American Journal of Transplantation 2004; 4: 15–21
Blackwell Munksgaard

doi: 10.1046/j.1600-6143.2003.00289.x

Minireview

Organ Donors with Malignant Gliomas: An Update

Federic P. Collignon[a], Eric C. Holland[b] and Sandy Feng[c,*]

[a] *Department of Surgery, (Division of Neurosurgery),*
[b] *Departments of Surgery (Division of Neurosurgery), Neurology, and Cancer Biology and Genetics, Memorial Sloane Kettering Cancer Center, New York, NY,*
[c] *Department of Surgery, University of California San Francisco, San Francisco, CA, USA*
**Corresponding author: Sandy Feng, fengs@surgery.ucsf.edu*

The escalating shortage of organs motivates frequent reconsideration of concepts that guide the decision to accept or decline organs from donors with central nervous system (CNS) malignancy. Currently, a minority of patients who die annually of CNS malignancies are organ donors. Specifically, the organs of less than 0.5% of the 13 000 patients dying from glioma are procured and transplanted every year in the United States. This review seeks to clarify the risk of cancer transmission from transplantation of organs from donors with glioma. After considering historical precedence, we will systematically outline the clinical features of a potential organ donor with glioma that might reflect upon the risk of cancer transmission. We will then present recent knowledge regarding basic glioma biology that speaks to their metastatic potential and suggest rational strategies for the post-transplant management of recipients of organs from donors with glioma.

Key words: CNS tumor, glioma, malignancy, organ donor, tumor transmission

Received 30 May, revised 11 August and accepted for publication 24 August 2003

The ever-widening disparity between the supply of and the demand for transplantable organs has led to a reconsideration of previously suggested and accepted guidelines regarding the transplantation of organs from donors with a known malignancy. The transplantation community has evolved a practice whereby donors with a known history of malignancy are generally excluded except for those with low-grade skin cancers and primary tumors of the central nervous system (CNS). There is, however, within the area of primary brain tumors, controversy as to the suitability of donors with gliomas in general and glioblastoma multiforme (GBM) in specific. This review seeks to clarify from several different perspectives the risk of cancer transmission from transplantation of organs from donors with glioma. First, we will summarize and synthesize the existing literature regarding transmission risk. Next, we will delineate the presentation, evaluation, diagnosis, treatment, and natural history of gliomas which will help a transplant physician or surgeon assess the risk associated with a particular donor. Finally, we will present new insights regarding basic glioma biology that color our understanding of their metastatic potential and that may suggest alternative management strategies for recipients of organs from donors with glioma.

Histologic Classification of Gliomas

Gliomas are a family of tumors that arise from glia or their progenitors. Glia are specialized connective tissue cells of the CNS and are divided into oligodendrocytes and astrocytes (Table 1). Oligodendrocytes produce myelin that insulate the neuronal axons, while astrocytes provide the scaffold that maintains the brain structure and that supports the functions of both neurons and oligodendrocytes. Astrocytomas can be divided into four clinical grades with the most aggressive – grade 4 – referred to as GBM. Classification is based on nuclear pleomorphism, mitosis, endothelial proliferation and necrosis (1). Gliomas with pure oligodendroglioma features do not typically reach grade 4 status (Table 2).

Risk of Cancer Transmission from Donors with CNS Tumors

From the transplantation perspective, the critical question is to what extent do occult metastatic glioma cells exist either in the circulation or in transplantable organs that can give rise to systemic glioma in immunosuppressed organ recipients. There are two primary sources of information regarding the risk of transmission of primary CNS malignancy through organ transplantation: individual case reports and registry data. Unfortunately, both of these data sources are likely incomplete in either the numerator and/or the denominator, resulting in under- or over-estimation of transmission risk. When reviewing the data *in toto*, one must remember that practice has definitely evolved over time. For example, it is well-known that organs from donors with active cancer and even organs with locally excised tumor were transplanted in the early days of transplantation. The high rate of transmission to recipients with resultant

Table 1: Histologic classification of common primary central nervous system tumors and their proposed cells of origin

Cell of origin	Tumor type	Grade/tumor subtype
Glial	Oligodendroglioma	Grade 2: Low grade
		Grade 3: Anaplastic
	Astrocytoma	Grade 1: Pilocytic
		Grade 2: Low grade
		Grade 3: Anaplastic
		Grade 4: Glioblastoma; variants: gliosarcoma and giant T-cell glioblastoma
	Mixed glioma	Grade 2 or 3 having features of both astrocytoma & oligodendroglioma differentiation
Neuronal	Medulloblastomas	
	Neuroblastomas	
	Esthesioneuroblastoma	

Table 2: Clinical grades of astrocytic gliomas and their histologic criteria

Grade	Designation	Histologic criteria[1]
1	Pilocytic astrocytoma	Rosenthal fibers, piloid cells; no criteria
2	Diffuse astrocytomas	One criterion, usually nuclear atypia
3	Anaplastic astrocytomas	Two criteria, usually nuclear atypia and mitosis
4	Glioblastoma multiforme	Three or four criteria; the two above plus endothelial proliferation and/or necrosis

[1]Four criteria are used to score the tumors: nuclear atypia, mitoses, microvascular proliferation, and pseudopalisading necrosis.

morbidity and even mortality changed practice dramatically, engendering our current cautious approach to donors with cancer. Although donors with primary CNS tumors have historically been regarded as suitable, cumulative data suggesting that aggressive interventions (craniotomy and ventricular shunting) and/or unfavorable histology (GBM and medulloblastoma) may pose a prohibitive transmission risk has refined our practice over time (2–4).

The published data demonstrating the risk of glioma transmission to organ recipients are sparse. From 1987 to the present, the literature has eight case reports of CNS cancer transmission involving seven donors (GBM = five; medulloblastoma = one; malignant meningioma = one; 5–12). Twenty organs were transplanted into 19 recipients (one recipient underwent simultaneous kidney-pancreas transplantation). Eleven recipients developed donor-transmitted cancer with five tumor-associated deaths. Notably, all liver (n = 3) and heart (n = 1) recipients with evidence of donor-transmitted cancer died. The other reported death was the kidney-pancreas recipient. All six survivors were kidney recipients who underwent nephrectomy with cessation of immunosuppression. Among these donors, five had GBM, corresponding to 15 transplanted organs (three livers, 10 kidneys, and two hearts) with seven cases of GBM transmission (three liver and four kidney recipients). All three liver recipients died while all four kidney recipients remain alive after nephrectomy and cessation of immunosuppression. Case reports comprise the numerator; unfortunately, the relevant denominator is entirely unknown.

Three registries have recently provided data regarding cancer transmission from organ donors with primary CNS tumors. In 2002, the United Network for Organ Sharing (UNOS) Transplant Tumor Registry reported on 397 donors (1/1/92–12/31/99) with history of CNS tumor or CNS tumor listed as the cause of death (13). Unfortunately, histologic diagnosis was available for only 30 of these donors (7.5%); 17 donors had GBM and two had medulloblastoma. No case of donor-transmitted tumor was identified in the 1220 recipients with mean follow up of 36 months (range 0–111 months) (13). In 1999, the Australian and New Zealand Organ Donation Registry reported on 46 donors with primary CNS tumors (1/89 12/96) of whom 28 had malignant tumors (four unspecified glioma, four GBM, 10 unspecified astrocytoma, five medulloblastoma, one malignant meningioma and four unspecified tumors) (14). None of 151 recipients with mean follow up of 40 months (range 1–96 months) demonstrated evidence of donor tumor transmission. In 1997, however, the Israel Penn International Transplant Tumor Registry (IPITTR) reported on 46 donors (1969–97) with primary CNS tumors with very different results (15). Eight donors transmitted tumor to 10 of 55 possible recipients for an incidence of nearly 18%. The reason for this apparent discrepancy is unclear but the broad timespan of the IPITTR data compared with that reported by the other two registries may explain the substantially different risk attributed to transplantation of organs from donors with primary CNS malignancy.

Presentation, Diagnosis and Treatment of Malignant Gliomas

Approximately 17 500 primary CNS neoplasms occur annually in the United States, accounting for 1.4% of all tumors and 2.3% of cancer-related deaths (16). The majority of gliomas are malignant and comprise of anaplastic

astrocytomas and GBMs. They are estimated to occur 10-fold more commonly in adults than in children. While they comprise up to 86% of newly diagnosed primary CNS tumors in the adult population (aged 35–64 years) (17), they constitute only 6–12% of primary CNS tumors in children (18). The percentage of gliomas that are GBMs correlate with advancing age. The majority of anaplastic astrocytomas and GBMs are supratentorial. Many grow to considerable size before they produce symptoms, typically headache, neurological deficits, and seizure. Radiographically, administration of intravenous contrast can show, in increasing order of frequency, no tumor enhancement, irregular enhancement, or diffuse enhancement. *As enhancement indicates leakage of intravenous contrast into the tumor, it signals disruption of the blood–brain barrier*. The incidence and pattern of contrast enhancement correlate with but are not always indicative of malignant grade. Magnetic resonance imaging (MRI) provides optimal tumor localization and characterization and has largely superseded computed tomography in both diagnostic and follow-up imaging of astrocytomas and GBMs. T1- and T2-weighted MRI images can demonstrate the frank tumor as well as surrounding edema and/or infiltrating tumor cells (Figure 1). The migratory and infiltrative nature of these tumors suggested radiographically has been substantiated histologically. Studies have documented the presence of tumor cells not only in the normal brain tissue immediately surrounding GBM tumors but also in distant brain tissue such as the contralateral hemisphere (19).

Treatment for gliomas begins with surgical resection if possible (usually) with a goal of removing the contrast-enhancing lesion which represents the frank tumor (Figure 1C). The residual infiltrating tumor cells are then treated by radiation followed commonly in the United States but rarely in Europe by chemotherapy. For tumors that are not surgically resectable, a biopsy is usually obtained for tissue diagnosis followed by radiation and chemotherapy.

Prognosis

In the United States, approximately 13 000 patients die of GBM annually: 15% or approximately 2000 annually are less than 45 years old; 58% or approximately 7500 are less than 65 years old (20). Currently, the Organ Procurement and Transplantation Network/UNOS data indicates that organs are procured from approximately 50–60 patients with primary CNS tumors annually, representing approximately 1% of the donor pool. GBMs are essentially 100% fatal; about half result in death within 1 year of diagnosis. Most GBMs arise *de novo* on first presentation (primary GBM), while a smaller number progress from lower-grade astrocytomas (secondary GBM). Primary GBMs typically occur in older patients, for whom there is a short history of symptoms. Secondary GBMs typically occur in younger patients who often have a long history (3–10 years) of symptoms. Progressive accumulation of genetic defects transforms a low-grade astrocytoma (grades 1 or 2) to an anaplastic astrocytoma (grade 3), and finally to a GBM (grade 4). As the rate of progression correlates directly with age, older patients progress more rapidly, resulting in shorter survival.

Glioma Invasion and Metastasis

End-stage GBM patients become progressively comatose and typically die of respiratory failure/sepsis. This clinical

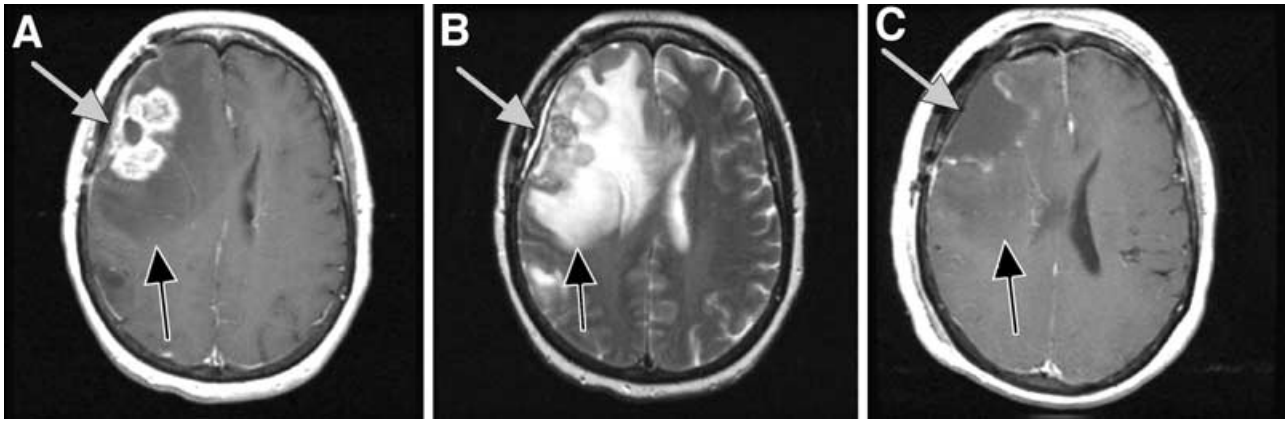

Figure 1: Pre- and postoperative MRI images of glioblastoma multiforme (GBM) tumor. (A) Pre-operative T1-weighted MRI scan of GBM tumor. The area of contrast enhancement (grey arrow) corresponds to frank tumor with disruption of the blood–brain barrier. The surrounding brain tissue into which GBM cells are invading is clearly edematous (black arrow). (B) Pre-operative T2-weighted MRI scan of the same tumor. In this series, the frank tumor (grey arrow) and the surrounding brain tissue with edema and invading tumor cells (black arrow) are both bright. Note that the abnormal signal area extends across the corpus callosum into the contralateral hemisphere. (C) Post-operative T1-weighted MRI scan. The region of frank tumor has been resected resulting in the absence of contrast enhancement (grey arrow) but residual areas of edema and residual infiltrating tumor remain (black arrow).

deterioration parallels massive tumor spread throughout the brain. The primary mechanism of spread for gliomas and specifically GBMs is clearly different from that of other cancer types. Unlike the hematogenous or lymphatic spread of cells from their primary location to metastatic sites, they spread throughout the brain as individual cells. Glioma cells migrate along white matter tracks, encircle neurons and blood vessels and pile up at the edge of the brain in the sub-pial space – collectively referred to as the Secondary Structures of Scherer (Figure 2). This migratory mode of metastasis appears to recapitulate the behavior of glial precursors as they migrate throughout the brain during normal CNS development (21). Several lines of molecular evidence support the notion that glial biology is driven by abnormalities in cellular differentiation status. First, gliomas exhibit a pattern of gene expression which mirrors that of glia. Second, several growth factors that regulate glial differentiation during normal CNS development (22,23) activate signaling pathways in gliomas that promote growth. In mouse models, experimental elevation of these signaling pathways can induce dedifferentiation of astrocytes and precipitate the formation of gliomas.

Although gliomas characteristically spread throughout the brain, they occasionally metastasize out of the central nervous system predominantly to the lung, pleura, lymph nodes, bone and liver at an estimated frequency of 0.4–2.3% (24). Traditionally, the infrequency of distant metastases has been attributed to the function of the blood–brain barrier and/or the short life-expectancy of affected individuals, which has not changed appreciably in the last few decades (3,4). Reports have identified craniotomy, ventriculo-peritoneal shunt, history of irradiation, and long interval between primary therapy and disease relapse (potentially correlating with secondary GBM) as risk factors for extraneural spread of malignant CNS tumors in general and especially GBM in particular (24). The mechanism for metastasis, although unknown, is believed to be hematogenous dissemination, as the brain has no lymphatics. Two important facts, however, make the rarity

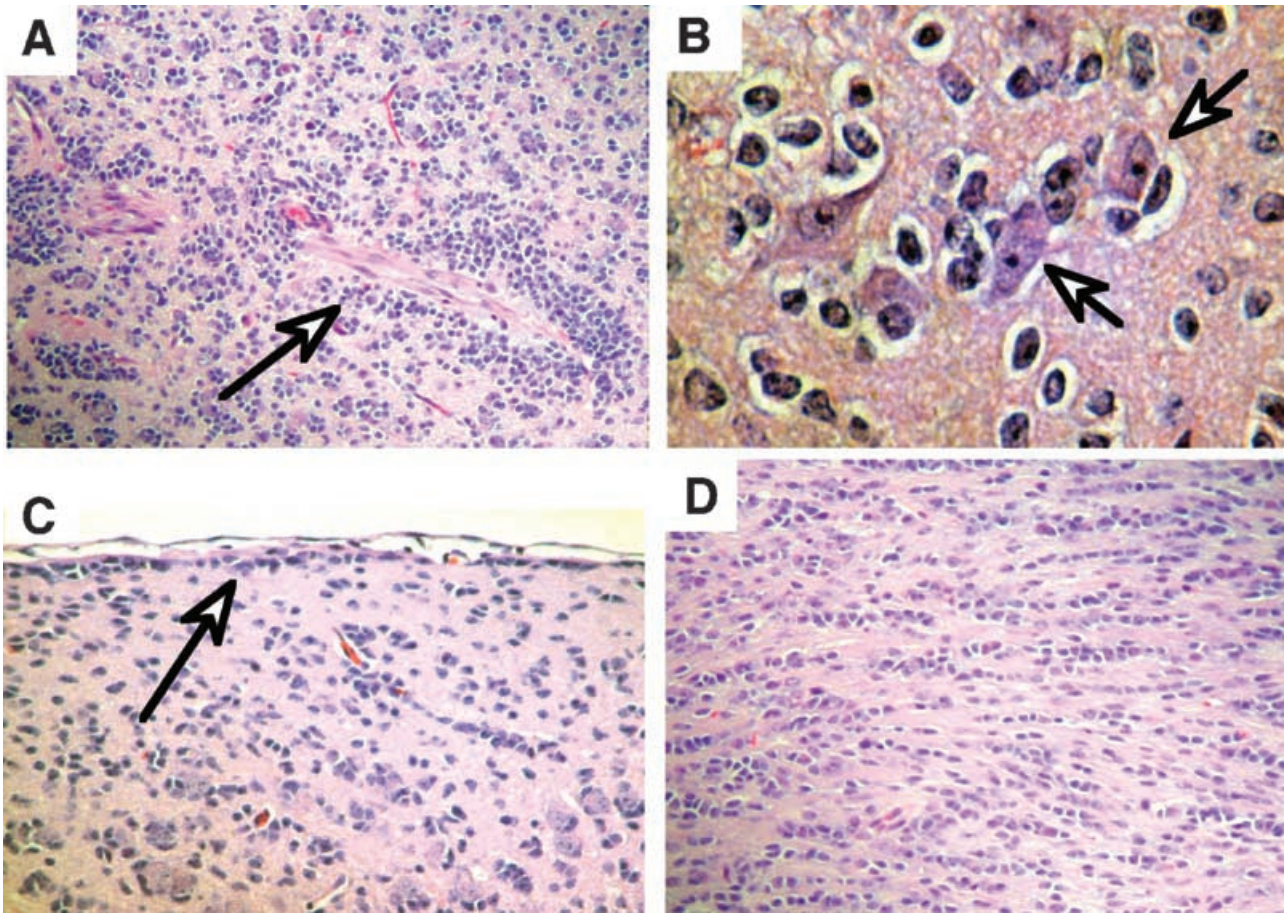

Figure 2: Histologic features of glioma invasion into normal brain structures. Photomicrographs showing invading glioma cells (A) encircling blood vessels, (B) encircling neurons, (C) collecting at the edge of the brain in the sub-pial space, and (D) migrating along white matter tracts.

of metastatic GBM disease somewhat surprising. First, the blood–brain barrier is in fact disrupted in nearly all GBMs by the nature of the tumor's growth as evidenced by tumor enhancement by intravenous contrast on radiographic examination. Second, the vast majority of patients undergo craniotomy for resection followed by radiation – both risk factors associated with metastasis – although few develop hydrocephalus and require shunting. A developmental view might explain this apparent contradiction: glioma cells rarely migrate outside the CNS because this behavior is simply not part of the developmental program of glial precursors.

Cellular Pathways to Malignancy and Potential Clinical Repercussions

Interestingly, some of the new findings regarding glioma biology suggest a potential pharmacological strategy to curtail tumor growth and metastatic potential. Gliomas exhibit substantially elevated activity of signaling pathways downstream of growth factor receptors (23) (Figure 3). Specifically, the activity of Ras and the Erk MAP kinase are elevated in all GBMs tested (22). Furthermore, 70% of GBMs exhibit hyper-elevated activity of Akt and its downstream component, mTOR (mammalian target of rapamycin) (25). The causative nature of these findings is illustrated by the fact that combined transfer of activated Ras- and Akt-signaling induces GBMs in mice (13). Elevated Akt activity is thought to promote survival of tumor cells in inhospitable environments (26), as potentially represented by environments outside of the CNS for glioma cells. Inhibition of these critical pathways may therapeutically prevent growth and/or metastasis of GBM tumors. Currently, there are ongoing studies in mice and humans to evaluate the impact of rapamycin and/or its analogs – drugs that function molecularly to block mTOR activity – against GBM tumors. Precedence has been set, as rapamycin analogs have been shown to be effective in therapeutic blockade of tumor cell types with pathologically elevated Akt levels (27). If indeed mTOR blockade exerts powerful anti-GBM tumor effects, then the potential benefits of rapamycin-based immunosuppression strategies for the transplant recipient of organs from donors with GBM should be explored.

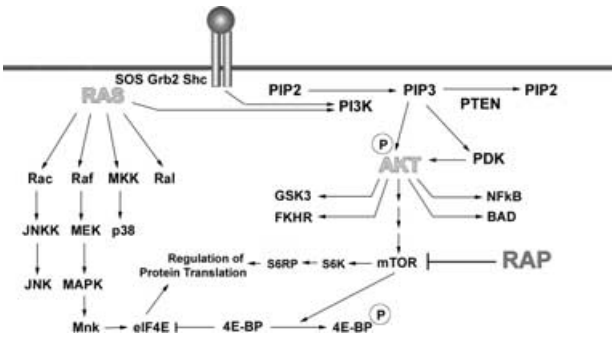

Figure 3: Signal transduction pathways abnormally active in glioblastoma multiformes (GBMs). Signal transduction pathways downstream of growth factors are shown. Ras is hyperactive in all GBMs while Akt and its downstream components are active in 70% of these tumors. Rapamycin (Rap) inhibits mTOR (mammalian target of rapamycin), which is critical to these pathways.

End of Life and Ethical Issues

The above review presents new details of glioma biology that contribute to the ongoing debate of whether it is safe and/or prudent to transplant organs from donors with glioma. Although there are a substantial number of deaths annually from malignant gliomas, it is worthwhile to pause and delineate the typical paths by which glioma patients die. Three courses can be identified, listed in order of increasing frequency:

1 A sudden and acute intracranial event such as hemorrhage with rapid neurological deterioration resulting in brain death in a hospital setting.
2 More gradual disease progression resulting in loss of consciousness and compromised airway protection leading to death from respiratory insufficiency/sepsis in a hospital setting. Typically, the patient and/or family has decided to forego aggressive resuscitation measures including intubation
3 Similar to the preceding course but the patient dies outside of the hospital, usually at home and/or with hospice care.

The first path, which can lead directly to organ donation in situations of family consent, is however, the path least traveled by glioma patients. Reluctance to utilize such organs on the part of the transplant community may represent the primary limitation to increasing the number of transplants resulting from such cases. Some of the glioma patients that travel the intermediate path may represent a second potential source of organs. For the intubated patients with grim prognosis whose families decide to withdraw support, organ donation may proceed according to protocols for nonheart-beating donors. However, for the nonintubated patients whose families decide to provide predominantly comfort care, the difficulty in predicting the timing of death and the frequent presence of infectious contraindications complicate the possibility of organ donation. The third and unfortunately the most traveled path by glioma patients clearly does not lead to organ donation as these patients similarly die in an uncontrolled setting frequently of overwhelming and untreated infection.

Conclusions

Transplantation of organs from donors with cancer in general and gliomas in specific always carry an additional risk,

that of cancer transmission. For any individual transplant candidate at the 'top of the list', the option of receiving the next organ from a donor without cancer may be most prudent in all but the most urgent of circumstances. However, the increasingly critical organ shortage demands that we as a community reassess our thresholds for acceptable risk, particularly as there are candidates that are not at the 'top of the list' whose lives would be saved by transplantation. We have outlined the clinical presentation, the natural history, and, most importantly, the recent developments in the understanding of glioma biology to provide a modern context for reconsideration of tumor transmission risk. Historically, the infrequent metastasis of gliomas has been attributed to the natural history of the tumor and the blood–brain barrier. Identified risk factors for tumor transmission have been GBM histology and therapeutic interventions such as craniotomy or ventricular shunting, presumably secondary to disruption of the blood–brain barrier. However, clinically, we now recognize that radiographic contrast enhancement signifies loss of blood–brain barrier integrity and that major craniotomy is widely prevalent as it is first line therapy for glioma. Biologically, we now understand that the migratory pattern of glioma growth and metastasis recapitulates the developmental program of glial precursors that does not include travel outside of the CNS. The occurrence of glioma metastases, however, may correlate with hyperactivity of critical signaling pathways. We hypothesize that the molecular signature of a GBM tumor may simultaneously stratify risk of metastatic potential and suggest efficacious pharmacologic antitumor strategies. While data to substantiate these intriguing and exciting hypotheses remain a promising horizon, we are faced today with a critical and compelling organ shortage. As members of the transplant community, we simply can no longer afford to refuse the organs of donors with glioma without thoughtful consideration. While case reports and registry data have certainly documented transmission of gliomas with resultant morbidity and even mortality, the loss of quality and quantity of life by those on the waiting list remains a staggering and sobering reality.

Acknowledgments

This collaborative review was a product of the 3rd Annual American Society of Transplant Surgeons' Winter Symposium entitled 'Tumors and Transplantation'. We wish to thank the Seroussi and Bressler Foundations for support (ECH).

References

1. Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumors. Brain Pathol 1993; 3: 255–68. Review.
2. Fecteau AH, Penn I, Hanto DW. Peritoneal metastasis of intracranial glioblastoma via a ventriculoperitoneal shunt preventing organ retrieval. Case report and review of the literature. Clin Transplant 1998; 12: 348–350. Review.
3. Healey PJ, Davis C. Transmission of tumours by transplantation. Lancet 1998; 4: 2–3.
4. Hoffman HJ, Duffner PK. Extraneural metastases of central nervous system tumors. Cancer 1985; 56: 1778–1782.
5. Bosmans JL, Ysebaert D, De Cock AM et al. Interferon-alpha and the cure of metastasis of a malignant meningioma in a kidney allograft recipient: a case report. Transplant Proc 1997; 29: 838.
6. Colquhoun SE, Robert ME, Shaked A et al. Transmission of CNS malignancy by organ transplantation. Tranplantation 1994; 57: 970–974.
7. Frank S, Muller J, Bonk C, Haroske G, Schackert HK, Schackert G. Transmission of glioblastoma multiforme through liver transplantation. Lancet 1998; 352: 31.
8. Jonas S, Bechstein WO, Lemmens HP, Neuhaus R, Thalmann U, Neuhaus P. Liver graft-transmitted glioblastoma multiforme. A case report and experience with 13 multiorgan donors suffering from primary cerebral neoplasia. Transplant Int 1996; 9: 426–429.
9. Lefrancois N, Touraine JL, Cantarovich D et al. Transmission of medulloblastoma from cadaver donor to three organ transplant recipients. Transplant Proc 1987; 19: 2242.
10. Morse JH, Turcotte JG, Merion RM, Campbell DA, Burtch GD, Lucey MR. Development of a malignant tumor in a liver transplant graft procured from a donor with a cerebral neoplasm. Transplantation 1990; 50: 875–877.
11. Ruiz JC, Cotorruelo JG, Tudela V et al. Transmission of glioblastoma multiforme to two kidney transplant recipients from the same donor in the absence of ventricular shunt. Tranplantation 1993; 55: 682–683.
12. Val-Bernal F, Ruiz JC, Cotorruelo JG, Arias M. Glioblastoma multiforme of donor origin after renal transplantation: report of a case. Hum Pathol 1993; 24: 1256–1259.
13. Kauffman HM, McBride MA, Cherikh WS, Spain PC, Delmonico FL. Transplant tumor registry: donors with central nervous system tumors. Tranplantation 2002; 73: 579–582.
14. Chui AK, Herbertt K, Wang LS et al. Risk of tumor transmission in transplantation from donors with primary brain tumors: an Australian and New Zealand registry report. Transplant Proc 1999; 31: 1266–1267.
15. Penn I. Transmission of cancer from organ donors. Ann Transplant 1997; 2: 14–17.
16. Boring CC, Squires ST, Tong T, Montgomery S. Cancer statistics 1994. Ca Cancer J Clinic 1994; 44: 7–26.
17. Velema JP, Percy CL. Age curves of central nervous system incidence in adults: variation of shape by histologic type. J Natl Cancer Institute 1987; 79: 623–629.
18. Pollack I. Brain tumors in children. N Engl J Med 1994; 331: 1500–1507.
19. Kelly PJ, Daumas-Duport C, Kispert DB, Kall BA, Scheithauer BW, Illig JJ. Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. J Neurosurg 1987; 66: 865–874.
20. Davis FG, McCarthy BJ, Berger MS. Centralized database available for describing primary brain tumor incidence, survival, and treatment: Central Brain Tumor Registry of the United Sates; Surveillance, Epidemiology, and End Results; and National Cancer Data Base. Neuro-oncol 1999; 1: 205–211.
21. Dai C, Celestino JC, Okada Y, Louis DN, Fuller GN, Holland EC. PDGF autocrine stimulation dedifferentiates cultured astrocytes and induces oligodendrogliomas and oligoastrocytomas from neural progenitors and astrocytes in vivo. Genes Dev 2001; 15: 1913–1925.
22. Guha A, Fedkamp MM, Lau N, Boss G, Pawson A. Proliferation of human malignant astrocytomas is dependent on Ras activation. Oncogene 1997; 15: 2755–2765.

23. Holland EC, Gliomagenesis. Genetic alterations and mouse models. Nat Rev Genet 2001; 2: 120–129.
24. Pasquier B, Pasquier D, N'Golet A, Panh MH, Couderc P. Extraneural metastases of astrocytomas and glioblastomas. Clinicopathological study of two cases and review of literature. Cancer 1980; 45: 112–125.
25. Thomas G, Hall MN. TOR signaling and control of cell growth. Curr Opin Cell Biol 1997; 9: 782–787.
26. Davies MA, Lu Y, Sano T et al. Adenoviral transgene expression of MMAC/PTEN in human glioma cells inhibits Akt activation and induce anoikis. Canc Res 1998; 58: 5285–5290.
27. Neshat MS, Mellinghoff IK, Tran C et al. Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. Proc Natl Acad Sci U S A 2001; 98: 10314–10319.
28. Hojo M, Morimoto T, Maluccio M. Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature 1999; 397: 530–534.