

# Intra-Arterial Chemotherapy in the Treatment of Malignant Brain Tumors

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## Abstract

*The capillaries of the cerebral endothelium possesses an unique Blood Brain Barrier (BBB) property due to a continuous basement membrane, tight endothelium and lack of pinocytosis. This specialized barrier prevents passage of systemic chemotherapy into the brain tumor. To obtain an effective concentration of the chemotherapeutic agent, a transient reversible disruption of the barrier is required which is achieved by intra-arterial methotrexate and intravenous cytoxan infusion. The degree of disruption of the barrier was monitored by means of radio-isotope brain scan. The neuroradiologic special procedure and its role in the management of advanced brain tumor by modification of the BBB is presented.*

**Key words:** *Blood brain barrier disruption, intra-arterial chemotherapy, osmotic blood brain barrier modification, multi-agent chemotherapy, brain tumor treatment, technique of blood brain barrier disruption*

The Blood Brain Barrier (BBB) prevents passage of systemic chemotherapeutic agents into brain tumors even when given in a high dose. In spite of successful treatment of many of the extra cerebral tumors, brain tumors remain to be beyond reach. More recent evidence indicates that the "barrier" is far more complex. The BBB may be disrupted in the center of the tumor but remains invariably intact at the proliferating edges of the tumor.<sup>1</sup> Intravenously infused radiolabeled methotrexate was concentrated in the center of the tumor in significant amounts but was very scanty at the periphery.<sup>2,3</sup> Similarly, intravenous administration of contrast agent shows inhomogeneous low enhancement of the tumor. In cases of small solid tumors, no enhancement was noted due to intact BBB. For an uniformly high concentration of the chemotherapeutic agent into the brain tumor, osmotic blood brain barrier disruption (BBBD) is essential. This was accomplished by the infusion of 25% mannitol into the arteries supplying the tumor followed by intra-arterial infusion of methotrexate (MTX), intravenous infusion of Cytosoxan (CTX) and oral procarbazine hydrochloride (Procarb Hcl). The effective BBBD was monitored by

isotope brain scan rather than contrast enhanced Computerized Tomography (CT) scan due to epileptogenic property of the contrast material especially following BBBD. In this paper, our experience in using this technique in 40 patients with malignant brain tumors is presented.

## Material and methods

Two hundred and fifty BBBD procedures on forty patients over a period of three years were performed. The age of the patients ranged from 13 to 67 years with a mean of 40 years. The brain tumor included primaries as well as secondaries. Out of forty patients, four had metastases (lung, breast, ovary and prostate), one had primary lymphoma of the brain and the remainder had various grades of gliomas. All of those patients had surgery at least once and a complete course of radio-and chemotherapy. The tumors had recurred in spite of those treatments. The patients had short life expectancy.

An informed consent was obtained from the patient and the immediate family following full explanation of the nature of the treatment, complications and the expected benefits.

As a pre-procedure protocol, all of the patients had complete physical and neurological evaluations, CT scan of the head, isotope brain scans, complete blood work-up and hepato-renal function tests.

All of the BBBD procedures were performed in the neuroradiology-special procedures room under the supervision of the neuroradiologist.

After induction of general anesthesia, a 5 French head hunter one (H1)\*, or HN4\*\* catheter was in-

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roduced into the femoral artery and advanced into the internal carotid or vertebral artery. A complete set of cerebral angiograms of carotids and vertebral arteries was obtained to evaluate the entire vascular supply, its variation and dominance.

The tip of the catheter was placed at C<sub>1</sub>-C<sub>2</sub> level in case of internal carotid and about C<sub>3</sub> level for vertebral artery.

Following placement of the catheter at the desirable level, a series of test injections of contrast material was made to determine an "adequate" amount (mls/sec) which refluxed into the external carotid artery and at the same time blocked the blood flow through the internal carotid artery. In case of vertebral artery, the reflux was observed through both of the vertebral arteries to prevent blood flow from the basilar artery.

After determination of the correct flow rate, final total volume of warmed, sterile and microfiltered 25% mannitol was calculated. It usually ranged between 90 and 270 mls. The rate of injection ranged from 6 to 12 mls per second, (average carotid - 8, vertebral - 6 ml/sec). This total amount of calculated mannitol was injected within 30-32 seconds through the arterial catheter utilizing automatic injector (330-450 PSI)\*. In case of internal carotid artery injection, balancing of the ipsilateral periorbital area, conjunctiva, fundus of the eye and retinal vessels were observed. Observation with an ophthalmoscope clearly visualized blanching and subsequent redistribution of the blood in the retinal artery. At the same time mydriasis was noted, suggesting a reliable indication of adequate blood replacement by mannitol. In case of vertebral injection, no blanching in the orbital area was noted but on occasion minimal mydriasis of the eye was noticed suggesting reflux of mannitol into the ophthalmic artery via the posterior communicating artery. Twenty to fifty mg/kg of CTX, 10 minutes before and 25 millicuries of Technetium Diethylenetriamine pentaacetic acid (99 mTcDTPA) immediately after mannitol infusion were injected intravenously (IV). Then MTX 1000-5000 mg was infused through the same intra-arterial catheter. The doses of the CTX and MTX were adjusted to higher doses according to the response and blood count. Usually, a trend of gradual increase in the dose with successive procedures was a part of the protocol. No contrast material was given after BBBD due to increased risk of neurotoxicity and seizures<sup>4</sup>. Hence, contrast enhanced CT of the brain was not obtained but safer and less sensitive isotope brain scan was done in two hours to assess the extent and adequacy of BBBD. After barrier modification, the catheter flush solution was decreased to a bare minimum of one drop/3 seconds to avoid excess fluid in the brain parenchyma.

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At the end of the procedure, the general anesthesia was terminated and the patient was sent to the recovery room and then to the neurosurgery intensive care unit.

The patient was discharged with the Leucovorin 10 mg p.o. every 6 hours x 27 doses, procarbazine 100 mg p.o. daily x 14, and Dexamethasone 2 mg p.o. daily.

This procedure (BBBD) was repeated every month.

## Results

At the end of the first treatment, some of the patients (30%) showed impressive improvement in general condition. They began to move, eat well, gain weight and were less dependent upon the medications. Their life style improved considerably. On a followup CT scan there appeared to be obvious decreased edema and mass effect.

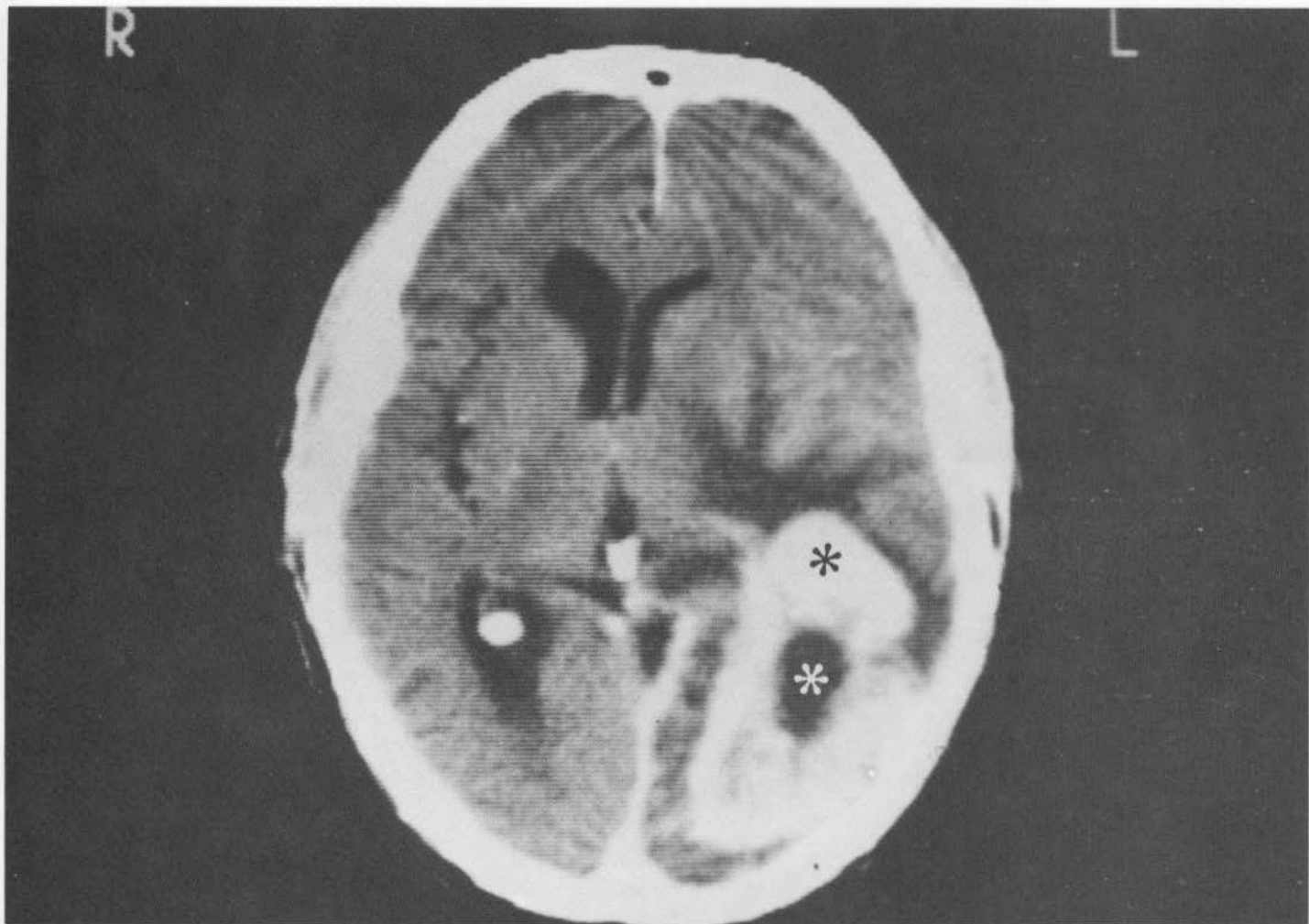
These patients were followed by time interval CT scans and arteriograms which showed:

- Control of the proliferating activity of the tumor (8 out of 40)(Figures 1a, b)
- Stationary size of the mass (no growth over several months)(6 out of 40)
- Visible regression of tumor and edema (8 out of 40)(Figures 2a, b)
- Proliferation of the tumor to the side away from the treatment area (5 out of 40)(Figures 3a, b)
- Slow increase of the tumor (6 out of 40)
- No visible tumor mass on CT over several months (3 out of 40)(Figures 4a, b, 5a, b, c, 6a, b)

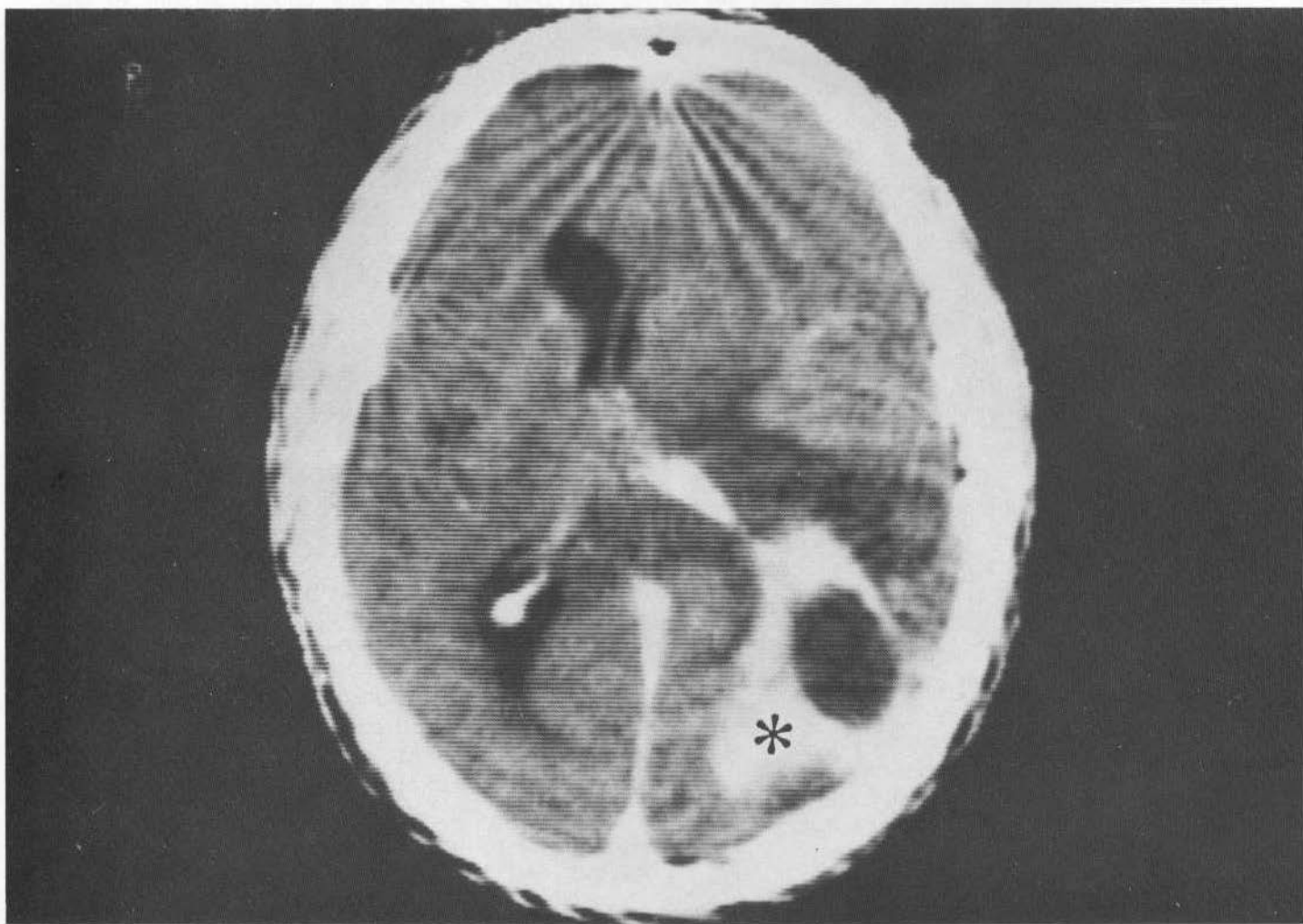
Three cases showed metastasis to other parts of the brain but those secondaries disappeared after subsequent BBBD treatment. It was interesting to observe that the main bulk of the primary focus remained unchanged but newer secondaries cleared with one or two treatments. None of the patients manifested additional neurological deficit due to BBBD procedures. Only one patient died while still in the hospital due to rapid brain edema and transtentorial herniation. The death was not related to the treatment. Two other patients died due to other organ system failure (respiratory/cardiac), obviously unrelated to the brain tumor or BBBD procedure.

## Discussion

The blood and brain are separated by a unique barrier at the cerebral capillary endothelial level due to a tight junction (zona occludens), continuous basement membrane, non-fenestration, paucity of pinocytosis and closely investing glial sheath composed of the "end feet" of astrocytes.<sup>5,6,7</sup> This barrier prevents passage of systemically circulating substances except on a selective basis. Substances with a high degree of lipid solubility, low degree of ionization at physiologic pH, and lack of plasma protein binding are permitted to pass through the BBB.<sup>8,9</sup> However, the entry of ionized water soluble

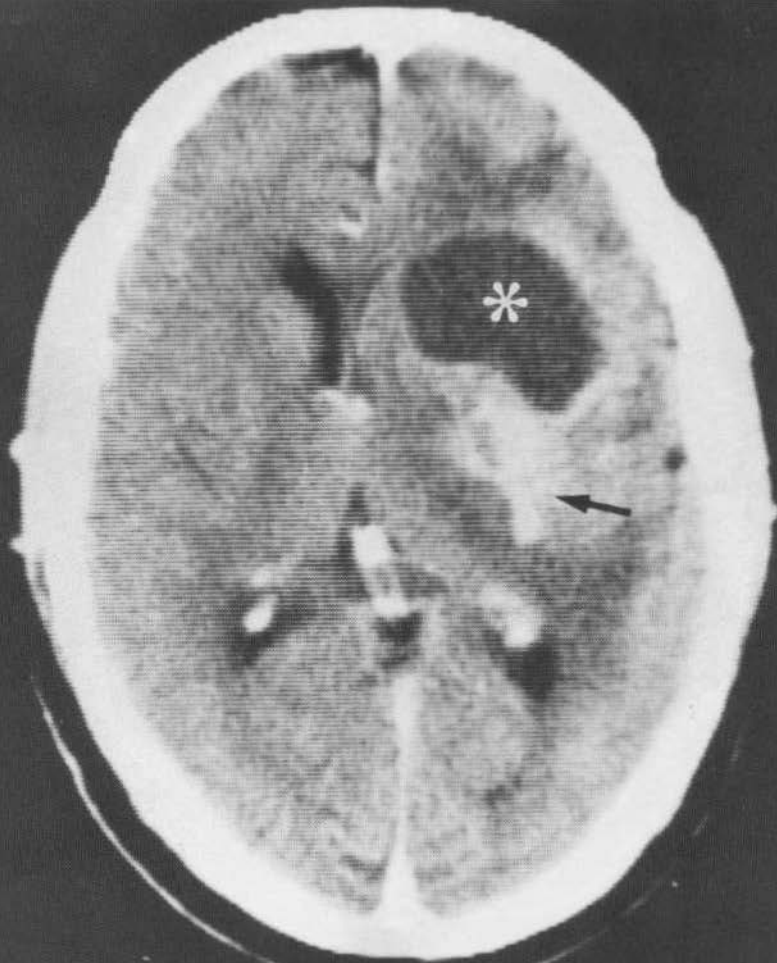


**Figure 1(a)** Large enhancing glioblastoma (black asterisk) in the left occipital lobe with central necrosis (white asterisk) and peripheral edema. Compression of the left lateral ventricle.

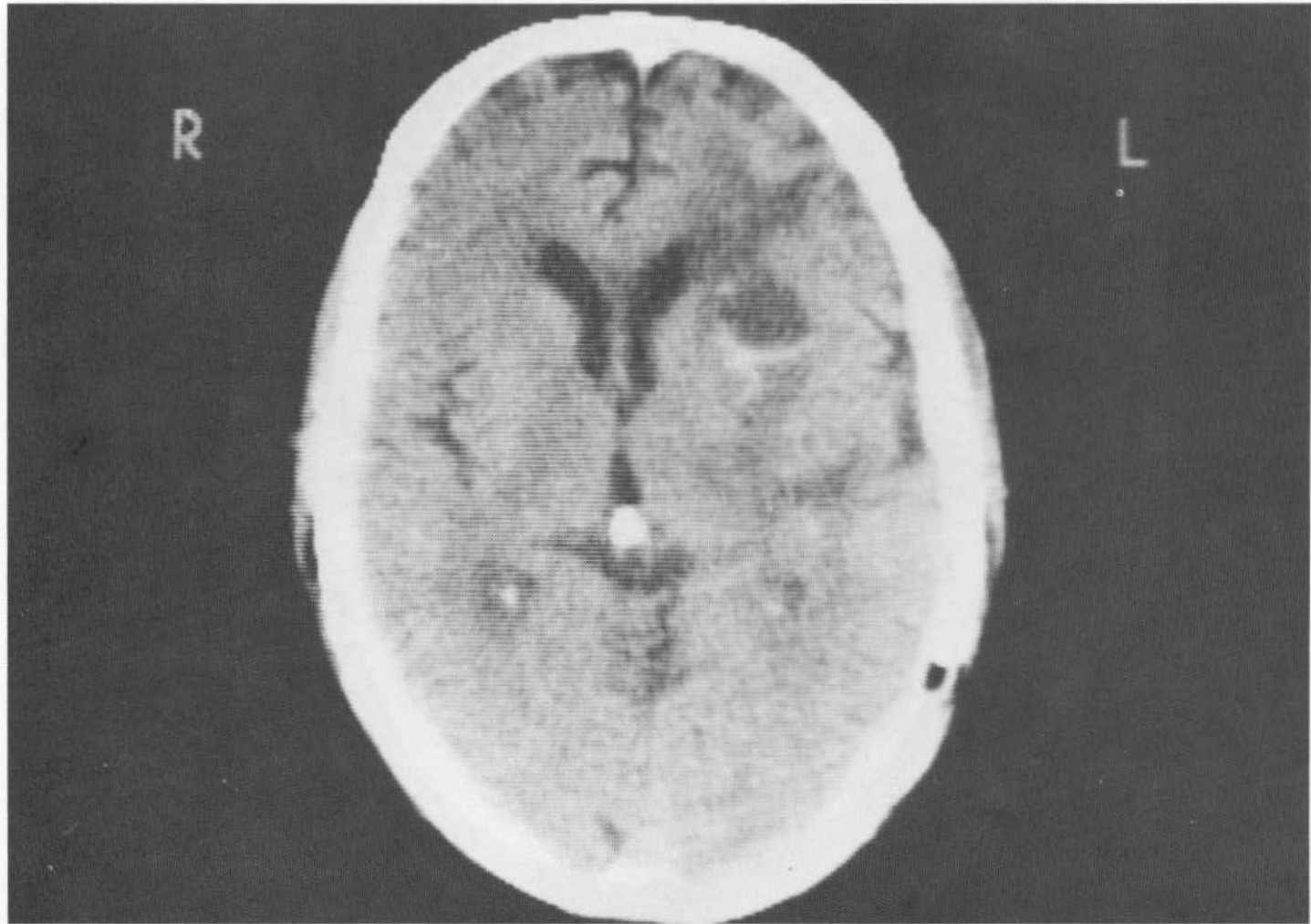


**Figure 1(b)** Decreased size of the mass following five BBBD treatments (black asterisk).

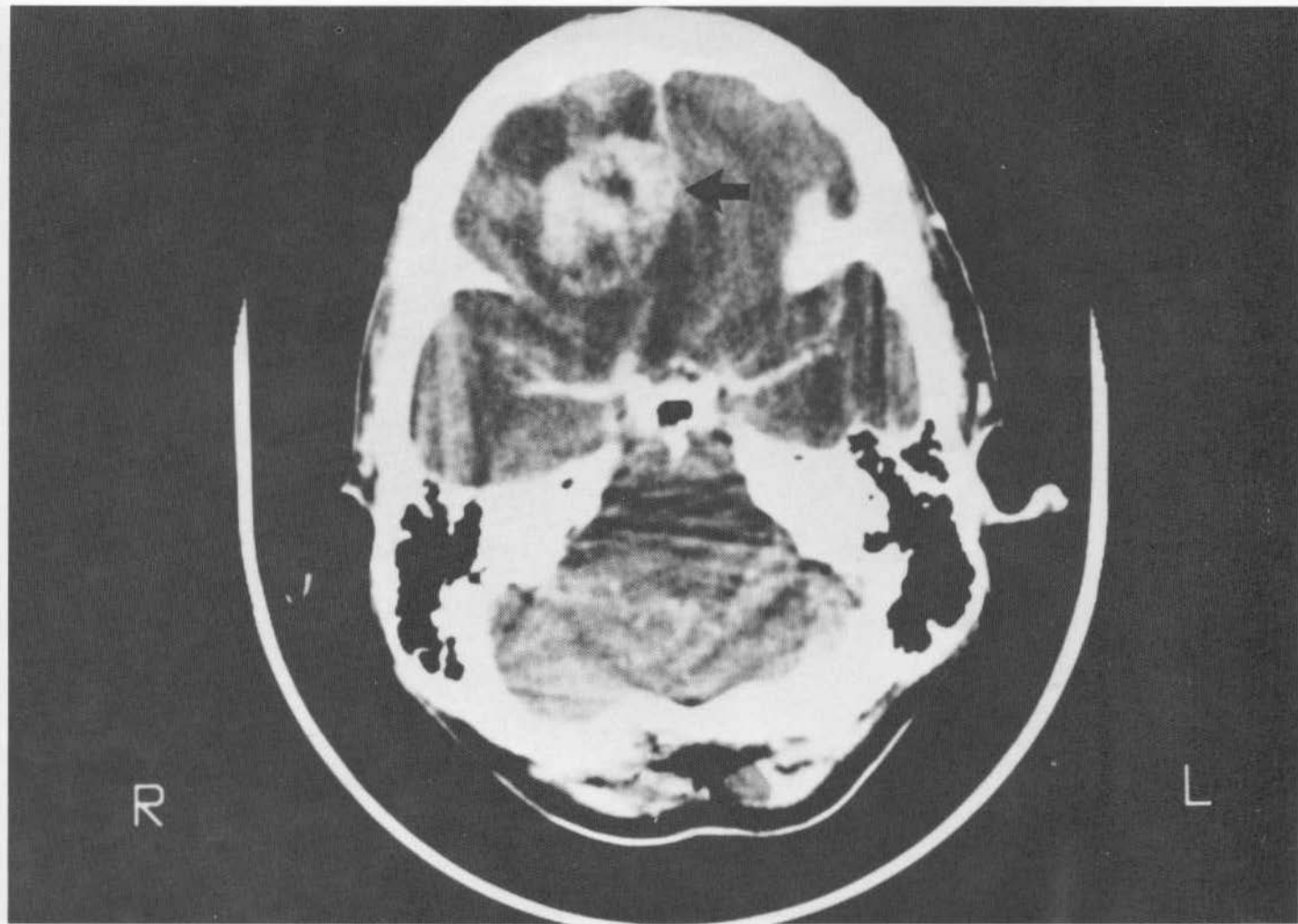




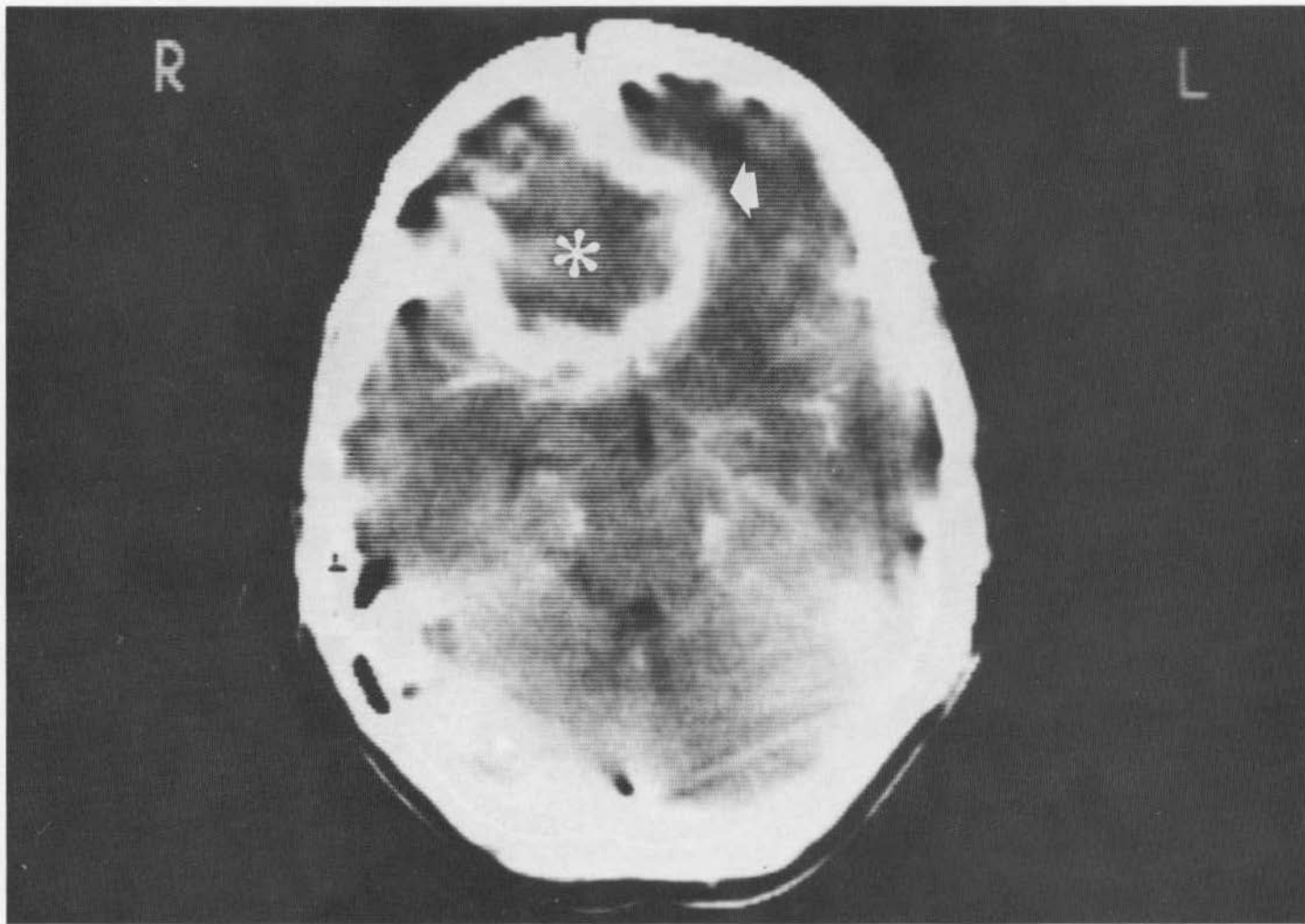
**Figure 2(a)** Large Left parietal glioma (arrow) with central cyst (white asterisk) compressing the left lateral ventricle.



**Figure 2(b)** Decreased size of the mass and cyst after two BBBD treatments. Cyst was partially aspirated. Now no significant mass effect.

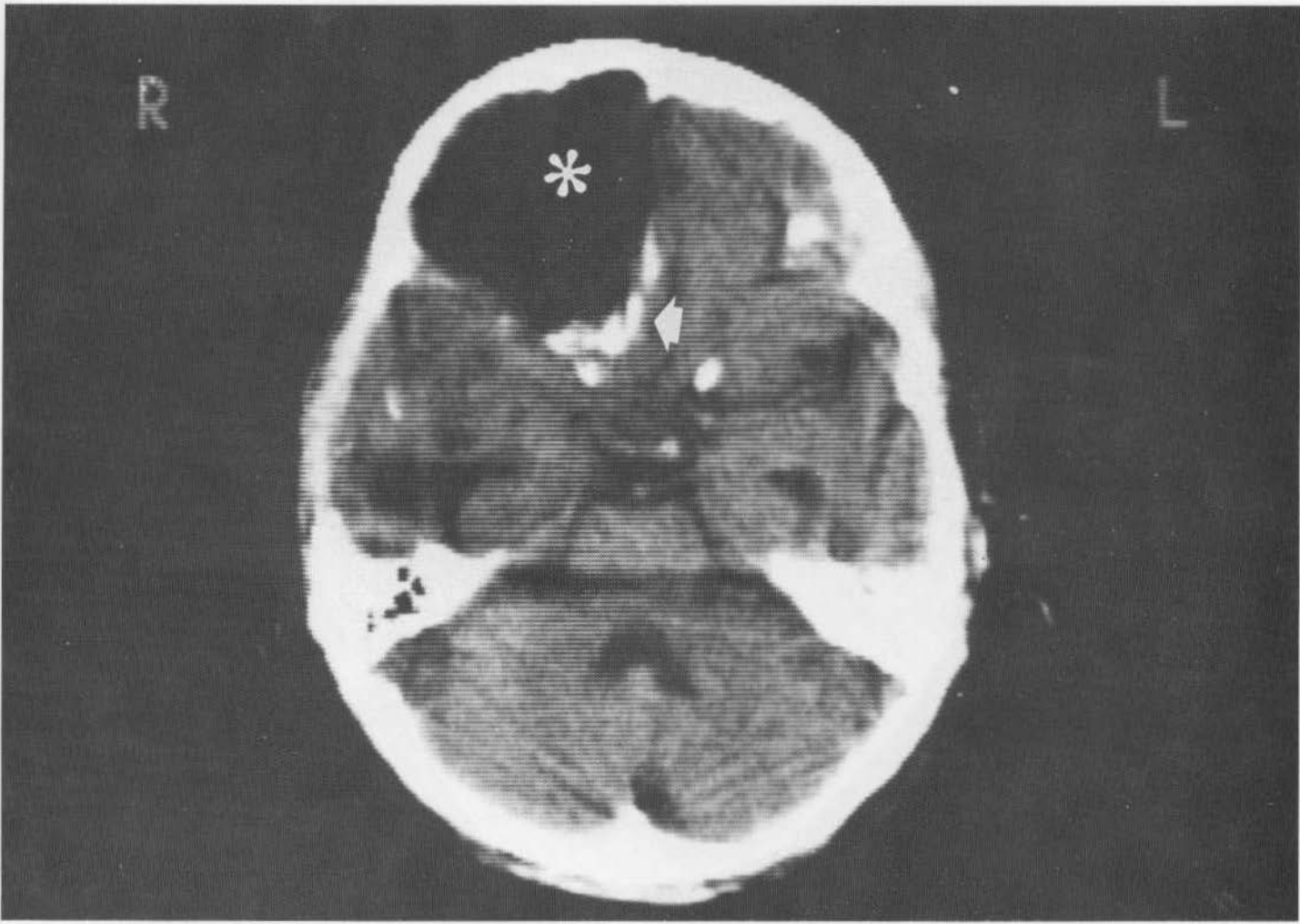


**Figure 3(a)** Large gliosarcoma in the low right frontal lobe (arrow).

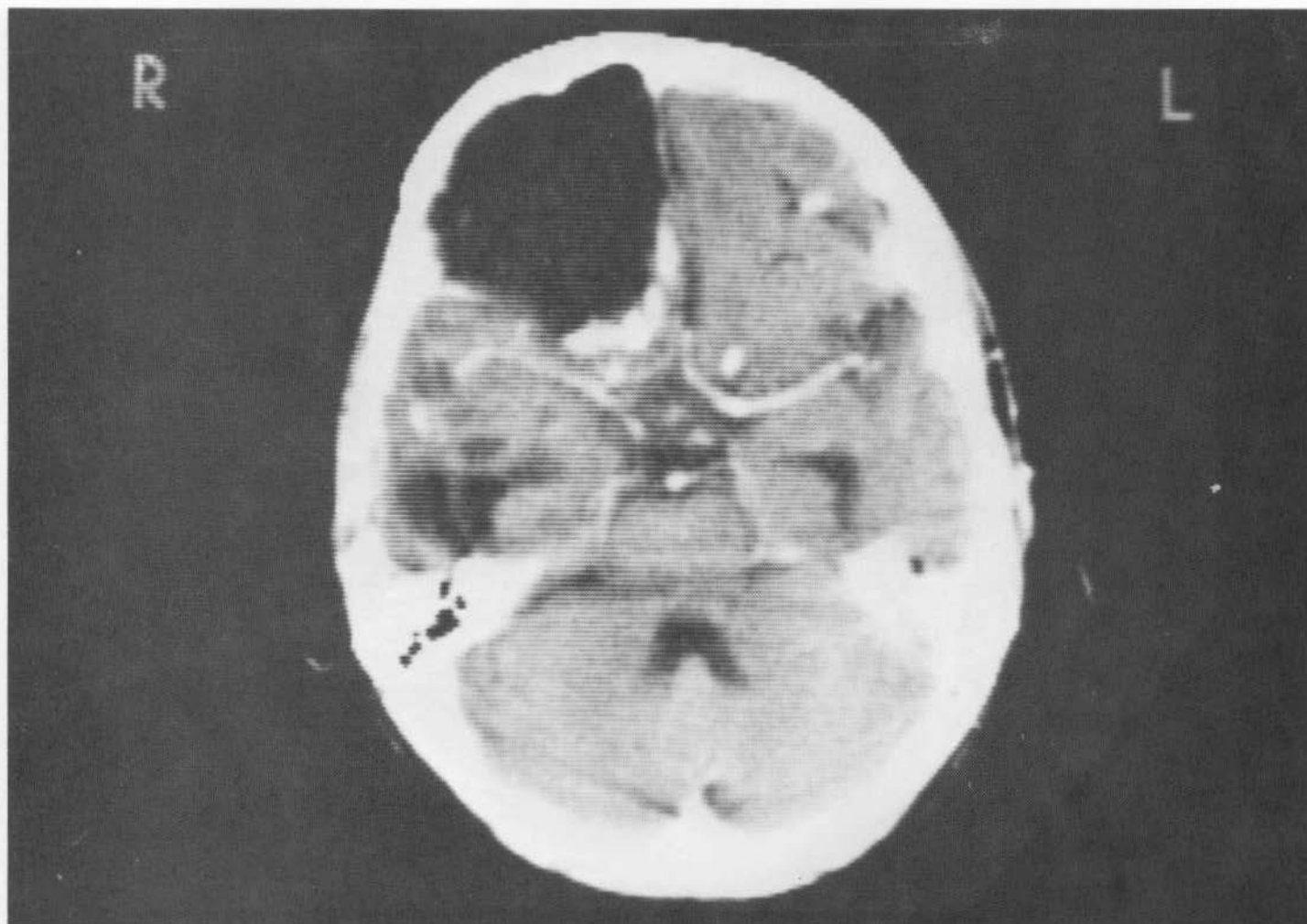


**Figure 3(b)** Very malignant tumor has increased considerably in size over 16 months. Crosses the midline (arrow). Now shows increased central necrosis (asterisk).

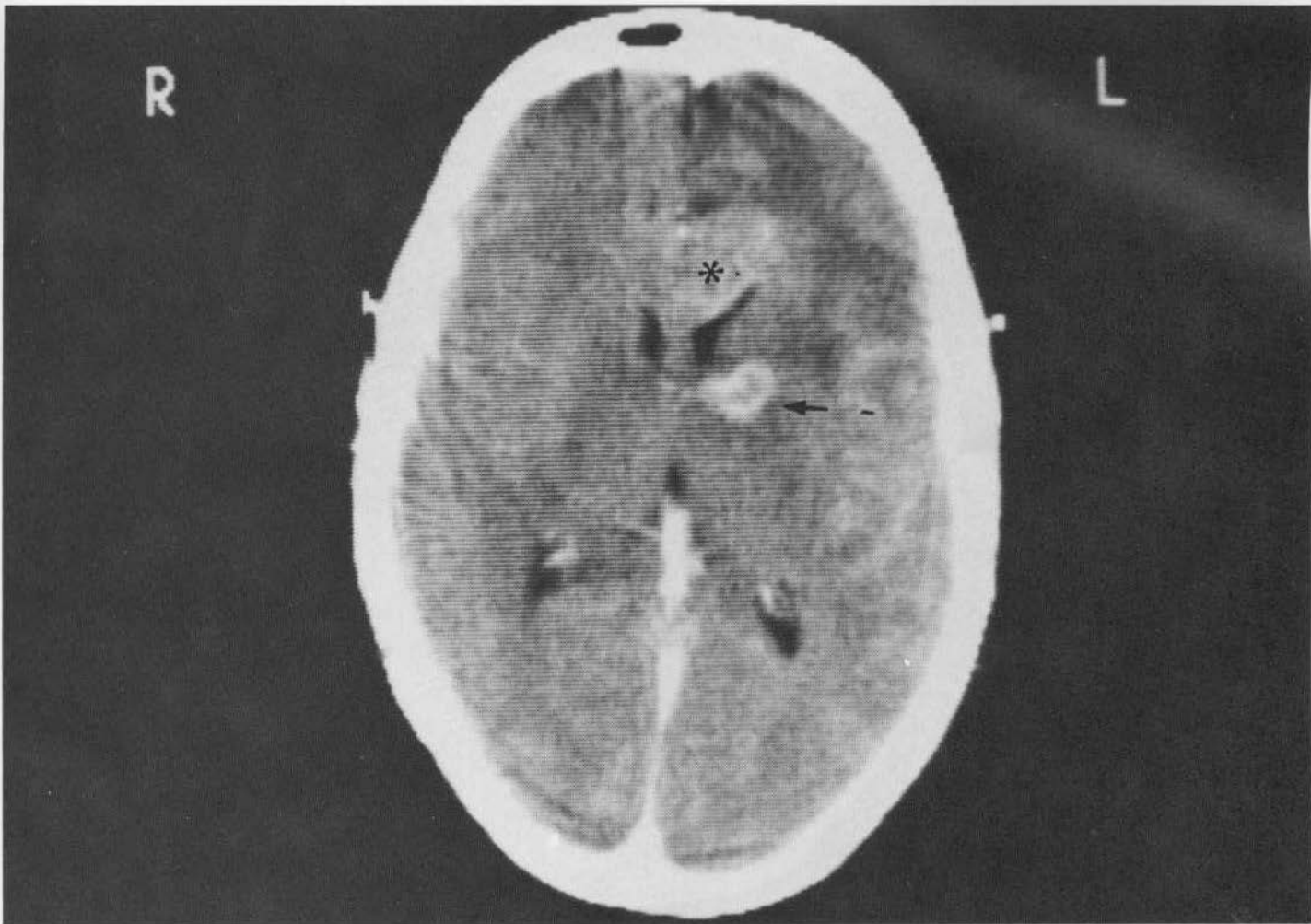




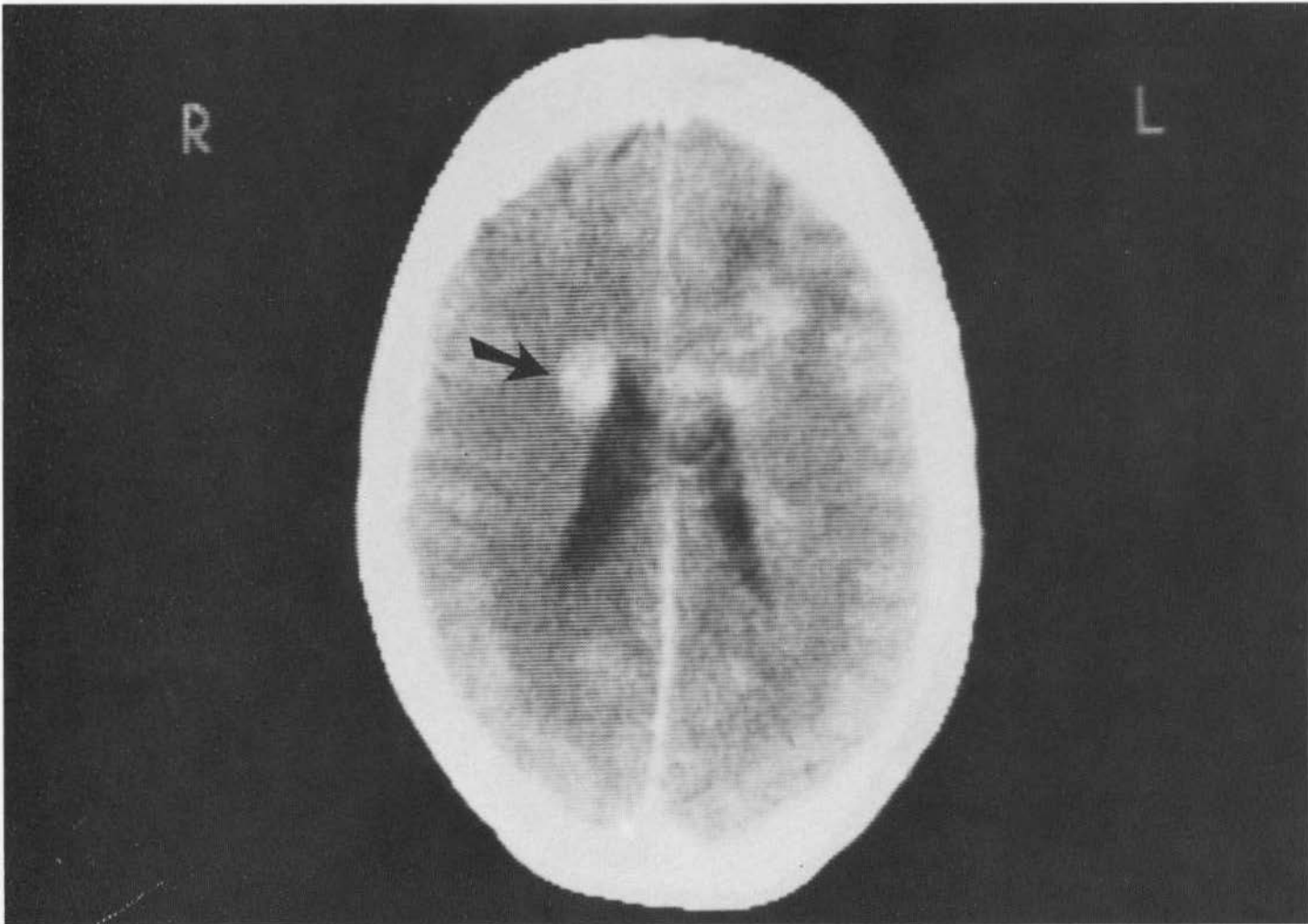
**Figure 4(a)** Right frontal astrocytoma (III) has been removed. The surgical defect is marked (white asterisk). Rim calcification (arrow) after several BBBD treatments. No visible tumor recurrence.



**Figure 4(b)** CT scan after contrast enhancement. No increased enhancement about the calcification area. Previously noted (not shown) large right temporal mass is no longer obvious.



**Figure 5(a)** Corpus callosum glioma (asterisk) with extension to left basal ganglia region (arrow). No mass effect.



**Figure 5(b)** After one BBBD procedure, the tumor has extended to the right (arrow).

R

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**Figure 5(c)** After seven treatments, no visible tumor on CT scan, or arteriogram (not shown).

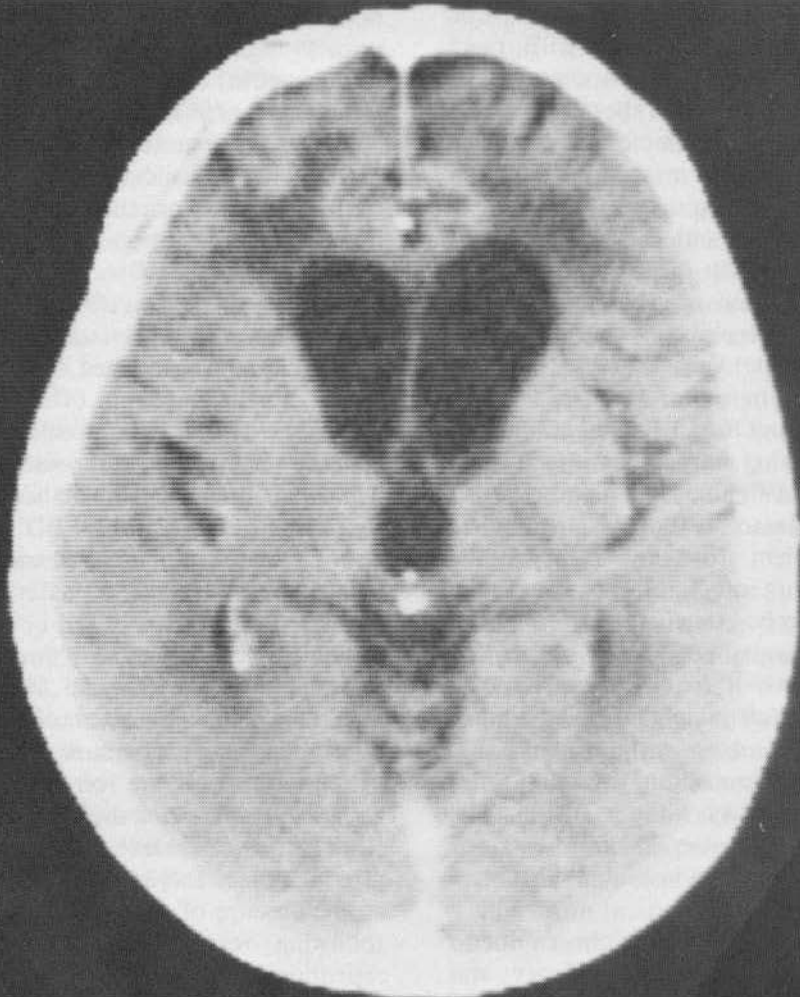




**Figure 6(a)** Bilateral enhancing masses (lymphoma)(arrows) with surrounding edema.

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L



**Figure 6(b)** After two BBBD treatments. No visible tumors.

drugs with molecular weight greater than 180 daltons is prevented. Almost all presently used chemotherapeutic agents have higher molecular weight than 180 daltons, usually between 200-1200 daltons (MTX=455, CTX=261).<sup>10</sup> MTX has a pH of 4.7 and is 99.8% ionized at a blood pH of 7.4. It is also lipid - insoluble.<sup>10,11</sup>

Due to the unfavorable properties of the chemotherapeutic agents and the unique BBB, there is a lack of entry of those agents into brain tumor in sufficient concentration even when they are given in high doses. It is also argued, by simple observation of contrast enhancement in the tumor during CT scan and isotope localization in brain scan, that there is BBBD due to tumor. Vick and Bigner<sup>12</sup> suggested that BBB was not a factor in the chemotherapy of brain tumors. This hypothesis was based on the finding that the metastatic lesions as well as gliomas possess fenestrated and discontinuous endothelium<sup>13</sup>. This holds true to some extent in cases of large tumors which disrupt the BBB in an ununiform manner. The proliferating border has intact BBB. Similarly, in small solid tumors there is no contrast enhancement due to intact BBB. This incomplete BBBD is not sufficient for the entry of the chemotherapeutic agents into the tumor in an adequate concentration, to be effective.<sup>1</sup>

To facilitate the entry of larger doses of chemotherapeutic agents, it requires hyperosmolar disruption of the BBB. Adequately infused mannitol disrupts the barrier and subsequently infused MTX and CTX reaches its concentration 10 to 100 times more than systemic pathway without BBBD. The reversible disruption of the barrier allows entry of high molecular weight and lipid insoluble substances into the brain.<sup>14</sup>

MTX, CTX and Procarb Hcl were chosen due to their least neurotoxicity and high efficacy and reliability. Other agents (BCNU, Cis - platinum, 5Fu and Adriamycin) are very toxic to the brain.<sup>14,15</sup> The latter agents do not require BBBD due to auto-BBB disruptive behavior. The systemic effects of MTX were minimized by folinic acid rescue (citrovorum factor).

Osmotic BBBD, after intra-arterial infusion of hypertonic solution, appears to be an all-or-none phenomenon. The osmotic BBB opening is reversible. It lasts about 1-2 hours and then slowly resumes its normal impermeability. The barrier closure is rapid to larger molecular weight substances<sup>16</sup>, so there is entrapment of the larger molecular substances (MTX and CTX) within the brain tumor.

This transient reversible BBBD does not produce long-term neurological deficit but transient changes have been demonstrated. Glucose consumption elevation, slightly decreased cerebral blood flow, and increase of brain water by 1-1.5% of wet weight are usually observed but usually clear in 24 hours.<sup>16,17</sup>

Along with BBBD there is also rential - ciliary epithelial barrier disruption. In concurrence with others<sup>18</sup>, there was no ocular damage or visual impairment directly related to the procedure.

The administration of high doses of corticosteroids prior to BBBD resulted in decreased barrier opening and low concentration of MTX and CTX.<sup>16</sup> So it is necessary to withdraw corticosteroids a few days prior to the procedure.

The contrast material (e.g., meglumine iohalamate 60%) is innocuous during cerebral angiography because of short contrast contact time (5-10 sec) and smaller volume of injection of the concentration of 1.6 osmol, but the same contrast agent injected for longer periods of time (20 sec) in larger doses produces barrier opening. Also, prolonged arterial spasm and increased contrast contact time as well as repeated injections at very short intervals (within minutes) produced increased neurotoxicity.<sup>19</sup> Hence, further injection of radio-contrast material following BBBD is contraindicated. Furthermore, contrast enhanced CT possess increased risk of neurotoxicity and seizure activity. This is the reason that an immediate post BBBD CT of the head was not obtained, and qualitative and quantitative assessment by less sensitive but safer radio-isotope brain scan was resorted to.

The proper choice, very precise placement of a catheter into the internal carotid and vertebral arteries as well as adequate reflux of the mannitol into the external, common carotid and opposite vertebral arteries are very essential. The proper catheterization and complete blockage of the blood flow during mannitol infusion ensures spasmless arterial system and adequate BBBD.

The absence of severe long term cerebral changes following reversible osmotic BBBD encourages repetition of the procedure every month as long as it is indicated.

## Conclusion

The BBBD procedure is safe, reversible, effective and repeatable as long as it is required to manage the patient. With our limited experience so far, we have found that it is worth pursuing because of improved general well-being of the patient. To be philosophically realistic - how many diseases have we cured? We have not cured hypertension, diabetes or other common ailments but have managed and prolonged the life of the patient which holds true for the brain tumor too.

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