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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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 \((n = 50 \text{ patients})\) 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 ≤3 cm that are not resectable and can also be considered for resectable tumors ≤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 ~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 ≤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-Radtk et al. observed a 50% rate of brain metastases (8/16 patients) in SCCB patients with advanced disease at presentation (≥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 (≥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 ≥3rd line therapy [107]. A majority of responders (88%) were PD-L1 positive, 2/16 had baseline brain metastases, and 61% experienced responses lasting ≥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 ≥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.

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