial study, 3/24 MVAC treated mUC patients developed intracranial failures; one patient with a complete response extracranially died of CNS complications 14 months post-treatment [32]. Follow-up studies documented a CNS failure rate of 18% following MVAC, with a median time to failure of 12 months (range: 6–42) after MVAC, and 2 month median OS (range: 1–21) after intracranial failure [20]. Approximately 50% of patients with BC brain metastases had no evidence of systemic relapse [20]. Of the 10 mUC patients with intracranial failure, the longest survivor

received whole brain radiation therapy (WBRT; 30 Gy) then resection [20]. Dhote et al. had similar findings, with a CNS failure rate of 16% after MVAC ($n = 50$ patients) for mUC, occurring at a mean of 21 months (range 7–38) post-treatment [33]. Patients had a mean OS of 4.4 months (range 1–10) from diagnosis following either WBRT or resection with adjuvant WBRT [33]. CNS failures following MVAC are believed to be related to improved extracranial disease control and reduced penetration of the blood-brain barrier by systemic therapy [18, 19, 33, 34].

Other retrospective series with larger mUC patient numbers reported similar increases in intracranial metastases after heterogeneous application of local and systemic therapy, with incidences between 1–7% [35–38]. Shinagare et al. reported that 5% of MIBC patients reviewed ($n = 150$) developed brain metastases; of note all had prior local therapy (57% RC, or chemotherapy+/– RT) [39]. Bianchi et al. reviewed the most common sites of UC metastases from 7,543 mUC patients in the Nationwide Inpatient Sample between 1998-2007, reporting a 3.1% incidence ($n = 237$) of brain metastases [40]. The likelihood of intracranial failure in this series was associated with the location of extracranial disease, with a 1% rate for abdominal metastases, and 7% rate for thoracic and bony lesions [40].

Reports of increases in BC brain metastases in small series and prospective trials using improved systemic therapy correlate with an increase in case reports on BC intracranial failures. Sarmiento et al. documented 250 cases of brain metastases from a review of >50 case series and case reports [41]. Common factors identified include: male predominance, solitary BC brain metastases, heterogeneous primary treatment, long interval ranges between completing primary therapy and intracranial failure, use of surgery and post-operative RT for intracranial disease, and poor survival after definitive CNS treatment from weeks to months [41]. BC brain metastases appear to have increased in incidence following introduction of more effective systemic therapy; however, CNS involvement is still rare in the modern era and routine surveillance with brain MRI is not recommended by the NCCN.

MANAGEMENT OF BLADDER CANCER BRAIN METASTASES

Systemic chemotherapy forms the backbone of mUC treatment as established in several randomized Phase III trials, with combination gemcitabine/cisplatin non-inferior and less toxic compared to MVAC [42–44]. The expected OS for unresectable mUC is poor, with median survival <12 months [44]. Of note, there is little information to guide optimal treatment of mUC patients with intracranial failure since they were typically excluded from randomized systemic therapy trials, likely due to poor performance status and concern regarding brain penetration by systemic therapy [18, 19]. ICB using pembrolizumab is now second-line therapy for mUC following first-line platinum-based regimens, yet the Phase II/III trials of ICB excluded active brain metastases so ICB efficacy for intracranial involvement is not defined [21, 22, 45–47]. Patients who develop UC brain metastases typically have either already received cisplatin-based chemotherapy or cannot tolerate it; only about 50% of mUC patients are eligible for cisplatin-based therapy [48]. Thus, treatment of UC intracranial failure is extrapolated from management of brain metastases from more common histologies such as non-small cell lung cancer (NSCLC) and melanoma.

Systemic therapy

Systemic therapy is standard-of-care for metastatic BC; however, its role in treating BC brain metastases is unclear. Management of mUC patients depends on whether they previously received or can tolerate platinum-based chemotherapy. Typical first-line agents include cisplatin-based regimens, usually cisplatin/gemcitabine, or dose-dense MVAC with growth factor support [7, 49]. Patients unable to tolerate cisplatin secondary to age, poor performance status, impaired renal or auditory function, or peripheral neuropathy may receive carboplatin/gemcitabine [44, 50]. The major trials in metastatic disease in the cisplatin era excluded patients with brain metastases.

ICB therapy has promise for treatment of BC brain metastases. While the CNS has classically been regarded as an immune privileged organ, resistant to penetration by mAbs and effector T cells due to the blood-brain barrier, pre-clinical and clinical data suggests a role for this therapy [18, 19, 51, 52]. Pre-clinical data indicates ICB efficacy against CNS lesions is $CD8^+$ dependent, greater for combined programmed cell death protein-1 (PD-1)/cytotoxic T lymphocyte antigen-4 (CTLA-4) ICB versus monotherapy, enhanced when extracranial disease is present, and facilitated by antigen priming in draining cervical lymph nodes [53]. Perhaps the

strongest clinical data comes from the melanoma experience where dual ICB targeting PD-1 and CTLA-4 was associated with a 40–60% response rate in brain metastases [54–57]. Additional compelling data from patients with NSCLC indicates that 25–30% of patients with active brain metastases from NSCLC exhibited objective clinical responses to ICB with nivolumab, and that patients with active brain metastases did not have worse OS compared to those without brain metastases suggesting that patients with brain metastases should be considered in future clinical trials [58].

There are currently five ICB's that are FDA-approved for mUC (PD-1: nivolumab, pembrolizumab; programmed death ligand 1 PD-L1: durvalumab, atezolizumab, avelumab), but data on the efficacy of these agents in patients who have BC brain metastases is not available. Several recent trials of ICB's have allowed patients with CNS lesions to be enrolled but have not reported outcomes for this patient population, including the IMvigor130 trial testing atezolizumab and KEYNOTE-361 (Phase III trial for treatment-naive mUC: pembrolizumab +/– platinum-based chemotherapy and gemcitabine) [59, 60]. The SAUL trial testing atezolizumab in relapsed BC patients did allow patients with controlled intracranial disease (1% of the study population) [61]. In the 14 patients with initial CNS involvement, median OS was significantly worse (3.7 months; range 1.5–7) compared to the whole cohort (8.7 months; range 7.7–9.9) [61]. At least 16 trials investigating ICB efficacy for brain metastases are ongoing; however, none address this question in patients with mUC [62]. Whether first-or second-line ICB treats or prevents intracranial failures in mUC is currently unknown.

Local therapy for bladder cancer brain metastases

In general, management of brain metastases centers around treating or preventing neurological symptoms and achieving local control (LC) through multimodality treatment combining surgical resection and adjuvant RT for resectable patients and RT alone for those who are not good candidates for surgery [63]. Stereotactic radiosurgery (SRS) can be considered in lieu of surgery for patients with a lower burden of intracranial disease. Although rare, long-term survival with brain metastases following treatment is possible, with a 10-year OS rate of 1.3% ($n = 23$/ 2000 studied; 1/23 attributed to BC), and most commonly observed in patients with solitary lesions, controlled primary disease, and excellent performance status [63]. Treatment plans for local therapy are derived based on results observed for more common histologies.

Surgery with or without RT

Primary management of brain metastases is dictated by lesion number, resectability, patient performance status, medical operability, histology, and extracranial disease status. For patients with a limited number of brain metastases that are amenable to resection, standard treatment for most solid malignancy histologies is surgery followed by either adjuvant stereotactic radiosurgery (SRS) to the surgical cavity or WBRT. Older retrospective series reported improved outcomes for surgical resection followed by adjuvant WBRT vs. surgery alone [35, 64, 65]; however, WBRT adversely affects neurocognitive abilities such as short-term memory. Adjuvant SRS to the surgical cavity is generally preferred to adjuvant WBRT in current practice based on results from phase III trials. In one such trial, post-operative SRS to the resection cavity (18–24 Gy) provided similar LC and OS as post-operative WBRT (30–37.5 Gy/10–15 fractions) with less adverse effects on neurocognition [66]. Patients treated with SRS had a statistically significant improvement in cognitive-deterioration-free survival on *post-hoc* analysis versus those treated with WBRT [66, 67]. In another large randomized trial, resection cavity SRS (12–16 Gy) for 1–3 brain metastases significantly reduced local recurrences compared to observation after surgery, suggesting adjuvant SRS as an alternative to adjuvant WBRT [68]. Several trials have investigated the optimal management for patients with a solitary brain metastasis in a non-eloquent region of the brain. Resection is preferred; however, resection in the absence of adjuvant RT resulted in inferior LC and increased risk of death from neurologic causes compared to resection and adjuvant RT [69, 70]. Local recurrence following resection without adjuvant treatment across histologies is approximately 30–50%, indicating that adjuvant RT should be recommended for all operative patients [68–71]. Patients with UC brain metastases were either excluded or not well represented in the randomized trials of surgery +/– RT for brain metastases, due to the low incidence of this presentation. Management of UC brain metastases is therefore

extrapolated from data for cancers that more commonly metastasize to the brain (e.g. NSCLC, breast cancer, and melanoma).

Retrospective reports on UC brain metastases, while useful for identifying common features of presentation and treatment recommendations associated with favorable outcomes, are hampered by small sample sizes and use of RT treatment techniques that do not represent modern approaches to CNS failures, with few patients treated with SRS. Common features across these series include a propensity for UC brain metastases to be solitary and improved outcomes for patients able to undergo surgical resection followed by adjuvant RT, usually WBRT delivered to 30 Gy over 10 fractions [33, 35, 64, 72–74]. The median OS for patients with solitary UC brain metastases in series treated with surgery and radiation (range 14–27 months) compares favorably to similarly treated patients with solitary brain metastases from other histologies as reported in the seminal Patchell trial (11–12 months) [69, 70], suggesting that there is a role for surgery and adjuvant RT for these patients. Siefker-Radtke et al. found mUC patients treated with metastatectomy ($n = 31$) had a median OS of 23 months and 5-year OS of 33%, although only 7% of patients had intracranial failure and outcomes were not further stratified, indicating that, similar to other histologies, patients with oligometastatic disease may benefit from aggressive local control [75]. The study by Fokas et al. identified no significant difference between surgery and adjuvant RT ($n = 13$) versus RT alone (WBRT or SRS, $n = 49$) for patients with multiple UC brain metastases, with a median OS of 9.6 months and 8.9 months respectively ($p < 0.70$), though patient numbers were modest [76]. In a case series from Cleveland Clinic, patients who underwent resection and adjuvant RT for solitary lesions lived longer than those who received only surgery or WBRT [65], but the results need to be interpreted cautiously given the small sample size. In a pooled analysis of three retrospective studies, resection plus adjuvant WBRT improved OS versus WBRT alone (7.8–29 months versus 1.4–2 months) for UC brain metastases [77]. Of note, none of these retrospective studies assessed the effects of adjuvant RT on patient quality of life or neurocognition.

An analysis of multiple Radiation Therapy Oncology Group (RTOG) trials reported improved OS for patients with brain metastases without extracranial metastatic disease and more favorable recursive partitioning analysis (RPA) class across multiple histologies [78, 79]. Case reports suggest long-term survival of >3 years is possible for UC intracranial failures managed with resection alone, though the generalizability of these findings is unclear and multimodality approaches are better supported [66, 80, 81]. For eligible patients, maximal safe surgical resection followed by SRS to the surgical bed is generally preferred, though resection followed by adjuvant WBRT is a reasonable option

Stereotactic radiosurgery alone

SRS is a reasonable alternative to surgery or WBRT for smaller tumors $\leq$3 cm that are not resectable and can also be considered for resectable tumors $\leq$3 cm in patients who are candidates for surgery. Because the risk of both neurotoxicity and local failure after SRS increase with increasing tumor size, surgery is favored for lesions >3 cm. SRS achieves local control rates of $\sim$70% at 1-year post-treatment in appropriately selected patients [71]. To-date, no trials of sufficient power comparing SRS alone vs. surgery plus post-operative RT have been completed. Shared decision-making and input from a multi-disciplinary team should help guide the decision on surgery plus adjuvant RT vs. SRS alone. For patients with a limited number of lesions not amenable to surgical resection, SRS (18–24 Gy in 1 fraction based on target size) may be preferable to WBRT for patients with good performance status, since SRS reduces the volume of normal brain irradiated and is associated with less cognitive deterioration at 3 months without compromising OS, although time to intracranial failure outside of the treated lesions is shorter compared to WBRT [82, 83]. While SRS has been traditionally employed to treat a limited number of tumors (often 4 or fewer), prospective non-randomized data suggest that up to 10 tumors with a cumulative volume $\leq$15 mL can be treated with SRS in a single treatment session with similar efficacy and no increase in side effects [84, 85].

Whole brain radiation therapy and best supportive care

The efficacy of RT for primary management of mUC intracranial failure has not been prospectively evaluated. For non-surgical patients with intracranial failure, RT improves LC and palliates neurological symptoms. Patients with multiple unresectable lesions, poor performance status, life expectancy <6 months, and symptomatic UC brain metastases may

benefit from WBRT or best supportive care, as extrapolated from the QUARTZ trial where dexamethasone (median 8 mg/day) with WBRT (20 Gy/5 fractions) did not improve OS for NSCLC brain metastases and provided minimal increase in quality-adjusted life years versus optimal supportive care [86]. On subgroup analysis, patients with better prognosis (*e.g.* age < 60) or those with a higher burden of intracranial disease (≥5 brain metastases) had improved OS with WBRT [86]. These results should be interpreted cautiously since they may not be applicable to UC brain metastases.

For patients not eligible for SRS or surgery, WBRT can palliate neurological symptoms, decrease steroid dependence, and reduce risk of additional intracranial failures. No randomized trials demonstrate an OS benefit for WBRT for non-resected NSCLC brain metastases [86]. Standard WBRT is 30 Gy/10 fractions, derived from randomized RTOG studies in the 1970s that observed equivalent LC and survival between 7 different WBRT schemes [28, 29]. In the RTOG studies, only 7 of 1895 patients had BC brain metastases, and only 2 were resected prior to WBRT [28, 29]. Recent data indicates the adverse effects of WBRT on neurocognition may be ameliorated with use of memantine (an *N*-methyl-D aspartate antagonist) during and after RT as well as hippocampal avoidance WBRT using intensity-modulated radiation therapy (IMRT) to reduce dose to the hippocampus [87, 88]. Hippocampal avoidance WBRT should only be considered for patients without disease ≤5 mm of the dentate gyrus and predicted survival ≥4 months since the neurocognitive benefit manifested at 4 months post-treatment; patients with a higher symptom burden who require prompt therapy may not be suitable since hippocampal avoidance WBRT requires more time for treatment planning [88].

Rades et al. compared WBRT with 20–30 Gy/10 fractions ($n = 21$) versus hypofractionated WBRT (20 Gy/5 fractions; $n = 12$) for mUC patients with ≥2 brain lesions [89]. On univariable analysis, 20 Gy/5 fraction WBRT had significantly improved LC at 6 months (83%; $p = 0.035$) compared to 20–30 Gy/10 fraction WBRT (27%); however, LC and OS with 20 Gy/5 fractions was not significant on multivariable analysis ($p = 0.036$; significance threshold of $p = 0.025$) [89]. Median OS for 20 Gy/5 fraction WBRT was 5 months, which compares favorably to the ≤3 month median OS for historical controls treated with 20–30 Gy/10 fractions [33, 64, 65, 75]. One explanation for LC improvement with hypofractionated WBRT is UC radioresistance responding favorably to higher RT doses per fraction [90]. Several trials demonstrated improved LC with hypofractionated RT for unresectable BC; however, combining hypofractionated RT with ICB may exacerbate treatment toxicity [91–93]. In the absence of larger, more robust data showing a consistent benefit for hypofractionated WBRT, we favor 30 Gy/10 fraction WBRT for multiple unresectable lesions, with consideration of hippocampal avoidance WBRT and concurrent and adjuvant memantine for eligible patients.

Rades et al. identified prognostic factors useful for guiding aggressiveness of palliative RT for mUC patients [94]. They stratified a small cohort of 46 patients with UC brain metastases by Karnofsky Performance Status (KPS; 2 points: ≤60, 4 points: >60), stage at initial presentation (4 points: stage I–III, 2 points: stage IV), and number of involved metastatic sites (4 points: 1 site, 2 points: ≥2 sites) [94]. At 6 months post diagnosis, patients with 10–12 points lived longer versus those with 6–8 points (46% versus 9% respectively; $p = 0.002$) [94]. A recently reported scoring system predictive for outcomes for mUC treated with ICB found that patients with lower platelet/neutrophil/monocyte-to-lymphocyte ratios (<300, <4.6, <0.55 respectively), higher baseline albumin (≥3.9 g/dL), absence of liver/bone metastases, and higher performance status (ECOG 0–1) had improved survival; 1/67 patients assessed had UC intracranial failure [95]. Thus, mUC patients with good performance status, late development of metastases after definitive treatment, and solitary intracranial failures may warrant aggressive multimodality therapy.

There are no prospective data regarding combining ICB with RT for unresected brain metastases. In a meta-analysis by Lehrer et al. encompassing 17 studies on brain metastases treated with SRS and ICB (>4 weeks before or after SRS), concurrent treatment improved 1-year OS (64.6% versus 51.6%; $p < 0.001$) and regional brain control (38.1% versus 12.3%; $p = 0.049$) [96]. Most CNS metastases were either melanoma, NSCLC, or renal cell carcinoma treated with SRS (18–24 Gy) and either CTLA-4 or PD-1 ICB mAbs [96]. A recent study found that RT before anti-PD-L1 ICB was associated with improved OS at 15 months post-RT versus ICB before RT, however sample sizes were limited [97]. The optimal sequence of ICB and RT for UC brain metastases remains to be determined. The potential for synergy with ICB and RT is an exciting area for future study.

Brain metastases from small cell carcinoma of the bladder (SCCB)

Intracranial failure in mUC is uncommon, but is significantly higher for patients with SCCB. These patients should undergo brain MRI during initial work-up [98]. Siefker-Radtke et al. found a 10.5% incidence of brain metastases for SCCB patients treated at MD Anderson between 1985-2002, with 62.5% developing metastatic disease at any site [99]. Bex et al. reviewed 51 SCCB patients treated at The Netherlands Cancer Institute between 1993-2009, where 10.3% of patients with limited disease ($n = 39$) developed symptomatic brain metastases (median follow-up 15 months, range 3–24). No intracranial failures were observed in SCCB patients with extensive disease (median follow-up 6 months, range 2–43), likely secondary to shorter survival times [100]. Four patients with SCCB brain metastases received WBRT (20–30 Gy/5–10 fractions), with a median OS of 7.5 months [100]. On pooled analysis of prior retrospective studies, Bex et al. calculated the incidence of symptomatic SCCB brain metastases at 10.5% (95% CI: 7.5–14.1%) [100]. Siefker-Radtke et al. observed a 50% rate of brain metastases (8/16 patients) in SCCB patients with advanced disease at presentation ($\geq$cT3b, N1+, or M+; $p = 0.004$) treated in a Phase II trial that compared ifosfamide/doxorubicin versus etoposide/cisplatin, suggesting an elevated risk for advanced SCCB patients compared to those with limited disease [101].

Patients with imaging-confirmed SCCB brain metastases are usually treated with WBRT. Decisions regarding whether to treat with WBRT or SRS may be guided by the FIRE-SCLC study comparing these approaches for small cell lung cancer (SCLC) brain metastases where it appears that SRS is a viable option for treating patients with limited intracranial disease without compromising OS [102]. Recent data suggest advanced SCCB patients may benefit from prophylactic cranial irradiation (PCI), as is done for localized SCLC in patients who respond to chemo-radiotherapy [103]. Lower rates of brain metastases were observed in an MD Anderson study for SCCB patients with advanced disease ($\geq$cT3b, N1+, and/or M+; no intracranial disease on imaging; $n = 29$) treated with PCI (30 Gy/15 fractions) following systemic therapy and definitive therapy to the bladder (13.8% versus 50% for historical control, median follow-up 13 months) [104]. No significant neurocognitive impairment was observed for the 19 PCI patients compared to their pre-treatment baseline at 13 months post-treatment ($p = 0.61$) [104]. In the EAU-ESMO 2019 consensus statement regarding management of advanced and variant BC, 74% of the oncologists on the panel did not recommend PCI for SCCB [105]. PCI may benefit SCCB patients with excellent performance status, higher stage at presentation and objective responses to local and systemic therapy; however, data is limited.

SCCB represents <1% of all BCs, and data regarding ICB efficacy as treatment or prophylaxis against intracranial failure is limited. Wilde et al. reported a radiographic response with 6th line pembrolizumab for hepatic SCCB metastases, suggesting that SCCB may respond to ICB [106]. The Phase III IMpower133 trial (pembrolizumab in advanced solid treatment-refractory cancers) pooled KEYNOTE-028 and 158 data, including SCLC patients with brain metastases [107]. Of 83 SCLC patients, 16% had stable CNS metastases at entry, and approximately 50% had prior WBRT, with objective responses in 20%, and improved median OS of 7.7 months versus a historical median OS of 4.4 months following $\geq$3rd line therapy [107]. A majority of responders (88%) were PD-L1 positive, 2/16 had baseline brain metastases, and 61% experienced responses lasting $\geq$18 months [107]. SCCB patients with PD-L1$^+$ brain metastases may benefit from pembrolizumab but more analysis is needed.

CONCLUSIONS

Brain metastases from BC have increased over the past 40 years in parallel with improvements in systemic therapy; however optimal management remains uncertain. Due to the relative rarity of intracranial involvement, brain MRI is not recommended during initial workup, though suspicion should be higher for patients following recurrence and with new neurological symptoms. Our review of the literature does not suggest that routine MRIs should be part of surveillance imaging for patients with metastatic disease and no prior history of intracranial involvement Systemic therapy is typically employed for advanced or recurrent BC, but the efficacy of chemotherapy or ICB against BC brain metastases remains unclear. Local therapy remains the treatment of choice for BC brain metastases. The available data suggests that it is reasonable to treat BC brain metastases in a similar fashion to how brain metastases are treated for other more common solid malignancies. For patients with limited intracranial disease and good

performance status, maximal safe resection when feasible followed by adjuvant stereotactic radiosurgery is generally preferred, although adjuvant WBRT is an option as well. Stereotactic radiosurgery alone can be considered for patients with a limited burden of intracranial disease, especially if lesions are not accessible or too numerous for surgery. For patients with more extensive intracranial disease, WBRT is a reasonable option. Patients with UC brain metastases treated with WBRT may derive benefits in preserving neurocognition with memantine and hippocampal avoidance WBRT if survival $\geq$4 months is predicted. SCCB brain metastases are commonly treated with chemotherapy and WBRT rather than SRS, though recent suggests that SRS may not be an inferior choice for select patients. ICB mAbs may represent a new option for preventing BC intracranial failures or treating known BC brain metastases, but more rigorous study is needed. Prognostic scoring systems may assist in determining aggressiveness of management for BC patients with intracranial failure.

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AUTHOR CONTRIBUTIONS

RB reviewed literature and clinical trial protocols, wrote, and critically revised manuscript. BB reviewed literature and clinical trial protocols, wrote, and critically revised manuscript. The other authors critically revised the manuscript.

ETHICAL CONSIDERATIONS

This paper is a literature review and discussion that does not present any primary results of the study it describes. As such, it is exempt from any requirement for Institutional Review Board approval.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

REFERENCES

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
[2] Sanli O, Dobruch J, Knowles MA, et al. Bladder cancer. Nat Rev Dis Primer. 2017;3:17022.
[3] Fischer-Valuck BW, Rao YJ, Henke LE, et al. Treatment Patterns and Survival Outcomes for Patients with Small Cell Carcinoma of the Bladder. Eur Urol Focus. 2018;4:900-6.
[4] Fischer-Valuck BW, Michalski JM, Contreras JA, et al. A propensity analysis comparing definitive chemoradiotherapy for muscle-invasive squamous cell carcinoma of the bladder vs. urothelial carcinoma of the bladder using the National Cancer Database. Clin Transl Radiat Oncol. 2019;15:38-41.
[5] Brenneman R, Fischer-Valuck BW, Gay HA, et al. A Propensity Analysis Comparing Definitive Chemo-Radiation for Muscle-Invasive Adenocarcinoma of the Bladder Versus Urothelial Carcinoma of the Bladder using the National Cancer Database (NCDB). Int J Radiat Oncol • Biol • Phys. 2018;102:e84-e85.
[6] Willis D, Kamat AM. Nonurothelial bladder cancer and rare variant histologies. Hematol Oncol Clin North Am. 2015;29:237-252, viii.
[7] Morera DS, Hasanali SL, Belew D, et al. Clinical Parameters Outperform Molecular Subtypes for Predicting Outcome in Bladder Cancer: Results from Multiple Cohorts, Including TCGA. J Urol. 2020;203:62-72.
[8] Burger M, Catto JWF, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63:234-41.
[9] Smith AB, Deal AM, Woods ME, et al. Muscle-invasive bladder cancer: evaluating treatment and survival in the National Cancer Data Base. BJU Int. 2014;114:719-26.
[10] Wu X-R. Urothelial tumorigenesis: a tale of divergent pathways. Nat Rev Cancer. 2005;5:713-25.
[11] Nadal R, Bellmunt J. Management of metastatic bladder cancer. Cancer Treat Rev. 2019;76:10-21.
[12] Christodouleas JP, Baumann BC, He J, et al. Optimizing bladder cancer locoregional failure risk stratification after radical cystectomy using SWOG 8710. Cancer. 2014;120:1272-80.
[13] Baumann BC, He J, Hwang W-T, et al. Validating a Local Failure Risk Stratification for Use in Prospective Studies of Adjuvant Radiation Therapy for Bladder Cancer. Int J Radiat Oncol Biol Phys. 2016;95:703-6.
[14] Mari A, Campi R, Tellini R, et al. Patterns and predictors of recurrence after open radical cystectomy for bladder cancer: a comprehensive review of the literature. World J Urol. 2018;36:157-70.
[15] Zaghloul MS, Christodouleas JP, Smith A, et al. A randomized clinical trial comparing adjuvant radiation versus chemo-RT versus chemotherapy alone after radical cystectomy for locally advanced bladder cancer. J Clin Oncol. 2016;34:356.
[16] Al-Husseini MJ, Kunbaz A, Saad AM, et al. Trends in the incidence and mortality of transitional cell carcinoma of the bladder for the last four decades in

the USA: a SEER-based analysis. BMC Cancer. 2019; 19:46.
[17] Flaig TW. NCCN Guidelines Updates: Management of Muscle-Invasive Bladder Cancer. J Natl Compr Cancer Netw JNCCN. 2019;17:591-3.
[18] Sprowls SA, Arsiwala TA, Bumgarner JR, et al. Improving CNS Delivery to Brain Metastases by Blood-Tumor Barrier Disruption. Trends Cancer. 2019;5:495-505.
[19] Fecci PE, Champion CD, Hoj J, et al. The Evolving Modern Management of Brain Metastasis. Clin Cancer Res Off J Am Assoc Cancer Res. 2019;25:6570-80.
[20] Sternberg CN, Yagoda A, Scher HI, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer. 1989;64:2448-58.
[21] Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18:1483-92.
[22] Fradet Y, Bellmunt J, Vaughn DJ, 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. 2019;30:970-6.
[23] Lower W, Watkins R. A Case of Primary Carcinoma of the Bladder With Metastasis to the Brain. Am J Med Sci. 1924;167:434-7.
[24] Leadbetter WF, Colston JAC. Brain Metastasis in Carcinoma of the Bladder. J Urol. 1937;38:267-77.
[25] Whitmore WF, Batata MA, Ghoneim MA, et al. Radical cystectomy with or without prior irradiation in the treatment of bladder cancer. J Urol. 1977;118:184-7.
[26] Babaian RJ, Johnson DE, Llamas L, et al. Metastases from transitional cell carcinoma of urinary bladder. Urology. 1980;16:142-4.
[27] Hust MH, Pfitzer P. Cerebrospinal fluid and metastasis of transitional cell carcinoma of the bladder. Acta Cytol. 1982;26:217-23.
[28] Gelber RD, Larson M, Borgelt BB, et al. Equivalence of radiation schedules for the palliative treatment of brain metastases in patients with favorable prognosis. Cancer. 1981;48:1749-53.
[29] Reddy S, Hendrickson FR, Hoeksema J, et al. The role of radiation therapy in the palliation of metastatic genitourinary tract carcinomas. A study of the Radiation Therapy Oncology Group. Cancer. 1983;52:25-9.
[30] Logothetis CJ, Dexeus FH, Finn L, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol Off J Am Soc Clin Oncol. 1990;8:1050-5.
[31] Campbell M, Baker LH, Opipari M, et al. Phase II trial cisplatin, doxorubicin, and cyclophosphamide (CAP) in the treatment of urothelial transitional cell carcinoma. Cancer Treat Rep. 1981;65:897-9.
[32] Sternberg CN, Yagoda A, Scher HI, et al. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. J Urol. 1985;133:403-7.
[33] Dhote R, Beuzeboc P, Thiounn N, et al. High incidence of brain metastases in patients treated with an M-VAC regimen for advanced bladder cancer. Eur Urol. 1998;33:392-5.
[34] Baumann BC, Kao GD, Mahmud A, et al. Enhancing the efficacy of drug-loaded nanocarriers against brain tumors by targeted radiation therapy. Oncotarget. 2013;4: 64-79.
[35] Anderson RS, el-Mahdi AM, Kuban DA, et al. Brain metastases from transitional cell carcinoma of urinary bladder. Urology. 1992;39:17-20.
[36] Anderson TS, Regine WF, Kryscio R, et al. Neurologic complications of bladder carcinoma: a review of 359 cases. Cancer. 2003;97:2267-72.
[37] Sengeløv L, Kamby C, von der Maase H. Pattern of metastases in relation to characteristics of primary tumor and treatment in patients with disseminated urothelial carcinoma. J Urol. 1996;155:111-4.
[38] Wallmeroth A, Wagner U, Moch H, et al. Patterns of metastasis in muscle-invasive bladder cancer (pT2-4): An autopsy study on 367 patients. Urol Int. 1999;62:69-75.
[39] Shinagare AB, Ramaiya NH, Jagannathan JP, et al. Metastatic pattern of bladder cancer: correlation with the characteristics of the primary tumor. AJR Am J Roentgenol. 2011;196:117-22.
[40] Bianchi M, Roghmann F, Becker A, et al. Age-stratified distribution of metastatic sites in bladder cancer: A population-based analysis. Can Urol Assoc J J Assoc Urol Can. 2014;8:E148-158.
[41] Sarmiento JM, Wi MS, Piao Z, et al. Solitary cerebral metastasis from transitional cell carcinoma after a 14-year remission of urinary bladder cancer treated with gemcitabine: Case report and literature review. Surg Neurol Int. 2012;3:82.
[42] von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol Off J Am Soc Clin Oncol. 2000;18:3068-77.
[43] von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23:4602-8.
[44] Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30:1107-13.
[45] Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017;18:312-22.
[46] Powles T, Durán I, van der Heijden MS, et al. 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 Lond Engl. 2018;391:748-57.
[47] Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017;376:1015-26.
[48] Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006;107:506-13.

[49] Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol Off J Am Soc Clin Oncol. 2001;19:2638-46.

[50] De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30:191-9.

[51] Achrol AS, Rennert RC, Anders C, et al. Brain metastases. Nat Rev Dis Primer. 2019;5:5.

[52] Boire A, Brastianos PK, Garzia L, et al. Brain metastasis. Nat Rev Cancer. 2020;20:4-11.

[53] Taggart D, Andreou T, Scott KJ, et al. Anti-PD-1/anti-CTLA-4 efficacy in melanoma brain metastases depends on extracranial disease and augmentation of CD8+T cell trafficking. Proc Natl Acad Sci U S A. 2018;115:E1540-E1549.

[54] Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012;13:459-65.

[55] Kluger HM, Chiang V, Mahajan A, et al. Long-Term Survival of Patients With Melanoma With Active Brain Metastases Treated With Pembrolizumab on a Phase II Trial. J Clin Oncol Off J Am Soc Clin Oncol. 2019;37:52-60.

[56] Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018;19:672-81.

[57] Tawbi HA, Forsyth PA, Algazi A, et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. N Engl J Med. 2018;379:722-30.

[58] Hendriks LEL, Henon C, Auclin E, et al. Outcome of Patients with Non-Small Cell Lung Cancer and Brain Metastases Treated with Checkpoint Inhibitors. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2019;14:1244-54.

[59] Grande E, Galsky M, Arranz Arija JA, et al. IMvigor130: Efficacy and safety from a phase III study of atezolizumab (atezo) as monotherapy or combined with platinum-based chemotherapy (PBC) vs placebo+PBC in previously untreated locally advanced or metastatic urothelial carcinoma (mUC). Ann Oncol. 2019;30:v888-v889.

[60] Powles T, Gschwend JE, Loriot Y, et al. Phase 3 KEYNOTE-361 trial: Pembrolizumab (pembro) with or without chemotherapy versus chemotherapy alone in advanced urothelial cancer. J Clin Oncol. 2017;35:TPS4590-TPS4590.

[61] Sternberg CN, Loriot Y, James N, et al. Primary Results from SAUL, a Multinational Single-arm Safety Study of Atezolizumab Therapy for Locally Advanced or Metastatic Urothelial or Nonurothelial Carcinoma of the Urinary Tract. Eur Urol. 2019;76:73-81.

[62] Lauko A, Thapa B, Venur VA, et al. Management of Brain Metastases in the New Era of Checkpoint Inhibition. Curr Neurol Neurosci Rep. 2018;18:70.

[63] Kotecha R, Vogel S, Suh JH, et al. A cure is possible: a study of 10-year survivors of brain metastases. J Neurooncol. 2016;129:545-55.

[64] Rosenstein M, Wallner K, Scher H, et al. Treatment of brain metastases from bladder cancer. J Urol. 1993;149:480-3.

[65] Mahmoud-Ahmed AS, Suh JH, Kupelian PA, et al. Brain metastases from bladder carcinoma: presentation, treatment and survival. J Urol. 2002;167:2419-22.

[66] Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18:1049-60.

[67] Trifiletti DM, Ballman KV, Brown PD, et al. Optimizing Whole Brain Radiation Therapy Dose and Fractionation: Results From a Prospective Phase 3 Trial (NCCTG N107C [Alliance]/CEC.3). Int J Radiat Oncol Biol Phys. 2020;106:255-60.

[68] Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18:1040-8.

[69] Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990;322:494-500.

[70] Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998;280:1485-9.

[71] Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29:134-41.

[72] Bloch JL, Nieh PT, Walzak MP. Brain metastases from transitional cell carcinoma. J Urol. 1987;137:97-9.

[73] Salvati M, Cervoni L, Orlando ER, et al. Solitary brain metastases from carcinoma of the bladder. J Neurooncol. 1993;16:217-20.

[74] Kabalin JN, Freiha FS, Torti FM. Brain metastases from transitional cell carcinoma of the bladder. J Urol. 1988;140:820-4.

[75] Siefker-Radtke AO, Walsh GL, Pisters LL, et al. Is there a role for surgery in the management of metastatic urothelial cancer? The M. D. Anderson experience. J Urol. 2004;171:145-8.

[76] Fokas E, Henzel M, Engenhart-Cabillic R. A comparison of radiotherapy with radiotherapy plus surgery for brain metastases from urinary bladder cancer: analysis of 62 patients. Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al. 2010;186:565-71.

[77] Patel V, Collazo Lorduy A, Stern A, et al. Survival after Metastasectomy for Metastatic Urothelial Carcinoma: A Systematic Review and Meta-Analysis. Bladder Cancer Amst Neth. 2017;3:121-32.

[78] Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997;37:745-51.

[79] Sperduto PW, Berkey B, Gaspar LE, et al. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys. 2008;70:510-4.

[80] Jankevicius F, Sruogis A, Ulys A, et al. Prolonged remission in a patient with transitional cell carcinoma of the bladder developing brain metastases after sys-

temic chemotherapy: a case report. Tumori. 2004;90: 420-1.

[81] Kartha GK, Sanfrancesco J, Udoji E, et al. Long-term Survival From Muscleinvasive Bladder Cancer With Initial Presentation of Symptomatic Cerebellar Lesion: The Role of Selective Surgical Extirpation of the Primary and Metastatic Lesion. Rev Urol. 2015;17: 106-9.

[82] Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys. 2000;47:291-8.

[83] Brown PD, Jaeckle K, Ballman KV, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA. 2016;316:401-9.

[84] Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol. 2014;15:387-95.

[85] Yamamoto M, Serizawa T, Higuchi Y, et al. A Multi-institutional Prospective Observational Study of Stereotactic Radiosurgery for Patients With Multiple Brain Metastases (JLGK0901 Study Update): Irradiation-related Complications and Long-term Maintenance of Mini-Mental State Examination Scores. Int J Radiat Oncol. 2017;99:31-40.

[86] Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet Lond Engl. 2016;388:2004-14.

[87] Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro-Oncol. 2013;15: 1429-37.

[88] Brown PD, Gondi V, Pugh S, et al. Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001. J Clin Oncol Off J Am Soc Clin Oncol. 2020;JCO1902767.

[89] Rades D, Meyners T, Veninga T, et al. Hypofractionated whole-brain radiotherapy for multiple brain metastases from transitional cell carcinoma of the bladder. Int J Radiat Oncol Biol Phys. 2010;78:404-8.

[90] Gospodarowicz MK, Warde PR. A critical review of the role of definitive radiation therapy in bladder cancer. Semin Urol. 1993;11:214-26.

[91] Duchesne GM, Bolger JJ, Griffiths GO, et al. A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. Int J Radiat Oncol Biol Phys. 2000;47:379-88.

[92] Hafeez S, McDonald F, Lalondrelle S, et al. Clinical Outcomes of Image Guided Adaptive Hypofractionated Weekly Radiation Therapy for Bladder Cancer in Patients Unsuitable for Radical Treatment. Int J Radiat Oncol Biol Phys. 2017;98:115-22.

[93] Tree AC, Jones K, Hafeez S, et al. Dose-limiting Urinary Toxicity With Pembrolizumab Combined With Weekly Hypofractionated Radiation Therapy in Bladder Cancer. Int J Radiat Oncol Biol Phys. 2018;101: 1168-71.

[94] Rades D, Manig L, Janssen S, et al. A Survival Score for Patients Assigned to Palliative Radiotherapy for Metastatic Bladder Cancer. Anticancer Res. 2017;37:1481-4.

[95] Shabto JM, Martini DJ, Liu Y, et al. Novel risk group stratification for metastatic urothelial cancer patients treated with immune checkpoint inhibitors. Cancer Med. Epub ahead of print 25 February. 2020. DOI: 10.1002/cam4.2932

[96] Lehrer EJ, Peterson J, Brown PD, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2019;130:104-12.

[97] Pomeranz Krummel DA, Nasti TH, Izar B, et al. Impact of Sequencing Radiation Therapy and Immune Checkpoint Inhibitors in the Treatment of Melanoma Brain Metastases. Int J Radiat Oncol Biol Phys. Epub ahead of print 11 February. 2020. DOI: 10.1016/j.ijrobp.2020.01.043

[98] Nccn.org. (2020). [online] Available at: https://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf [Accessed 25 Jan.. 2020].

[99] Siefker-Radtke AO, Dinney CP, Abrahams NA, et al. Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: a retrospective review of the M. D. Anderson cancer experience. J Urol. 2004; 172:481-4.

[100] Bex A, Sonke GS, Pos FJ, et al. Symptomatic brain metastases from small-cell carcinoma of the urinary bladder: The Netherlands Cancer Institute experience and literature review. Ann Oncol Off J Eur Soc Med Oncol. 2010;21:2240-5.

[101] Siefker-Radtke AO, Kamat AM, Grossman HB, et al. Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27:2592-7.

[102] Rusthoven CG, Yamamoto M, Bernhardt D, et al. Evaluation of First-line Radiosurgery vs Whole-Brain Radiotherapy for Small Cell Lung Cancer Brain Metastases: The FIRE-SCLC Cohort Study. JAMA Oncol. Epub ahead of print 4 June 2020. DOI: 10.1001/jamaoncol.2020.1271

[103] Resio BJ, Hoag J, Chiu A, et al. Prophylactic cranial irradiation is associated with improved survival following resection for limited stage small cell lung cancer. J Thorac Dis. 2019;11:811-8.

[104] Choi S, Campbell MT, Shah AY, et al. Prophylactic cranial irradiation (PCI) significantly decreases risk of brain metastases in patients with bulky, higher stage small-cell urothelial cancer. J Clin Oncol. 2019;37: 486.

[105] Witjes JA, Babjuk M, Bellmunt J, et al. EAU-ESMO Consensus Statements on the Management of Advanced and Variant Bladder Cancer-An International Collaborative Multistakeholder Effort†: Under the Auspices of the EAU-ESMO Guidelines Committees. Eur Urol. 2020;77:223-50.

[106] Wilde L, Ali SM, Solomides CC, et al. Response to Pembrolizumab in a Patient With Chemotherapy Refractory Bladder Cancer With Small Cell Variant Histology: A Case Report and Review of the Literature. Clin Genitourin Cancer. 2017;15:e521-e524.

[107] Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. Epub ahead of print 20 December 2019. DOI: 10.1016/j.jtho.2019.12.109