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Synchronous and Metachronous Malignant Gliomas: CT Findings

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Twenty-one cases of malignant gliomas showing multiple tumor foci on CT are described. In 11 patients multiple lesions were evident on the initial CT scan (synchronous lesions); the other 10 patients developed one or more lesions months to years after the original gliomas (metachronous lesions) were documented. Distinctions between multifocal and multicentric gliomas are discussed and CT patterns presented. A diagnosis of synchronous multicentric or multifocal glioma should be considered in patients with multiple parenchymal masses and no known primary tumor elsewhere.

A multicentric or multifocal presentation of cerebral gliomas is well known but uncommon. CT has contributed greatly to the identification of multiple lesions. We report our experience with 21 cases of malignant astrocytomas that demonstrated multiple lesions on CT. Of these, 11 patients showed multiple lesions on the initial scan (synchronous lesions) and 10 patients developed one or more lesions months to years after the initial diagnosis of a glioma (metachronous lesions). Cases that demonstrated gross CT evidence of subependymal or corpus callosal spread of tumor were excluded.

Materials and Methods

We reviewed the CT scans of 21 patients with malignant gliomas presenting as multiple mass lesions seen at our institute between 1980 and 1986. In some cases the initial pretreatment scan was performed at an outside hospital before the patient was referred to our institute. Our own studies were performed on a variety of scanners with section thickness ranging from 4–10 mm. Contrast scans were performed using a rapid infusion of 300 ml of 30% iodinated contrast medium.

All the surgical and autopsy specimens in this series were examined by one of us. A three-tiered grading system was used, with grade I called astrocytoma, grade II called anaplastic astrocytoma, and grade III called glioblastoma multiforme [1]. The astrocytoma is characterized by increased cell density; mitoses and cellular atypia are rare. An anaplastic astrocytoma demonstrates increased cell density, cellular and nuclear pleomorphism, mitoses, and vascular endothelial proliferation. Glioblastoma has the features of anaplastic astrocytoma plus necrosis.

Results

The 21 patients in this series were divided into two groups on the basis of the temporal CT presentation of the tumors. There were 11 patients in the synchronous lesion group and 10 in the metachronous group. The entire group of 21 constituted 4.8% of 440 malignant gliomas evaluated during a 6-year period.

Synchronous Lesion Group (Table 1)

Cases in the synchronous group demonstrated two or more discrete parenchymal masses without gross radiographic evidence of connection on the initial CT scan (no contrast enhancement connecting the lesions). The group consisted of

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six women and five men with an age range at presentation of 21–76 years (mean, 48 years). Six patients had lesions confined to one hemisphere and five had bilateral lesions. All patients had biopsy of the most surgically accessible lesion. One patient had eventual sampling of bilateral lesions (Fig. 1).

Two patients were initially judged to have metastatic brain disease, although no primary site was found, and both underwent cranial radiotherapy. Biopsies were later obtained when the patients' disease progressed. There were six anaplastic astrocytomas and five cases of glioblastoma multiforme.

TABLE 1: Synchronous Lesion Group

Case No.	Location of Lesions	Biopsy Result	Autopsy Result
1	L frontoparietal, R frontoparietal	AA, R frontoparietal	—
2	L frontal, L parietal	GBM, L parietal	—
3	L frontoparietal, R frontoparietal	AA, L frontoparietal	—
4	L parietal x2, R frontal	GBM, R frontal	—
5	L parietal, R frontal x2	GBM, R frontal	—
6	L frontal, L temporal	GBM, L temporal	—
7	L basal ganglion	—	—
8	L parietal x2	GBM, L parietal	—
9	R basal ganglion, R thalamus	AA, R basal ganglion	—
10	L internal capsule, R temporal	AA, L internal capsule	—
11	L temporal, L frontal, L parietal	AA, R temporal	AA, all lesions; all connected microscopically (multifocal tumor by pathology criteria)
12	L parietal, L frontal x2	AA, L parietal	AA, all lesions; all connected microscopically (multifocal tumor by pathology criteria)

Note.—L = left, R = right, AA = anaplastic astrocytoma, GBM = glioblastoma multiforme.

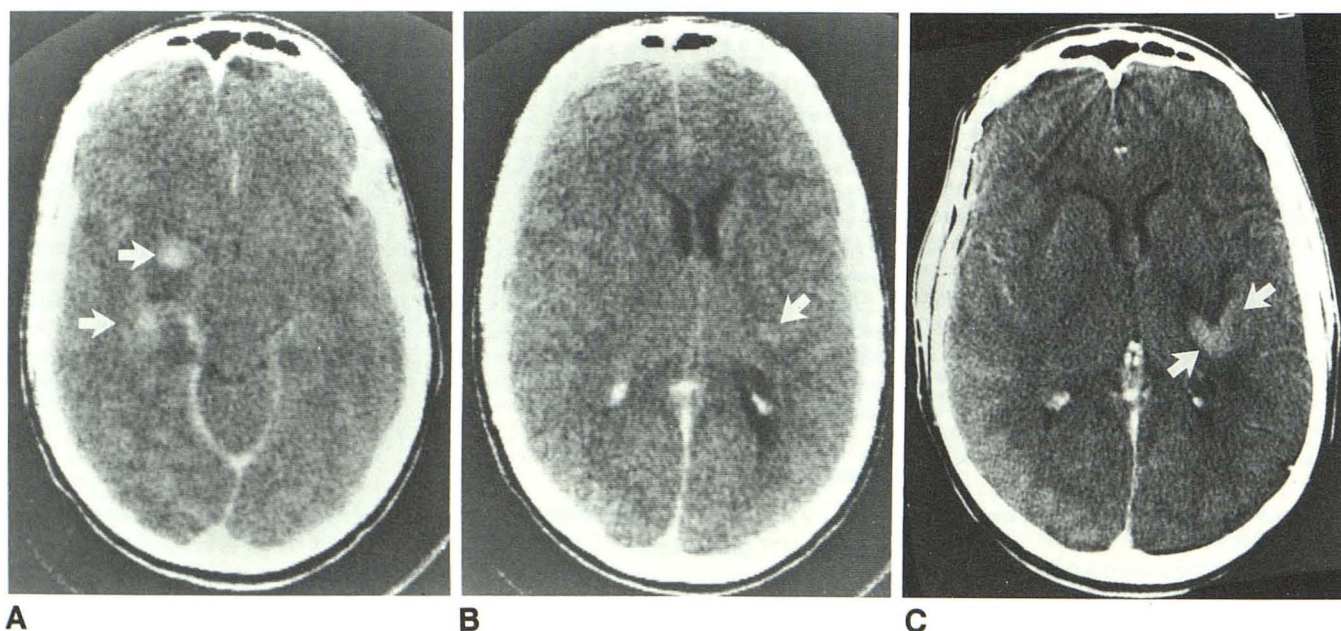


Fig. 1.—Synchronous lesions.

A, Contrast CT demonstrates separate foci of enhancement in upper, medial right temporal lobe and inferior basal ganglia (arrows). Partial temporal lobectomy at another hospital revealed anaplastic astrocytoma.

B, Scan done same date as A. Small lesion in left upper internal capsule (arrow), not seen initially.

C, Contrast CT 2 months later shows growth of left-sided lesion (arrows). Biopsy of this mass also yielded anaplastic astrocytoma.

Four cases in the synchronous group demonstrated all solidly enhancing lesions on CT, four had all ring-enhancing lesions, and three had a mixture of solid and ring-enhancing lesions. The biopsy results correlated with the CT appearances of the lesions in 10 cases, with anaplastic astrocytomas demonstrating solid enhancement and glioblastomas showing an irregular rim enhancement. One case of a rim-enhancing lesion had biopsy results of anaplastic astrocytoma, probably due to incomplete tumor sampling at biopsy. Two of the 11

cases in the synchronous group came to autopsy, and in both cases microscopic connecting tumor bridges were found between discrete ipsilateral lesions (Fig. 2), identifying these cases as multifocal gliomas (see Discussion).

Metachronous Lesion Group (Table 2)

The metachronous group consisted of four women and six men, ranging in age at diagnosis from 27 to 62 years (mean,

Fig. 2.—Synchronous lesions.
A and B, Contrast scans. At autopsy these separate lesions were connected by microscopic tumor (multifocal anaplastic astrocytoma).

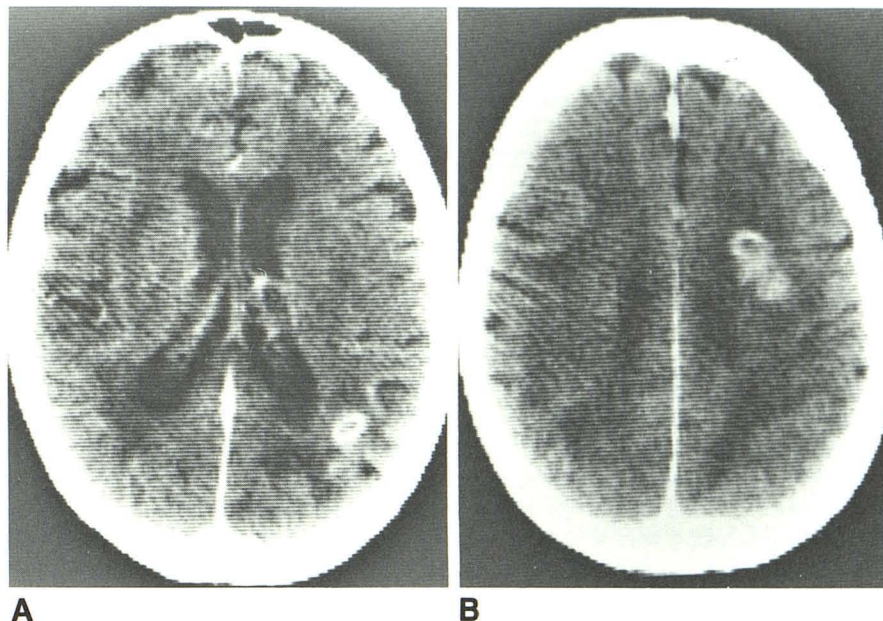


TABLE 2: Metachronous Lesion Group

Case No.	Time from 1st to 2nd Lesion on CT (months)	Location of 1st Lesion	Location of 2nd Lesion	Biopsy 1st Lesion	Biopsy 2nd Lesion/Autopsy
1	8	L frontoparietal	L frontal	GBM	—
2	7	L thalamus, L caudate head	L parietal	AA	—
3	12	R temporal	L basal ganglion, L paraventricular	GBM	—
4	12	R frontoparietal	R temporal, R parietal, L parietal	A	—
5	2	L parietal	L frontoparietal x2	GBM	—
6	2	R parietal	R parietal	AA	—
7	13	R frontal	R temporal	GBM	GBM
8	84	L frontal, L temporal	L temporal	A	AA
9	96	R frontal, R temporal	R temporal	A	GBM
10	13	L temporooccipital	L frontal	GBM	GBM; autopsy: no continuous connection between lesions (multicentric tumor by pathology criteria). Additional tumor foci present (see text and Fig. 4).

Note.—L = left, R = right; A = astrocytoma, AA = anaplastic astrocytoma, GBM = glioblastoma multiforme.

49 years). All 10 patients initially had a single lesion with a proved diagnosis of an astrocytic tumor (three astrocytomas, two anaplastic astrocytomas, and five glioblastomas). Six cases had a gross total or subtotal tumor resection, and four had biopsy only. All patients had radiotherapy postoperatively, either with 66 Gy to the tumor site or 50 Gy whole brain with a 15 Gy boost to the tumor site. Four patients also received IV or intracarotid chemotherapy with various drug regimens postoperatively and before the development of metachronous lesions.

All 10 patients developed an additional parenchymal lesion(s) from 2 months to 8 years after diagnosis of the original tumor. The mean time was 9.6 months for the glioblastomas, 7.6 months for the anaplastic astrocytomas, and 64 months for the astrocytomas. There was no consistent correlation between the CT appearance of the original tumor and the subsequent lesions. In eight cases the metachronous lesion(s) was on the same side as the primary tumor and contralateral in one case. One case had bilateral metachronous lesions. The majority of the ipsilateral lesions were at a distance of many centimeters from the primary tumor.

Three patients had biopsy of the metachronous tumor, and, interestingly, ipsilateral frontal and temporal lobes were involved in each case. The CT presentation in two of the three was that of a hypodense, nonenhancing mass located in the frontal and temporal lobes of one hemisphere. In both cases the diagnosis was astrocytoma. Surgical and radiation treatments in both were followed years later by development of a ring-enhancing mass in the ipsilateral temporal lobe. The metachronous lesion was anaplastic astrocytoma in one (7-year interval between lesions) and glioblastoma in the other (8-year interval) (Fig. 3). The third patient had no surgical or

CT evidence of temporal lobe tumor when he presented with a right frontal glioblastoma. However, 13 months later, a new ring-enhancing mass (proved glioblastoma) was present in the right temporal lobe without obvious recurrence in the frontal lobe.

There was one autopsy in the metachronous group. In this case there had been previous biopsy and irradiation of a left temporooccipital glioblastoma. The most current CT scan, done several months prior to death, revealed edema extending between residual ring enhancement at the primary site and a left frontal enhancing nodule (Fig. 4A). At autopsy, necrotic brain but no viable tumor was present at the original tumor site. There were multiple, isolated areas of glioblastoma involving the external capsule, left frontal lobe, left corpus callosum, and right frontal lobe (Fig. 4B). Radiation effects were also present in these locations. No continuity of tumor could be demonstrated between the left posterior temporal and frontal lobes or across the genu of the corpus callosum, classifying this tumor as multicentric (see Discussion).

Discussion

Glioblastoma presenting as multiple tumor foci has long been recognized by neurosurgeons and neuropathologists, and there has been much confusion over terminology. We prefer to use the term multicentric to mean separate lesions with no gross or microscopic connections [2, 3]. Discrete lesions that are found to have parenchymal connections or evidence of spread via CSF pathways have been described as multiple [2] or multifocal [4, 5] tumors. A frequently cited explanation for the origin of multicentric gliomas is that of Willis, who hypothesized that multicentric lesions occur as a

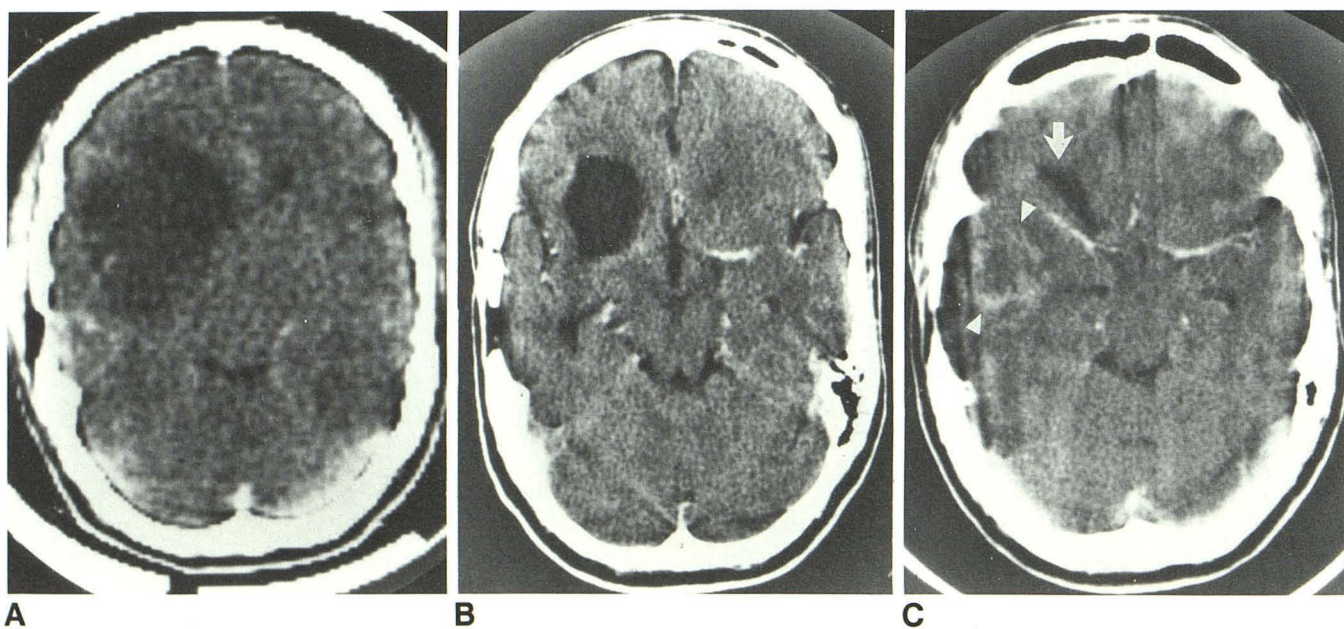


Fig. 3.—Metachronous lesions.

A, Contrast scan shows hypodense, nonenhancing area of mass effect in right frontal and temporal lobes (astrocytoma).

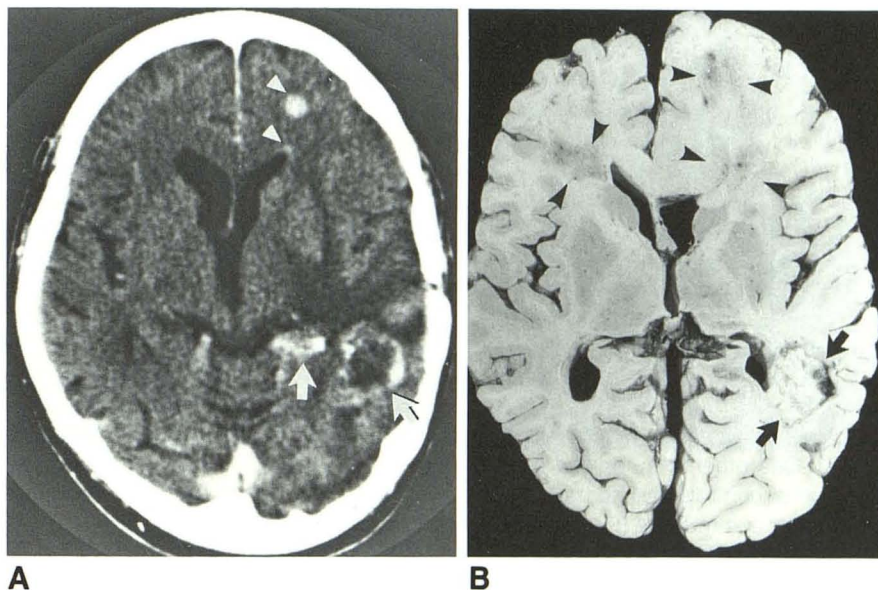
B, Contrast scan 7 years later. Surgical porencephaly in right frontal lobe. No temporal lobe abnormality demonstrated.

C, Contrast scan 14 months later. New ring-enhancing lesion in right temporal lobe (arrowheads) compressing the frontal porencephaly (arrow).

Fig. 4.—Metachronous lesions.

A, Postoperative contrast scan compatible with residual tumor in left temporooccipital region (arrows). Enhancing nodules in left frontal white matter and adjacent to frontal horn (arrowheads), not present on previous scans. Edema nearly connects the anterior and posterior abnormalities.

B, Autopsy specimen 6 months after scan in A. Radiation effects without identifiable tumor were present in left temporooccipital area (arrows). Scattered sites of microscopically discontinuous (multicentric) glioblastoma bilaterally (arrowheads). Mass effect from tumor and edema in left frontal lobe.



two-stage process [6]. In the first stage a wide field of tissue undergoes neoplastic transformation; in the second stage areas within this field show tumor proliferation at different rates, giving rise to discrete lesions. Later, the separate foci of tumor may fuse together and the initial multicentricity is not detected [2, 6, 7].

The reported incidence of multicentric malignant glioma has ranged from 0.5–10% [2, 8], with this discrepancy attributed to variability in meticulous sectioning of the brain at autopsy and inclusion of multifocal cases with true multicentric ones [2,3, 6,7]. Previously, the most reliable figure for the incidence of true multicentricity in astrocytic tumors was 2.5% [2, 3]. A recent report of a large autopsy series of gliomas found a 7.5% incidence of multicentricity after obtaining whole brain celloidin-embedded sections in addition to routine paraffin wax blocks [9]. The frequency of discovery of multifocality and multicentricity is dependent upon the extent to which the brain is sampled [3, 9]. The distinction between multicentric and multifocal gliomas is made by pathologic criteria at autopsy, and it is not possible to confidently differentiate these on the basis of radiologic studies [5]. We find it more satisfactory to categorize these cases as synchronous and metachronous lesions on the basis of the CT presentation and follow-up, and later to group them as multicentric or multifocal when postmortem examination is available.

The radiographic features of multiple foci of glioma were first reported by Prather et al. [4], who presented radionuclide and angiographic findings in a proved case each of multicentric and multifocal glioblastoma. The CT appearances of such tumors were later reported by Rao et al. [5], with pathologic correlation in two of four cases. Several other papers also illustrated the CT findings in proved or suspected multicentric and multifocal gliomas [10–12]. Most of the previously reported cases are of lesions that presented synchronously, with a minority of cases having tumor foci separated by time (metachronous) [3, 5, 7]. In our series of 21 patients, there

were 10 cases of metachronous lesions. This appears to be the largest number reported, and may represent a complication of malignant gliomas when the patient does not rapidly succumb to the effects of tumor at the primary site. This tumor behavior was slightly more frequent with glioblastoma than with anaplastic astrocytoma or astrocytoma. In the two patients who had delayed development of a temporal lobe glioma with a different CT appearance from the original frontotemporal tumor, it is not known whether these metachronous lesions were radiation-induced or represented regrowth of tumor previously sterilized by radiation therapy [13]. In the six patients who did not have biopsy of the metachronous lesion, radiation necrosis is a diagnostic consideration. However, tumor, as opposed to radiation necrosis, is believed to be more likely since the metachronous lesions occurred within 2–12 months of radiation therapy and were not located in the part of the brain receiving the highest dose.

The lack of contrast enhancement of tumor between discrete masses in the two synchronous cases autopsied may be explained by different degrees of damage to the blood brain barrier. In areas of limited endothelial cell proliferation and minimal blood brain barrier damage, it is expected that either no abnormality or only vasogenic edema will be seen on the enhanced CT, as the larger molecules of the contrast agent would not diffuse through the capillary walls [14]. Our experience with MR imaging in multifocal and multicentric gliomas is limited. Because of its increased ability to detect abnormal water content in the brain, MR will be a more sensitive method for identifying connections between apparent discrete masses seen on CT. However, distinguishing strands of tumor from edema in a region of abnormal signal intensity between two masses will remain problematic even with paramagnetic agents, due to the same dependency on significant blood brain barrier damage for tumor identification. Also, the sites of enhancement either with CT or MR do not delineate true tumor margins [15].

The lack of contiguous tumor between the ipsilateral temporooccipital and frontal lesions in the autopsied metachronous case may reflect an inability for sustained tumor growth along the entirety of a white matter tract, perhaps due to nutritional factors, giving rise to interrupted or skip lesions. Alternatively, this case may exemplify a true multicentric glioblastoma. We had expected streaming of tumor along the external capsule (multifocal tumor), in keeping with Cowley's postulates of association fiber bundles providing a means for tumor spread [16]. In the three unautopsied metachronous lesion cases with tumor in ipsilateral frontal and temporal lobes there was presumed extension of tumor along the uncinate fasciculus. This U-shaped white matter tract connects frontal and temporal cortical regions and courses just deep to the sylvian fissure and inferior to the external capsule (Fig. 5). One other unautopsied metachronous case had CT evidence of contralateral spread of enhancing tumor through the anterior commissure (Fig. 6). Cases of the more common variety of tumor dissemination via the corpus callosum were excluded from this series.

Our data suggest that the synchronous and metachronous patterns most often represent multifocal tumors. In many cases the CT appearance of synchronous type lesions is significantly influenced by variability in disruption of the blood brain barrier. That is, if different grades of glioma exist within a single tumor, this inhomogeneity results in different degrees of contrast enhancement and may inaccurately display the lesion as two or more smaller masses rather than as one large or infiltrative mass. The metachronous pattern is frequently compatible with subsequent tumor infiltration from the original mass along white matter tracts; however, less commonly, it may also reflect true multicentric lesions, as may

the synchronous pattern. Two of the 11 cases in the synchronous group had such separate lesions in opposite hemispheres that no fiber tract connection seemed feasible.

Finally, as others have noted, the CT appearance of parenchymal brain metastases and a synchronous multicentric or multifocal glioma may be quite similar [10, 11]. We also found this differentiation difficult; however, seven of the 11 cases in the synchronous group exhibited one or more of the following features that would be unusual in metastatic disease: large, solidly enhancing lesions without central necrosis; lesions deep in the hemisphere away from a corticomedullary junction; lesions in the same hemisphere without contralateral masses; or lesions without a smooth, rounded shape. Such features should lead one to question the CT diagnosis of metastatic disease to the brain, especially if no primary tumor can be found elsewhere. In these instances, biopsy of an accessible lesion should be performed to allow proper treatment planning, since a much higher dose of radiation is given for primary brain tumors as compared with that for brain metastases [11, 12].

Addendum

Since the submission of this paper, we have encountered one additional synchronous case and two metachronous cases. The multiple lesions were in an ipsilateral cerebral hemisphere in all three cases, and MR scans were obtained in each. Biopsy of one of the two lesions in the synchronous case revealed glioblastoma and MR showed no intervening white matter signal abnormality between the two masses (Fig. 7), suggesting a multicentric tumor. Both the metachronous

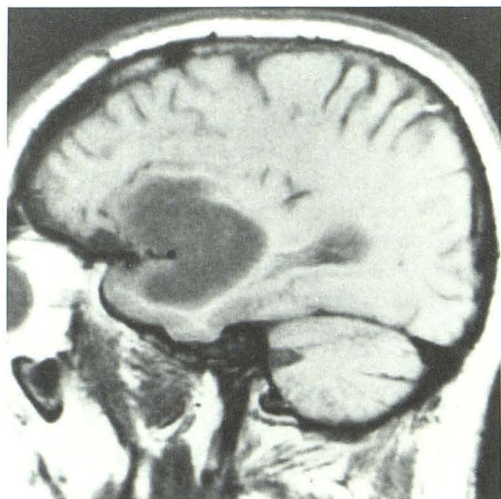


Fig. 5.—Sagittal MR (TR 600, TE 20) of a patient not in this series. Hypointense tumor (astrocytoma) follows course of uncinate fasciculus between frontal and temporal lobes.

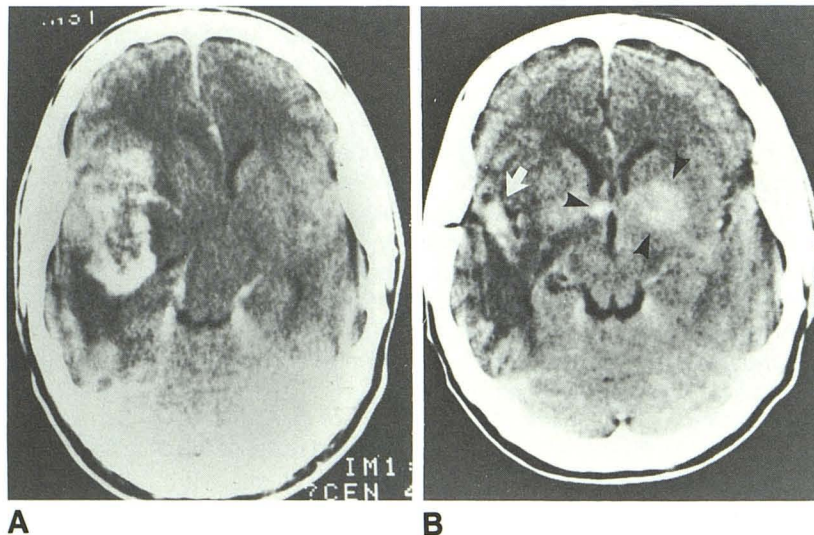
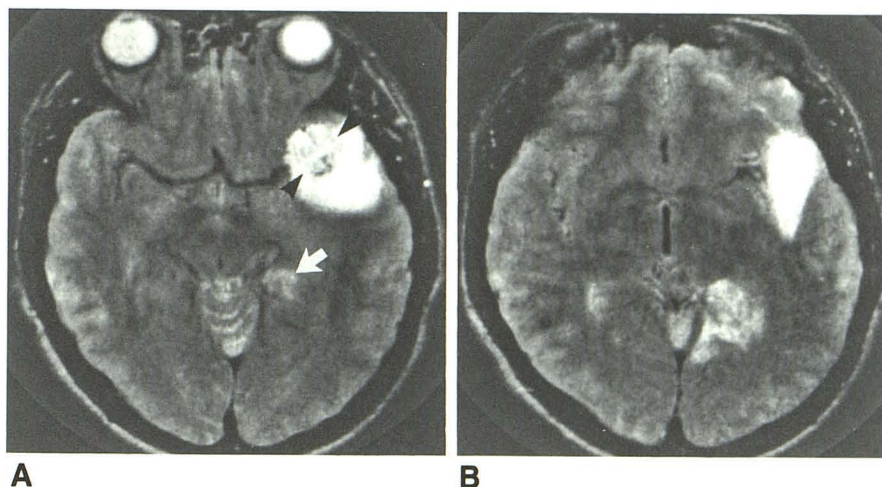


Fig. 6.—Metachronous lesions.
A, Contrast scan shows ring-enhancing right frontotemporal glioblastoma.
B, Contrast scan 12 months later demonstrates postoperative changes and residual/recurrent tumor in right temporal lobe (arrow), as well as new enhancement near anterior third ventricle and in contralateral basal ganglia (arrowheads). Findings consistent with tumor extension through anterior commissure, but not biopsy proved.

Fig. 7.—Synchronous lesions.

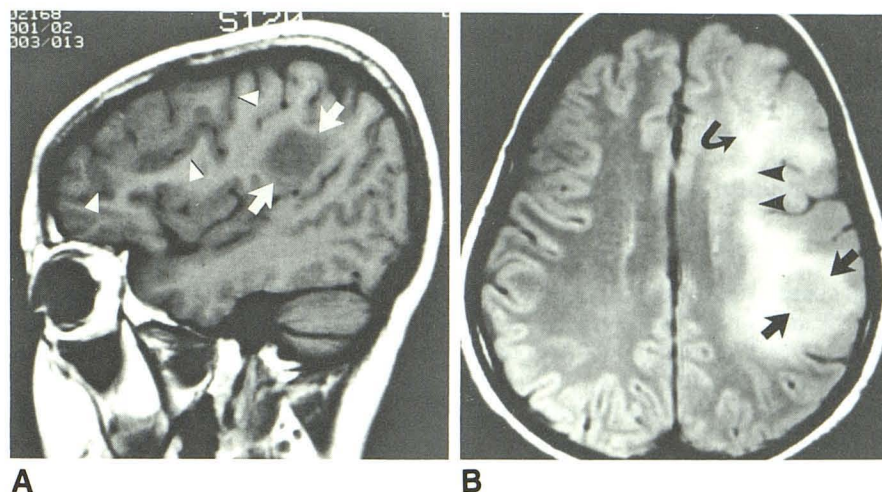
A, Axial MR (TR 2500, TE 80). Arrowheads demarcate less hyperintense rounded mass (glioblastoma) from surrounding edema. Lower edge of second lesion is seen (arrow) without white matter signal abnormality between the two lesions.

B, Slightly higher section shows frontotemporal edema and presumed tumor mass in medial occipital lobe.

**Fig. 8.—Metachronous lesions.**

A, Sagittal MR (TR 600, TE 20). Gyral enlargement and abnormal hypointensity in previously biopsied and radiated left frontal lobe (arrowheads). Arrows indicate metachronous lesion in left parietal lobe.

B, Same patient, axial MR (TR 2000, TE 20). Previously treated astrocytoma in left frontal lobe (curved arrow) and new parietal mass (straight arrows, anaplastic astrocytoma) with intervening bright white matter signal (arrowheads) between the two lesions.



cases originally had a frontal lobe tumor. In one of these the mass was only biopsied (astrocytoma), followed by radiation (54 Gy). Two years later, CT revealed a new mass in the ipsilateral parietal lobe. MR demonstrated an abnormal white matter tract signal connecting the left frontal and parietal regions, consistent with multifocal spread of edema and tumor (Fig. 8). Biopsy of the parietal mass yielded tumor plus radiation effects, but no necrosis. MR in the second patient with findings compatible with metachronous tumor also demonstrated white matter hyperintensity on T2-weighted images between recurrent right frontal glioblastoma and a new right temporoparietal mass (not shown). Areas of involvement appeared to include the uncinat fasciculus, insula, and portions of the superior longitudinal fasciculus and internal and external capsules. Although there is no biopsy of the metachronous mass and the patient had been irradiated 5 years previously, it is doubtful that the new lesion represents radiation necrosis, as an MR scan 7 months earlier had shown no parenchymal abnormality in the area where the second mass later appeared.

In both these metachronous cases we found the T1-weighted images useful for demonstrating the rounded, hypointense tumor masses. The tumors displayed less of a bright signal than did adjacent edema on proton-density images, and this sequence was useful for distinguishing tumor from edema.

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