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Urological Cancer Metastasis to the Brain: When Should We Resect?

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ABSTRACT

Introduction: Although metastasis from urological malignancies to the brain occur late in the disease process and are typically associated with a poor prognosis, prolonged survival and excellent quality of life is achievable in a small, select population of patients. Surgical management has historically been utilized with large brain metastases, resulting in rapid increases in intracranial pressure and/or severe neurological deficits; however, the indications for surgical resection in the nonemergent setting are less clear.

Methods: The National Library of Medicine search engine PubMed was used to search for terms, including "brain metastasis, renal cell carcinoma," "brain metastasis, bladder cancer," "brain metastasis, prostate cancer," and "brain metastasis, nonseminomatous testicular germ cell tumors."

Results: Patients with renal cell carcinoma who typically have well circumscribed, firm radio and chemoresistant brain metastasis and patients with nonseminomatous testicular germ cell tumors who are generally younger with synchronous brain metastasis should be considered for aggressive surgical resection. Patients with brain metastasis from bladder or prostate cancer have a poor overall prognosis, and surgical resection is typically used only to improve quality of life, if not marginally extend survival.

Conclusion: Brain metastasis from urologic cancers are a late disease manifestation and surgical therapy is reserved for patients with a good Karnofsky Performance Status (> 70), minimal-to-no systemic disease, solitary large lesions (preferably > 3 cm), and those with a life expectancy of more than 3 months.

INTRODUCTION

Advances in chemotherapeutic regimens, surgical technique, imaging modalities, and multidisciplinary oncologic care have led to an increased life expectancy for patients with primary urologic malignancies [1-3]. Although metastases from urological

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Table 1. Published reports analyzing clinical outcomes following surgical resection among patients with brain metastases from renal cell carcinoma.
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Authors, year	N =	Age, years	Disease-free interval, months	Patients with solitary tumors, N = (%)	Median survival, months[b]
Wronski et al. [6] 1996	50	60[c]	17[c]	41 (82)	12.6
[a]Badalament et al [7] 1990	22	56[d]	30[c]	19 (86.4)	20.9
Shuch et al. [4] 2008	21/138	57[d]	16.2[d]	NR	10.7
Paek et al. [26] 2005	13/208	59[c]	NR	9 (69)	8
Shuto et al. [27] 2010	11	61 ± 7[d]	1.8[d]	8 (73)	9

Abbreviations: SD, standard deviation; NR, not reported
[a]Patients incorporated into Wronski et al. [6] (Memorial Sloan-Kettering Cancer Center)
[b]Following diagnosis of brain metastasis
[c]Median
[d]Mean

malignancies to the brain occur late in the disease process and are associated with a poor prognosis [2,4], prolonged survival with a reasonable quality of life is achievable for some patients. Surgical management, with the goal of relieving symptoms, has historically been utilized with large brain metastases that result in rapid, increased intracranial pressure and/or severe solitary neurological deficits.

This review seeks to critically analyze the literature regarding the surgical treatment of brain metastasis from renal cell carcinoma (RCC), bladder cancer, prostate cancer, and nonseminomatous testicular germ cell tumors (NSTGCT). We also discuss the feasibility and survival outcomes in the elective clinical setting.

RENAL CELL CARCINOMA

RCC accounts for > 90% of primary kidney tumors and has had an increased incidence of 58 000 cases per annum [5]. Current estimates of brain metastasis from RCC range from 2 to 17%. While such metastases are typically symptomatic with localizing and non-localizing signs (specific signs not specified), a study by Shuch et al. [4] reported that asymptomatic disease was present in up to ⅓ of all affected patients.

Wronski et al. [6] reported on 50 patients from the Memorial Sloan-Kettering Cancer Center treated between 1974 and 1993 that underwent surgical resection for metastatic brain lesions from RCC (Table 1). Among these patients were 38 men (median 60 years) and 12 women (median 62 years). Ten patients (20%) had synchronous onset of brain metastasis (< 60 days after the diagnosis of RCC) and 40 patients (80%) had metachronous brain metastasis (median onset of 17 months). The majority of patients presented with a single metastasis (N = 41, 82%). Five patients died within 30 days of resection (10%), and 14 patients (28%) had persistent neurological deficits or underwent reoperation. The median survival following surgical resection for all 50 patients was 12.1 months, while it was 12.6 months for the 45 patients who lived more than 30 days postoperatively. A second retrospective report by Shuch et al. [4] detailed the clinical outcome of 138 of 1 855 patients (7.4%) with RCC who developed brain metastasis and reported a mean disease-free interval (DFI) of 16.2 months. Thirty-seven patients (27%) presented with CNS metastasis at the time of RCC diagnosis and the majority of patients (N = 92, 68%) had solitary lesions, with a mean size of 1.83 cm (range 0.2 to 4.0 cm). Among these 138 patients, 21 patients (16%) underwent surgical resection with a mean tumor size of 2.2 ± 0.93 cm and achieved a median survival of 10.7 months.

Brain metastases from RCC are very uncommon. However, given that RCC is both radio and chemoresistant and that most RCC brain metastasis are well circumscribed and relatively firm, surgical resection remains the preferred therapy to achieve locoregional control [6]. RCC patients who develop brain

Table 2. Published reports analyzing clinical outcomes following surgical resection among patients with brain metastases from bladder cancer.
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Authors, year	N =	Age, years (mean ± SD)	Disease-free interval, months	Patients with solitary tumors, N = (%)	Median survival, months[a]
Fokas et al. [9] 2010	13	NR	> 16 months -7	NR	9.6
			< 16 months - 6	NR	
Rosenstein et al. [10] 1993	8/19	57 ± 11	NR	8 (100)	19[c]
Salvati et al. [2]	6	65 ± 8	6[b]	6 (100)	5.9
Mahmoud-Ahmed et al. [1] 2002	3	63 ± 10	18 ± 13[c]	1 (33)	2.8
Dhote et al. [28] 1998	3/8	56 ± 5	26[b]	NR	7
Anderson et al. [8] 1992	3/9	59 ± 5	9[b]	7/9 (78)	27

Abbreviations: SD, standard deviation; NR, not reported
[a]Following diagnosis of brain metastasis
[b]Median
[c]Mean

metastasis greater than 1 year following nephrectomy may be a unique subgroup with undetected tumors, and they may have a distinct survival advantage after resection, but additional data is needed [7]. Surgical resection for patients with RCC brain metastasis is indicated for patients who have controlled or minimal systemic disease; large (> 2 to 3 cm), solitary, and accessible tumors; and are in the setting of emergent clinical indications.

BLADDER CANCER

Bladder cancer is the fifth most common cancer in the US, with an incidence of 70 530 cases per year and approximately 14 680 deaths per year [5]. The precise incidence of brain metastases from bladder cancer is uncertain; however, more studies have reported a 1 to 3% rate [1,8]. Some authors have suggested that advances in new chemotherapeutic regimens, particularly the MVAC regimen (methotrexate, vinblastine, doxorubicin, and cisplatin), have resulted in prolonged disease remission [1,2] and may result in an increased incidence of brain metastasis, which is usually a late manifestation of bladder cancer. Table 2 details the only published reports for the treatment of brain metastasis from bladder cancer.

Fokas et al. [9] reported on 13 patients among a cohort of 62 patients who underwent surgical resection for brain metastasis from bladder cancer. All 62 patients had concomitant WBRT. Nine patients (70%) were < 61 years of age, 4 (31%) were ≥ 61 years of age, 6 (46%) had a DFI < 16 months, and 7 (54%) had a DFI ≥ 16 months. Surgical resection did not confer a survival advantage, as median overall survival was 9.6 months compared to 8.9 months in patients who did not have resection ($p < 0.70$). Rosenstein et al. [10] reported on 8 patients among a cohort of 19 patients (42%) with brain metastasis from bladder cancer who underwent surgical resection. These patients had a mean age of 57 ± 11 years. Seven of the 8 patients received concomitant WBRT, 6 of the 8 had a Karnofsky Performance Status (KPS) ≥ 80, and all had solitary tumors. In contrast to the report by Fokas et al. [9], Rosenstein et al. [10] reported that patients who underwent SR had a mean survival of 19 months compared to only 6 months for patients who did not undergo resection ($p < 0.001$). And finally, Salvati et al. [2] from La Sapienza University in Rome reported on 6 patients with solitary bladder brain metastasis who underwent SR and concomitant WBRT. The mean age was 65 ± 8 years and the median DFI was 6 months. All patients had a good functional status with a median KPS of 75; however, the median survival was 5.9 months with the progression of systemic disease being the cause of death in 5 of the 6 cases.

Table 3. Published reports analyzing clinical outcomes following surgical resection among patients with brain metastases from prostate cancer.
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Authors, year	N =	Age, years	Median Disease-free interval, months	Patients with solitary tumors, N = (%)	Survival[a]
Salvati et al. [13] 2005	10/13	64	45[c]	11/13 (85	10 months[b]
McCutcheon et al. [14] 1999	9	62 ± 11	25[b]	6 (67)	6 months[b]
Lynes et al. [29] 1986	2	60 ± 8	6[c]	2 (100)	pt 1: NED 60 months pt 2: DOD 9 months
Tsai et al. [30] 2001	2	63 ± 10	96 ± 68[c]	2 (100)	pt 1: NED 18 months pt 2: NED 12 months
Sweets et al. [31] 2009	1	48	48[b]	1 (100)	NED 60 months
Erasmus et al. [32]	1	70	0	1 (100)	DOD 4 months

Abbreviations: SD, standard deviation; NR, not reported; pt, patient; NED, no evidence of disease; DOD, dead of disease
[a]Following diagnosis of brain metastasis
[b]Median
[c]Mean

Surgical resection for brain metastasis from bladder cancer is a rare event, and it is difficult to analyze the impact since prognosis in all cases is ultimately poor. Despite this, it would appear that patients with solitary tumors and a good KPS (> 75) might be considered for surgery [10]. Patients with multiple lesions are not surgical candidates unless they are experiencing emergent neurologic symptoms that are otherwise not manageable [9,10]. Regardless of the treatment chosen, brain metastasis from bladder cancer is one of the most highly resistant primary cancers to treat, and palliative care is usually the best option for most patients [11].

PROSTATE CANCER

Although prostate cancer is currently the most common malignancy among men in the USA with an annual incidence of almost 250 000 cases [5], brain metastasis from prostate cancer is rare, occurring in only 0.5 to 0.6% of affected men [12]. Some have suggested that the brain may be unusually resistant to metastatic spread from primary prostate cancer [12]. Only 6 reports of brain metastasis for prostate cancer have been published, including 4 studies reporting on only 1 or 2 patients (Table 3).

Salvati et al. [13] have published the largest surgical study to date on prostate cancer brain metastasis, involving 13 patients, 10 of whom (77%) underwent surgical resection and WBRT. The mean age of all patients was 64 years. Eleven of 13 patients (85%) had solitary metastasis, and the reported medial survival for all patients was 10 months. McCutcheon et al. [14] reported on 38 of 7 994 patients (0.5%) with prostate cancer who also had concurrent brain metastasis. Twelve patients (32%) had solitary lesions and 9 patients (mean age 62 ± 11 years) underwent surgical resection, 8 of whom also received WBRT (indications not specified). The median DFI for this cohort was 25 months, among the 6 patients who had solitary brain lesions. The overall median survival among all 9 surgical patients was 6 months.

Brain metastasis from prostate cancer represents a late manifestation of disease with a poor prognosis, even after surgical resection [13,14]. Salvati et al. [13] have noted that death is typically the result of systemic disease in patients with brain metastasis, and that treatment of brain disease usually results in disease control and a decreased susceptibility to brain relapse. Surgical therapy for prostate cancer brain metastasis, while not conferring a survival advantage, may improve the overall quality of life for symptomatic patients [13].

Table 4. Published reports analyzing clinical outcomes following surgical resection among patients with brain metastases from nonseminomatous testicular germ cell tumors.
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Authors, year	N =	Age, years	Median Disease-free interval, months	Patients with solitary tumors, N = (%)	Survival[a]
Fossa et al. [17] 1999	synchronous - 10/56	27[b]	0	7 (70)	SR: 2-year OS 80% no SR: 2-year OS 49%
	metachronous - 25/83	29[b]	9	NR	SR: 2-year OS 40% no SR: 2-year OS 4%
Salvati et al. [18] 2006	15	34 ± 11[c]	NR	7 (47)	37.7 months[c] 5-year OS 53%
Bokemeyer et al. [16] 1997	6	27[b]	16	NR	SR - 3 months
					SR + WBRT + Chx - 144 months[b]
Nonomura et al. [15] 2009	5	28 ± 6[c]	NR	4 (80)	95 months[b]
Mahalati et al. [33] 1999	4	27 ± 6[c]	NR	3 (75)	22 months[b]
Spears et al. [34]	3	28[b]	10	3 (100)	pt 1: NED 75 months pt 2: DOD 4 months pt 3: NED 84 months

Abbreviations: SD, standard deviation; NR, not reported; pt, patient; DSS, disease specific survival; OS, overall survival; SR, surgical resection; WBRT, whoe brain radiation therapy; Chx, chemotherapy; pt, patient; NED, no evidence of disease; DOD, dead of disease
[a]Following diagnosis of brain metastasis
[b]Median
[c]Mean

NONSEMINOMATOUS TESTICULAR GERM CELL TUMORS

Testicular cancer is the most common malignancy in young men (ages 15 to 35), with an incidence of approximately 8480 new cases per year in the US [5,15]. The International Germ Cell Cancer Collaborative Group have noted that brain metastasis from NSTGCT occurs in 1 to 2% of affected patients, with an incidence of 10 to 15% in those with advanced NSTGCT [16,17]. Although NSTGCT is primarily chemosensitive, most chemotherapeutic drugs do not cross the blood-brain barrier, leaving brain metastasis uninhibited [15]. As a result, while the overall survival rates for patients with testicular cancer continues to improve with 5-year overall survival estimates of 70 to 80% [12], those who develop brain metastasis have a diminished 5-year overall survival of only 33 to 36% [15-17]. Only 6 studies on NSTGCT have been published, including 2 with more than 15 patients (Table 4).

In the largest published series to date, Fossa et al. [17] reported on 139 patients with brain metastasis from malignant germ cell tumors, 16 of which originated in the testis (83.5%). Among these patients, 56 (40.3%, median age 27 years old) presented with synchronous brain metastasis, and 83 (59.7%, median age 29 years old) presented with metachronous brain metastasis. Ten patients (17.9%) with synchronous metastasis (7 solitary lesions) underwent surgical resection and experienced a 2-year overall survival of 80% compared to 49% for 46 patients who did not undergo surgery (reason for who received and did not receive surgical treatment was not reported) ($p < 0.021$). Twenty-five patients (30.1%) with metachronous brain metastasis underwent surgical resection with a DFI of 9 months. Among these patients, the 2-year overall survival was 40% for patients who underwent surgical resection compared to 4% for

the 58 patients who did not undergo resection ($p < 0.0001$). Salvati et al. [18] recently analyzed 15 patients with NSTGCT brain metastasis, with a KPS score > 60 on admission and a life expectancy of more than 3 months. The mean age was 34 ± 11 years of age and 7 patients (47%) had solitary metastases. Among these patients, 6 (86%) of the 7 patients were alive for > 60 months compared to only 2 (25%) of 8 patients with multiple lesions. Salvati et al. [18] reported an overall mean survival time of 37.7 months and a 5-year survival rate of 53%. Given the young age of the population generally affected with NSTGCT, aggressive treatment is typically pursued. Surgical resection of NSTGCT brain metastasis is recommended for patients with a good KPS, isolated disease, favorable DFI, and life expectancy > 3 months.

Patients with NSTGCT brain metastasis and multiple lesions have a worse overall survival compared to patients with solitary lesions; however, they too may benefit from surgical resection if life expectancy exceeds 3 months, the lesions are amenable to resection and surgery, and it may improve quality of life. Given a tendency for these tumors to bleed, chemotherapy is often withheld until metastasectomy is performed [18].

FUTURE PROSPECTS FOR TREATMENT

In addition to surgical resection of urological cancer metastasis to the brain, a number of recent radiologic developments have advanced care for these patients. Whole-brain radiation therapy (WBRT) has been advocated concomitantly with surgical resection and may be beneficial as primary therapy for patients with unresectable and/or widespread metastatic disease [19]. Stereotactic radiosurgery (SRS) has also been recommended in patients with multiple brain metastases, in addition to patients with incidentally identified, asymptomatic brain lesions [20]. Radiologic advancement also continues to provide alternative and minimally invasive modalities for treating urological malignancies. Proton beam therapy has recently been advocated for use in prostate cancer treatment [21], in addition to cryotherapy [22] and high-intensity focused ultrasound (HIFU) [23]. Furthermore, cryotherapy, HIFU, and radiofrequency ablation continue to expand the management of RCC [24] and testicular tumors [25].

CONCLUSION

Brain metastases represent a late manifestation of urological cancers and are associated with a poor prognosis as the majority of patients have concurrent extracranial metastases that ultimately prove fatal. However, certain patients with RCC (circumscribed, firm, radio and chemoresistant tumors) and NSTGCT (who are typically young patients with synchronous metastasis) should be considered for aggressive surgical resection of their brain metastases. Patients with brain metastasis from bladder or prostate cancer have a poor overall prognosis, and surgical resection is typically used emergently or to improve quality of life since it only appears to marginally extend survival, if at all. In general, brain metastases from urologic cancers are a late disease manifestation and surgical therapy is reserved for patients with a good KPS (> 70), minimal to no systemic disease, solitary large lesions (preferably > 3 cm), and those with a life expectancy of greater than 3 months.

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