

Case Report

Solitary cerebral metastasis from transitional cell carcinoma after a 14-year remission of urinary bladder cancer treated with gemcitabine: Case report and literature review

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Abstract

Background: Brain metastases are the most common adult brain tumors, frequently arising from primary tumors in the lung, breast, skin, kidneys, and colon. Transitional cell carcinoma (TCC), the most common type of urinary bladder cancer, is a rare cause of brain metastasis with an ominous prognosis.

Case Description: A 68-year-old female presented with right-sided paresis and focal motor seizures of her right upper and lower extremities 14 years after being diagnosed and treated for primary TCC of the urinary bladder with gemcitabine-based chemotherapy. MRI imaging revealed a 3.1 × 3.1 × 2.7 cm heterogeneously enhancing mass located along the posterior aspect of the left frontal convexity. The lesion was accessed using a transsulcal approach and was surgically debulked along the motor cortex with motor strip mapping, followed by adjuvant whole-brain radiation therapy. Pathological examination confirmed metastatic carcinoma with features of TCC, a rare entity among metastatic brain tumors.

Conclusion: Brain metastases may present several years later in patients with TCC of the urinary bladder who have been treated with surgery and chemotherapy. Chemotherapeutic agents that penetrate the blood–brain barrier, such as gemcitabine, may delay development of cerebral metastasis from primary TCC of the urinary bladder.

Key Words: Brain tumor, cerebral, intracranial, metastatic, transitional cell carcinoma, urinary bladder cancer

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BACKGROUND

Brain metastases are the most common adult brain tumors and account for 13–39% of intracranial tumors.^[34,61,100]

The incidence rate of all forms of brain metastasis in the United States is approximately 170,000 per year.^[52] It is estimated that 20–40% of all cancer patients develop some form of intracranial metastases.^[34,68,86] The most

common adult primary tumors that metastasize to the brain, in decreasing order of frequency, are lung, breast, skin (melanoma), renal, and colon cancers.^[49,61,100]

The estimated incidence of new urinary system cancer cases in 2009 is 131,010, of which 70,980 (54.2%) stem from the urinary bladder, 57,760 (44.1%) stem from the kidney and renal pelvis, and 2,270 (1.7%) stem from the ureter and other urinary organs.^[43] Transitional cell carcinoma (TCC) accounts for over 90% of the reported urinary bladder cancers in the United States, while less than 5% result from squamous cell carcinomas (SCC), and less than 2% result from adenocarcinomas.^[89] Urinary bladder cancer has great potential to metastasize, and sometimes the frequency of metastasis can be as high as 67%.^[48] A 2011 retrospective study of 392 patients with urinary bladder cancer reported the most common sites of metastasis to be the lymph nodes (104 patients, 69%), followed by bone (71 patients, 47%), lung (55 patients, 37%), liver (39 patients, 26%), and peritoneum (24 patients, 16%).^[84] It is rare for TCC of the urinary bladder to metastasize to the brain, and reported incidences in patients with urinary bladder cancer range anywhere from 0% to 7%.^[17] The prognosis for patients with brain metastasis from urinary bladder cancer is ominous, regardless of treatment. Treated patients have a median survival of 2–4 months,^[58,77] while untreated patients' survival ranges from several days to 1.75 months.^[1,23,45,58] We present an unusual case of a 68-year-old female with a history of urinary bladder cancer 14 years prior that was discovered to have a left frontal mass after presenting with seizures and right-sided paresis.

CASE DESCRIPTION

History

A 68-year-old, right-handed, Caucasian female nurse, with a past medical history of TCC of the urinary bladder, presented with a chief complaint of right-sided weakness and seizures. The patient was diagnosed with urinary bladder cancer in 1996. At that time, she was treated with forty-five cycles of gemcitabine, paclitaxel, and cisplatin chemotherapy. In 2005, she received local radiation therapy to the urinary bladder. In 2006, liver metastases were discovered, and the patient responded well to palliative chemotherapy with six additional cycles of cisplatin with gemcitabine. In 2008 she presented with hydronephrosis secondary to a large distal right ureteral recurrence of the TCC. The patient underwent a laparoscopic nephroureterectomy and cystoscopy that year. The patient denied tobacco, alcohol, or drug abuse. At her latest admission in 2010, the patient reported a 2-week history of right arm and leg weakness and a 1-day history of uncontrollable shaking of her right upper and lower extremity. The shaking was brief and resolved spontaneously. The patient denied loss of consciousness,

nausea, vomiting, dysarthria, headaches, visual changes, cognitive changes, or difficulty ambulating.

Neurologic exam and imaging

Neurologic examination revealed right-sided gait disturbance, as well as proximal more than distal paresis of muscle groups in her right upper and lower extremity (4 to 4+/5). The medical exam and the remainder of the neurologic exam were without focal deficits.

Initial imaging by the emergency room, noncontrast enhancing computed tomography (CT) of the brain, revealed an isodense lesion of the left frontal lobe with associated vasogenic edema [Figure 1]. Magnetic resonance imaging (MRI) of the brain showed a 3.1 × 3.1 × 2.7 cm heterogeneously enhancing mass located along the posterior aspect of the left frontal convexity [Figure 2]. The patient was placed on high-dose corticosteroids and antiepileptics. The metastatic evaluation, which included contrast-enhanced CT of the chest, abdomen, and pelvis, showed no evidence of local recurrence, lymphadenopathy, or metastatic disease. The patient elected for craniotomy and resection of the tumor with motor strip mapping.

Operation

The tumor was accessed via a left parietal craniotomy after the outline of the tumor was marked with the frameless stereotactic system (*Germany*). A transsulcal approach was used to access the tumor, which was located just anterior to the motor strip. Intraoperative findings consisted of an extra-axial left frontal–parietal tumor that was gray in color with a firm and rubbery consistency. There was a surgical plane around the tumor and we achieved a near complete resection. The posterior margin of the tumor was unresectable given motor strip mapping indicated motor cortex territory, so we left a small rim of tumor to avoid causing the patient further weakness.

Pathological findings

Pathological examination included a histologic analysis of three portions of firm tan-white tissue, measuring 1.0 × 1.0 × 0.2 cm in aggregate frozen section. A second brain biopsy, consisting of firm tan-white tissue measuring 3.5 × 2.5 × 0.7 cm in aggregate, was analyzed. The final pathological diagnosis of our left parietal brain tumor biopsy was metastatic carcinoma with features of TCC [Figure 3].

Postoperative course

On awakening, the patient showed mild expressive aphasia and weakness, both of which improved on discharge on postoperative day five. No significant complicating factors were noted on postoperative MRI scan [Figure 4]. She then underwent adjuvant whole-brain radiation therapy. At her 12-month follow-up, the patient had residual weakness of her right upper extremity, a condition that had improved only slightly since surgery. She evidenced no progression of metastatic disease, and there was no

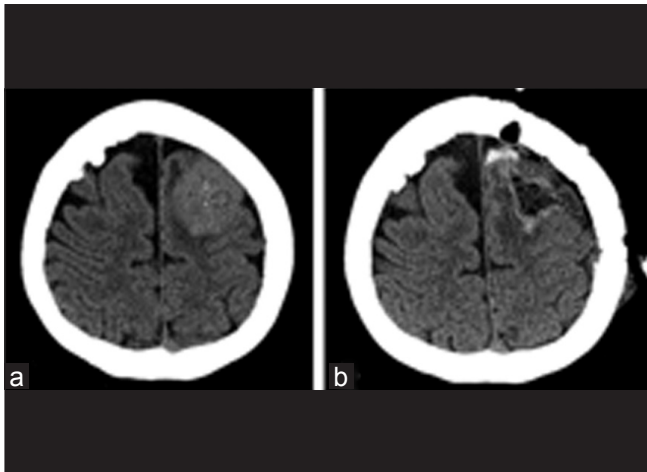


Figure 1: Precontrast axial CT scan showing a left frontal lobe lesion with surrounding edema (a), Postoperative precontrast axial CT scan status after left frontoparietal craniotomy showing a residual area of hypodensity in the operative bed caused largely by edema (b)

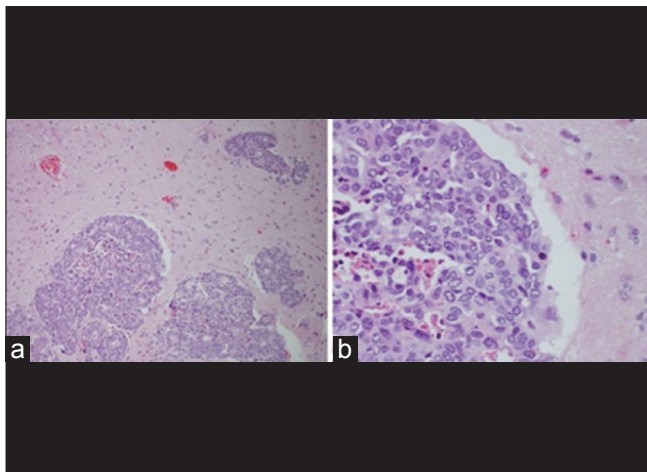


Figure 3: Groups of poorly differentiated papillary urothelial carcinoma cells invading into brain parenchyma. (a): ×100, (b): ×400

increase in the size of the residual tumor.

DISCUSSION

The first case of TCC metastasis to the brain was reported by Lower and Watkins in 1924, where they presented a 48-year-old male patient without a history of tobacco use. Complaining of irritative urinary symptoms, he was found to have hematuria and proteinuria in a physical examination, which had been required for obtaining life insurance. Shortly after a cystectomy was performed, and after pathological examination confirmed malignant transitional epithelial cells, the patient developed difficulty with ambulation and dysarthria. He was referred to the eminent neurosurgeon, Dr. Walter E. Dandy, who extirpated a solitary metastatic tumor measuring 2 cm from the right internal capsule. The

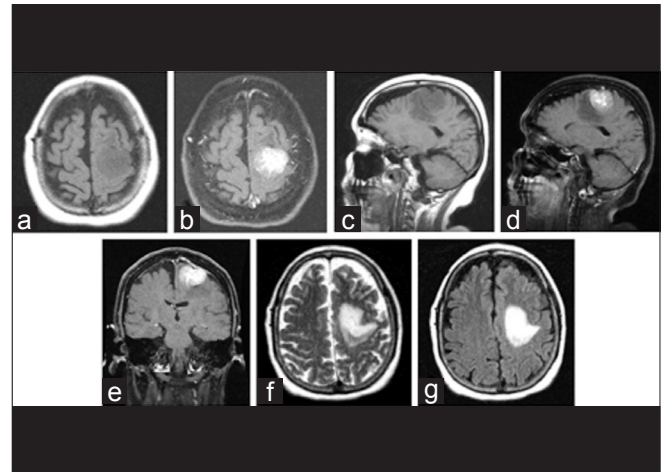


Figure 2: Precontrast axial T1-weighted MRI (a), postcontrast axial T1-weighted MRI (b), precontrast sagittal T1-weighted MRI (c), postcontrast sagittal T1-weighted MRI (d), coronal T1-weighted MRI (e), axial T2-weighted MRI (f), axial FLAIR image showing a solitary lesion with surrounding edema (g)

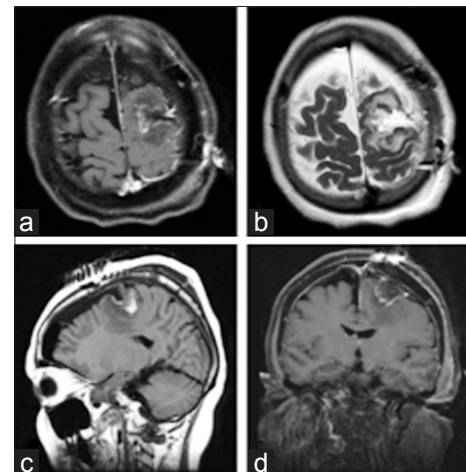


Figure 4: Postoperative precontrast axial T1-weighted MRI (a), Axial T2-weighted MRI (b), Sagittal T1-weighted MRI (c), Coronal T1-weighted MRI status after left frontoparietal craniotomy showing no significant complicating factors (d)

patient died 10 months later due to recurrence of brain metastases.^[56]

Historical incidences of TCC metastases have been low. In 1988, Graf reported four patients (1.7%) with brain metastases originating from urinary bladder cancer among the 230 cases of brain metastases taken from a sample of 15,000 autopsies between 1969 and 1984.^[33] Our review of the literature revealed 290 reported cases of TCC metastasis to the central nervous system [Table 1]. There are 54 case reports and small case series (up to three patients) reporting intracranial metastasis of TCC [Table 2]. Of these, the clinical presentation of central nervous system symptoms from intracranial metastasis preceded

Table 1: Incidence of transitional cell carcinoma of the urinary bladder to CNS metastatic sites

Metastatic site ^[Legend]	Total (n = 290) (%)	
Brain parenchyma ¹	231	79.7
Meninges ²	28	9.6
Spine ³	7	2.4
Orbital/ocular ⁴	24	8.3

1. [1,2,4,7,9,14,17,19,22,26,28,30,35,40,42,45,50,58,62,64,67,70,72,75,77,79,82,84,90,91,95,97,99,103-105]

2. [8,10-13,18,23,31,36,37,39,40,41,44,47,55,59,60,73,74,80,88,92,96,101]

3. [2,40]

4. [3,6,15,16,24,25,27,32,38,46,51,53,63,66,69,76,81,83,85,87,102,106]

the diagnosis of urinary bladder cancer in 11 cases (20.4%).^[12,14,17,19,29,40,44,71,74,78,82] The distribution among all cases tended to be skewed toward males and single or solitary lesions over multiple metastases. Metastasis to the frontal lobe seemed to be the most common location of single or solitary lesions, followed by the temporal and parietal lobes. The occipital lobe typically had the least number of metastases. Gross hematuria and irritative urinary symptoms were the most common presentations for urinary bladder cancer. Common neurologic symptoms in patients with TCC intracranial metastasis included headache, nausea, vomiting, speech impairment, ataxia, cognitive impairment, dizziness, and hemiparesis.

Treatment modalities for brain metastases consist of surgery, systemic chemotherapy, and radiation therapy in the form of whole-brain radiation or stereotactic radiosurgery. These treatment methods may be used alone or in combination. Reports from various authors demonstrate the differences among modalities for the treatment of TCC brain metastases [Table 3]. The largest series of patients with TCC brain metastases was reported in 2010 by Fokas *et al.*, who analyzed 62 patients and identified recursive partitioning analysis (RPA) I class (relative risk [RR]: 7.45; 95% confidence interval [CI]:2.27-24.41) and the lack of extracerebral metastases (RR: 1.90; 95% CI: 1.09–3.29) as the two most useful independent prognostic factors indicating overall survival for patients with TCC brain metastases.^[26]

The brain is postulated to act as a sanctuary site for metastatic tumor cells, since they are partially protected from systemic drugs by the blood–brain barrier (BBB) and blood–tumor barrier.^[65] It is then possible to understand why tumors that had rarely been known to spread to the brain previously are now more frequently acting as the first sign of secondary recurrence in patients treated with novel chemotherapy regimens. To further this point, Dhote *et al.* noted that brain metastases normally occur late in the natural course of advanced urinary bladder cancer, and the inability of the MVAC chemotherapy regimen (methotrexate, vinblastine, adriamycin/doxorubicin, cisplatin) to cross the BBB allows for systemic control of the disease, but leaves late

Table 2: Number of case reports and small case series (up to three patients) reporting intracranial metastasis of transitional cell carcinoma

Metastatic site ^[Legend]	Total (n = 54) (%)	
Cerebrum ¹	21	38.9
Meninges ²	24	44.4
Cerebellum	7	13.0
(single or solitary mets) ³		
Pituitary/sella ⁴	2	3.7

1. [4,9,14,17,20,28–30,35,42,62,64,70,78,90,95,97,99,103–105]

2. [8,10-13,18,23,31,36,37,39,40,41,44,47,55,59,60,73,74,80,88,92,96,101]

3. [19,22,40,50,67,82,90]

4. [71,75]

metastatic foci in the inaccessible brain.^[21] Thus, MVAC may increase the risk of metastatic disease in patients with prolonged remission.

Neurosurgeons may expect to see more cases of brain metastases from unusual sources as a result of increased survival rates from newer, more effective systemic chemotherapy regimens. With respect to the oncologic treatment of primary TCC, the MVAC chemotherapy regimen has conferred a survival advantage over the traditional single-agent cisplatin, reducing response rates, increasing duration of remission, and improving overall survival in patients with urinary bladder cancer.^[54] In 1989, Sternberg *et al.* reported 121 patients with advanced TCC who were treated with the MVAC chemotherapy regimen. Nineteen of the 121 patients (16%) developed brain metastases.^[91] Another 1998 study by Dhote *et al.* reviewed 50 patients with advanced TCC treated with the MVAC chemotherapy regimen and reported eight cases (16%) of intracranial metastases.^[21] These data suggest that the advent of more effective chemotherapy regimens has increased the incidence of brain metastases as secondary recurrences in patients with controlled primary or systemic urinary bladder cancer, since patients who achieve local and systemic control of their cancer may be living long enough to develop cerebral metastasis.

We report a case involving subtotal resection of a solitary cerebral TCC metastasis along the motor cortex of a 68-year-old female patient with a history of urinary bladder cancer 14 years prior. To the best of our knowledge, this case represents the first patient reported to develop isolated brain parenchyma relapse after treatment with gemcitabine for primary urinary bladder cancer, and the longest time interval between primary urinary bladder cancer diagnosis and development of TCC brain metastasis. The high metastatic potential of TCC of the urinary bladder is exemplified by our patient, who suffered multiple recurrences in the 5 years prior to presentation with cerebral metastasis. Given the aggressive nature of this tumor, one plausible explanation for TCC cerebral metastasis is early invasion of brain

Table 3: Primary cancer treatment, time interval from primary cancer diagnosis to cerebral metastasis presentation, and metastasis treatment from transitional cell carcinoma of the urinary bladder

Author	Year	n	Gender	Single or multiple brain metastases	Primary bladder carcinoma treatment	Interval from diagnosis to mets presentation	Brain metastasis treatment	Survival after mets diagnosis
Steinfeld <i>et al.</i> ^[90]	1987	2	Male: 2	Single	Case 1: surgery Case 2: surgery + RT	6 wk 10 yr	WBRT + steroids WBRT + steroids	8 wk N/R
Bloch <i>et al.</i> ^[9]	1987	2	Male: 2	Single	Case 1: surgery Case 2: surgery + chemo (T)	1 wk 8 yr	Surgery + WBRT Surgery + WBRT	4 mo 1 yr
Kabalin <i>et al.</i> ^[46]	1988	4	Male: 3 Female: 1	Single	Case 1: chemo (CMV) + RT Case 2: surgery + chemo (CMV) Case 3: surgery + RT + chemo (CMV) Case 4: surgery	11 mo 20 mo 15 mo 5 mo	No treatment Surgery + WBRT WBRT Surgery + WBRT	Several days Within 4 mo Within 4 mo 4 mo
Anderson <i>et al.</i> ^[11]	1992	9	Male: 6 Female: 3	Single: 7 Multiple: 2	Surg + RT: 5 Surg: 3 RT: 1	23 mo (mean) 9 mo (median) 2 wk-72 mo (range)	Surgery + WBRT: 3 pts WBRT: 5 pts Steroids: 1 pt	29 mo (mean) ¹ 7 wk (mean) 4 wk
Angulo <i>et al.</i> ^[4]	1992	2	Male: 2	Single: 1 Multiple: 1	Case 1: no treatment Case 2: no treatment	Synchronous presentation	None	N/R
Eng <i>et al.</i> ^[23]	1993	2	Male: 2	Multiple	Case 1: surgery + chemo (MVAC) Case 2: chemo (MC)	6 yr 2 yr	RT + steroids ABX	9 wk 1 mo
Rosenstein <i>et al.</i> ^[77]	1993	19	Male: 15 Female: 4	Single: 13 Multiple: 6	Chemo (MVAC)	N/R	Chemo (M) Surgery + RT: 7 pts RT: 10 pts	3 mo 19 mo (mean) 6 mo (mean)
Salvati <i>et al.</i> ^[79]	1993	6	Male: 4 Female: 2	Single	Surgery + RT: 4 Surgery + RT + chemo (MC): 2 Chemo (MVAC)	5.9 mo (mean) 1-13 mo (range) 21 mo (mean)	Surgery + WBRT Surgery + RT: 3 pts RT: 5 pts	N/R N/R 5.5 mo (mean) 4-25 mo (range) 7 mo (mean)
Dhote <i>et al.</i> ^[21]	1998	8	Male: 44 Female: 6	Single: 6 Multiple: 2	Chemo + RT + Surg: 5 Chemo + RT: 5 Surgery + RT: 3 Chemo (CMV or MVAC): 1 None: 2	7-38 mo (range) 8 mo (median) 0-69 mo (range)	Surgery + WBRT: 2 pts Surgery: 1 pt WBRT: 11 pts SRS: 1 pt	2.8 mo (mean) 7.75 mo (median) 1.25 mo 2 mo (median) 12 mo
Protzel <i>et al.</i> ^[70]	2002	1	Male: 1	Multiple	Surgery	2 yr	No treatment: 1 pt WBRT + chemo (G) WBRT: 3 pts	1.75 mo 15 mo 1 mo (median)
Anderson <i>et al.</i> ^[2]	2003	4	N/R	Single: 1 Multiple: 3	N/R	10 mo (median) 0-18 mo (range) ²		
Fokas <i>et al.</i> ^[26]	2010	62	Male: 31 Female: 31	16 < 3 mets 46 > 3 mets	N/R	35 < 16 mo 27 > 16 mo	RT + Surgery: 13 pts RT: 49 pts	9.6 mo (median) 8.9 mo (median)

wk: weeks, mo: month(s), yr: year(s), Chemo: Chemotherapy, RT: Radiation therapy, WBRT: Whole-brain radiation therapy, SRS: Stereotactic radiosurgery, ABX: Antibiotics, CMV: Cisplatin, methotrexate, vinblastine, MVAC: Methotrexate, vinblastine, adriamycin, cisplatin, MC: Methotrexate, cisplatin, G: Gemcitabine, M: Methotrexate, T: Thiotepa, mets: metastases, pt(s): patient(s), N/R: Not reported, ¹Two patients in this group were alive and disease-free at 60 months, ²Describes three patients only. The 4th patient's diagnosis of brain metastases preceded the discovery of the primary urinary bladder tumor

parenchyma by tumor cells that remain dormant.^[57] These micrometastases may then be activated at a later time, eventually forming macroscopic tumors. This process may serve as a contributing factor leading to cerebral metastasis, and is consistent with a “sanctuary effect,” providing the chemotherapeutic agents are truly impervious to the BBB.

Our case is unique, given the time span of 14 years from primary diagnosis of urinary bladder cancer in 1996 to presentation of the solitary brain lesion in 2010. The patient underwent a CT scan in 2008 that showed no evidence of brain metastases. A 1998 review of the literature for metastatic TCC presenting as a solitary brain lesion by Clatterbuck *et al.* reports the median time of development of brain metastases as 12 to 18 months, with a range from 2 weeks to 9 years.^[17] A 66-year-old male patient reported by Steinfeld in 1987 underwent transurethral resection of the urinary bladder, cystectomy, pelvic radiation therapy, and chemotherapy treatment with cyclophosphamide and platinum before developing cerebral metastasis 10 years after diagnosis of superficial urinary bladder cancer.^[90] In another case series published in 1987, Bloch reported a 51-year-old male patient who developed TCC of the urinary bladder and was treated with multiple transurethral resections and thiotepa intravesical chemotherapy, as well as nephroureterectomy. This patient developed a frontal lobe metastasis 8 years after his primary cancer diagnosis.^[9] We feel that our patient’s chemotherapy regimen of cisplatin with gemcitabine may have contributed to her long time interval from urinary bladder cancer diagnosis to clinical presentation of cerebral metastasis.

Gemcitabine is a deoxycytidine analogue chemotherapy agent with a broad spectrum of activity against several solid tumors, including non-small-cell lung cancer, breast and ovarian cancer, pancreatic cancer, and urinary bladder cancer.^[94] Gemcitabine plus cisplatin (GC) has replaced MVAC as the standard of care for patients with locally advanced and metastatic TCC. A 2000 randomized control study demonstrated a comparable survival advantage between patients with TCC urinary bladder cancer who were treated with GC or MVAC; however, a better safety profile and tolerability was observed in the GC group.^[98] It is important to note that this trial excluded patients with TCC central nervous system metastases. We are unaware of any prospective or randomized studies showing the effectiveness of GC in patients with TCC brain metastases. Interestingly, Fokas’ 2010 retrospective analysis failed to show any overall survival benefits to chemotherapy in patients treated for TCC with cerebral metastases.^[26] The type of chemotherapy regimen(s) used was not reported in the study.

Gemcitabine has shown differential uptake in brain tumors in rat experiments,^[5] and it has been used in

combination with radiation therapy for the treatment of TCC brain metastases with favorable results.^[70] Gemcitabine appears to be able to cross the BBB, ostensibly due to its low size and molecular weight, through the luminal membrane endothelial cells by the nucleoside transporter, ENT1.^[93] Treatment with GC for TCC of the urinary bladder may afford patients some protection against cerebral metastasis by reaching latent metastatic intracranial foci that have been otherwise unreachable, thus prolonging the time interval in which patients present with cerebral metastatic disease.

In light of the increasing incidences in brain metastases due to advances in chemotherapy potency, there may be a role in screening neuroimaging to detect asymptomatic brain metastases, but there is currently inconclusive evidence to support such efforts. Finally, the prudent surgeon should include intracranial TCC metastases in the differential diagnosis of patients presenting with neurologic symptoms and a history of primary urinary bladder cancer.

CONCLUSION

Brain metastases may present several years later in patients with TCC of the urinary bladder who have been treated with surgery and chemotherapy. Chemotherapeutic agents that penetrate the BBB, such as gemcitabine, may delay development of cerebral metastasis from primary TCC of the urinary bladder.

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