CLINICAL VALUE AND LIMITATIONS OF ^{99m}Tc BRAIN SCAN: AN AUTOPSY CORRELATION

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The value and limitations of brain scanning as a diagnostic tool have been assessed in the literature by several authors (*1–6*). In the reports cited, the accuracy of brain scan diagnoses was evaluated by comparison with that of diagnoses made by conventional neurological and neuroradiological techniques. In only a few cases were diagnoses confirmed at autopsy. The evaluation of brain scanning on this basis may, of course, result in spurious conclusions.

Neuroradiological techniques themselves may err in demonstrating lesions. Correlations based on the patient's clinical history are equally tenuous as a means of evaluation. It is not uncommon to encounter a patient with a large tumor that has obviously developed over a long period without outward manifestations. In short, neurological and neuroradiological techniques are not sufficiently accurate in themselves to permit judgments on the accuracy of another diagnostic method.

With these objections in mind, we initiated a study to evaluate brain scan correlations with autopsy only. A secondary aim was to find out what types of lesions contribute to false-negatives. With this information we hoped to suggest ways by which the diagnostic procedure might be improved. We reviewed 84 cases in this retrospective study. No attempt was made to reinterpret the scans. The original report sent at the time of the scan was taken from the chart. In all, autopsy was obtained within 6 weeks after brain scanning. At autopsy, the lesions were located precisely by a neuropathologist. Lesions with diameters of 1 mm or more were accurately measured. The relatively brief scan-to-autopsy interval (6 weeks or less), coupled with precise measurement and localization of the lesion at autopsy, permitted a critical evaluation of brain scanning.

MATERIALS AND METHOD

All the patients in this series had neurological abnormalities at the time of brain scanning. Most of the scans were obtained on an emergency basis, either because the patient had a sudden onset of neurological symptoms or because he had a known primary neoplasm elsewhere and had developed cerebral symptoms, the brain scan being requested to help rule out metastases. Most of the patients were male, ranging in age from 22 to 85 years. The scan was usually made within a week of the onset of symptoms. All the scans were obtained 30–45 min after intravenous or intramuscular injection of 15 mCi of ^{99m}Tc-pertechnetate preceded by an oral choroid plexus blocking dose of 200 mg of potassium perchlorate. Two Picker Magnascanners were used, one with a 3-in., the other with a 5-in., crystal. All the scans were made by the same three technicians over a 3-year period. Anterior, posterior, and two lateral views were obtained routinely. All patients had a minimum of three views. In a few cases, the patient's physical condition precluded taking one or another of the views. A 3-in., fine-focusing, low-energy collimator (55 holes) was used. The information density was set to be the same as the voltage at 700–800. The pulse discriminator was set to record the energy range 120–160 keV.

Clinical information and interpretation of scan. At the time the brain scans were made, a brief summary of clinical information pertaining to the nervous system was obtained. Information on skull x-ray, cerebrospinal fluid (CSF), and clinical localization of the lesion was noted on the flow sheet. The results of the contrast media studies were not known at the time of scan interpretations. Prior to the scan, most of the patients had been seen by a neurologist, a neurosurgeon, or an internist.

The scans were first divided into two groups, nor-

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TABLE 1. SCAN AND AUTOPSY CORRELATION OF 84 CASES

Scan normal, autopsy normal	Scan abnormal, autopsy abnormal (pos. corr.)	Scan normal, autopsy abnormal (false neg.)	Scan abnormal, autopsy normal (false pos.)
22 (26%)	33 (39.8%)	28 (33%)	1 (1.2%)
Correct correlation—65.8%		Incorrect correlation—34.2%	

TABLE 2. SIZE OF LESIONS IN 28 FALSE-NEGATIVE CASES

Size of lesion	No. of cases
1–5 mm	8
5–10 mm	3
10–20 mm	3
More than 2 cm	14

TABLE 3. AUTOPSY DIAGNOSIS IN 28 FALSE-NEGATIVE CASES

Type of lesion	No. of cases
Cerebrovascular disease (infarction, hemorrhage)	21
Metastatic tumors	5
Primary brain tumors (acoustic neurinoma lymphosarcoma)	2

TABLE 4. LOCATION OF LESIONS IN 28 FALSE-NEGATIVE CASES

Region	No. of cases
Temporal	8
Near midline	8
Multiple regions	6
Parietal	4
Occipital	1
Postcranial fossa	1
Frontal	0

TABLE 5. LOCATION, NUMBER, AND ETIOLOGY OF LESIONS AT AUTOPSY IN 33 CASES WITH POSITIVE CORRELATION

No. of lesions	No. of cases	Etiology	Region	Side
Single	20	CVA-9 Metastasis-5 Primary-6	Frontal-5 Temporal-5 Parietal-9 Post. cranial fossa-1	Right-6 Left-13 Post. cranial fossa-1
Multiple	13	CVA-7 Metastasis-6 Primary-0		

mal and abnormal. No further comments were made on normal scans. The abnormal brain scans were further divided into two subgroups: tumors and vascular lesions. Scan findings played a prominent role in making this decision.

Tumors were suggested by one or more of the following criteria: (A) a history of gradual onset of symptoms, (B) increased CSF protein with normal cell count, and (C) well-circumscribed scan abnormality. Well-circumscribed scan abnormalities were further differentiated as follows: any well-circumscribed abnormality was interpreted as a tumor; a lesion parasagittal in multiple views which did not extend to the base in the lateral views was interpreted as a tumor; an increased localized uptake along the base of the brain, but not following the main course of one of the three major intracranial vessels, was interpreted as a tumor; an abnormality in the scan with a known extracranial neoplasm was interpreted as a metastatic tumor; and multiple areas of increased uptake without a known primary cancer elsewhere were designated as either metastatic lesions or a fragmented resolving vascular lesion.

Vascular lesions included cerebral thrombosis or embolism, intracerebral hemorrhage, and subdural hematoma. A vascular lesion was suggested by (A) a history of sudden onset of symptoms, (B) xanthochromic fluid and normal CSF protein, and (C) significant increased tracer uptake along the course of one of the three major intracranial vessels. An area of increased uptake extending from the base of the brain to the superior sagittal sinus (more basal activity than vertex activity) was interpreted to be vascular in origin. Increased peripheral uptake in the anterior or posterior views, not necessarily seen in the lateral views, was interpreted as a subdural hematoma.

Autopsy observation. Autopsies were obtained on all 84 patients. Brain sections were evaluated by one of the authors (UT) with respect to the nature, site,

TABLE 6. ETIOLOGIC LESION DIAGNOSED FROM SCAN AND AUTOPSY FINDINGS IN 33 CASES WITH POSITIVE CORRELATION

Scan interpretation diagnosis	Autopsy diagnosis	No. of cases	Results
CVA	Tumor	2	Incorrect diagnosis by scan 24%
Tumor	CVA	6	
CVA	CVA	8	Correct diagnosis by scan 64%
Tumor	Tumor	13	
CVA or tumor	CVA-2 Tumor-2	4	Inconclusive diagnosis by scan 12%

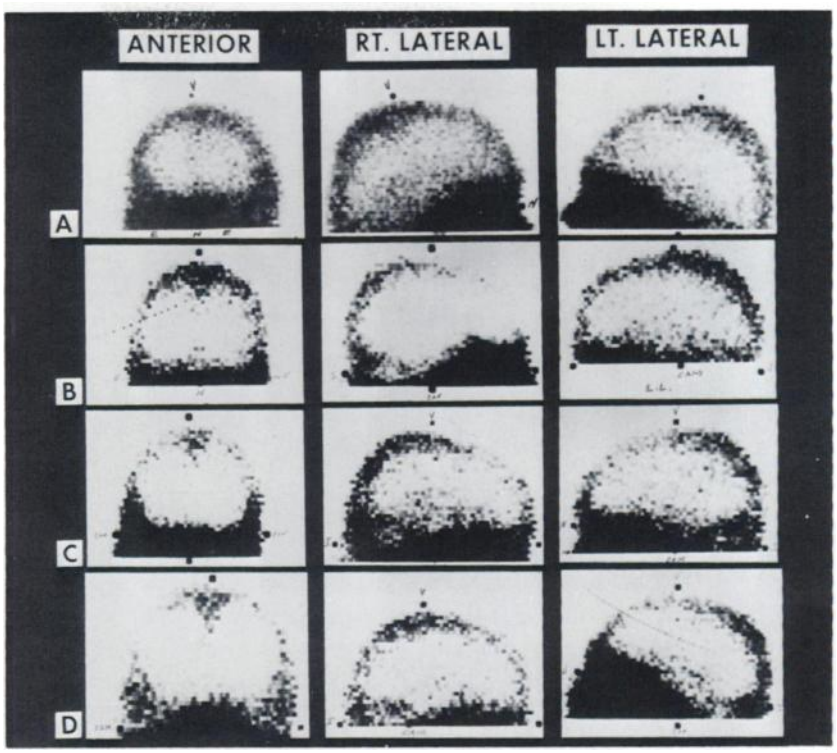

FIG. 1. Brain scans of four patients made with ^{99m}Tc-pertechnetate. All scans were interpreted to be normal. Slightly increased uptake along left skull margin in anterior view in Patient A was attributed to recent trauma. In four cases posterior scans were not obtained, as patients could not lie in prone position.

and size of the lesion. The final pathological diagnosis was made after microscopic study.

RESULTS

In the period from January 1967 to December 1969 a total of 2,258 brain scans were performed using ^{99m}Tc-sodium pertechnetate. Only those scans with scan-to-autopsy intervals of less than 6 weeks were chosen. Of the 2,258 scans, 84 cases met this criterion.

Table 1 shows the scan and autopsy correlation. Of 84 cases, 22 (26%) of the brain scans were normal, with no lesions at autopsy. In 33 cases (39.8%), the brain scans were abnormal and there were lesions at autopsy (positive correlation). Thus in 65.8% of the cases, the scan-autopsy correlation was correct. In 28 cases (33%), the scan was normal but the brain showed lesions at autopsy (false-negative). In only one case (1.2%) was the scan abnormal and no lesion found at autopsy (false-positive). In 34.2% of the cases, therefore, the scan-autopsy correlation was incorrect.

Table 2 shows the size of the lesions in the 28 false-negative cases. In over half of the false-negative group, the lesion size was more than 2 cm. Table 3 gives the autopsy diagnosis of these 28 cases. It is evident that 21 of 28 (75%) were vascular lesions. Only two were primary neoplasms (one was an acoustic neurinoma, the other a lymphosarcoma); the remaining five were metastatic tumors. Table 4 indicates the location of the lesions of all 28 cases. It is evident from the table that temporal, parietal, and midline lesions most frequently did not visualize on the scans. Frontal lobe lesions were not missed.

Table 5 shows the location, number, and etiology of lesions in the 33 positively correlated cases. Vascular and metastatic lesions may be single or multiple. Because primary neoplastic lesions are usually single, such neoplasms are ruled out when there is more than one lesion by scan.

All of the lesions correctly identified by brain scan were more than 2 cm in diam, with the exception of one of 0.5 cm. In all positively correlated cases, the localization of the lesion by scan corresponded correctly with autopsy for lesions more than 2 cm in size. Of 13 multiple-lesion cases, two of the seven patients with vascular lesions and one of the six patients with metastatic lesions showed one or two lesions more at autopsy which were not detected by scan (Table 5).

Table 6 shows the results of the diagnoses of basic lesions based on scan configuration, interpreted with the knowledge of clinical information. The correct etiologic diagnosis could be predicted in 64% of the abnormal scans. Diagnoses were wrong in 24% and inconclusive in 12% of the cases.

Figure 1 illustrates four cases with normal scans where lesions of over 2 cm were found at autopsy. Figure 2 shows the type of lesion found at autopsy in Cases A, B, and C. (In Case D a gross photograph was not obtained.) In Case A the scan-to-death interval was 15 days. The anterior scan shows a

slightly increased tracer concentration on the left side. At the time of the scan there was a suggestion of recent trauma, and the increased concentration of tracer was attributed to scalp trauma. A left subdural hematoma was found at autopsy (A_1 in Fig. 2). In Case B the scan-to-death interval was 26 days. At autopsy a 4-cm metastatic lesion was found in the left occipital region (B_1 in Fig. 2). In Case C the scan-to-death interval was 7 days. At autopsy a bilateral subdural hematoma was found (C_1 in Fig. 2). In Case D the scan-to-death interval was 9 days. Autopsy showed a left temporal infarction measuring 2 cm (not shown in Fig. 2).

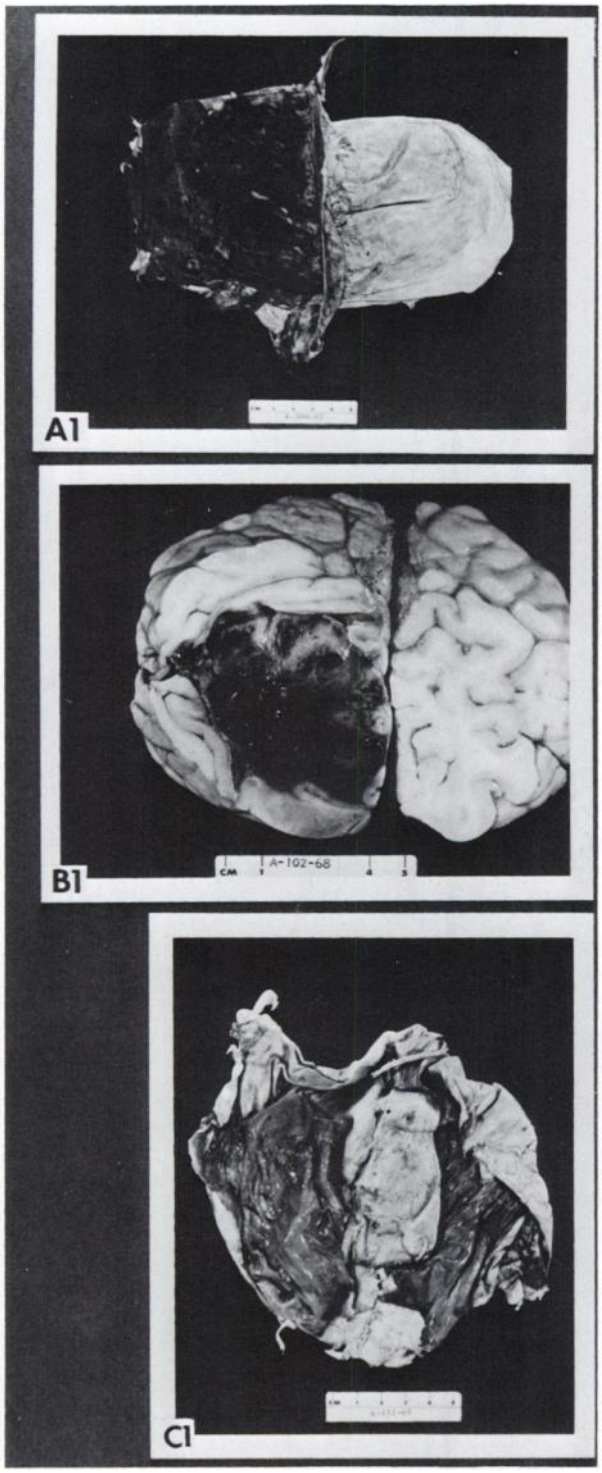

FIG. 2. Autopsy findings in three of four cases shown in Fig. 1. A_1, B_1, and C_1 are photographs of gross specimens of intracranial findings in patients A, B, and C. Patient A had left subdural hematoma; Patient B had metastatic tumor on left side; and Patient C had bilateral subdural hematomas. Patient had left temporal infarction (not shown in figure).

DISCUSSION

To the best of our knowledge, this is the first report of the results of brain scanning where every case studied had autopsy confirmation. Admittedly a lesion might have occurred during the 6-week interval between the scan and autopsy, but the relative shortness of the interval tends to minimize this possibility. Because we excluded patients who had undergone surgery and were living, there is a chance of under- or over-estimation of the true diagnostic sensitivity of brain scanning. Our aim is to point out where brain scanning is relatively insensitive and to suggest improvements. We have tried, using clinical information and scan configuration, to predict the basic nature of the lesion. We hope, in addition, to assess the diagnostic specificity of brain scanning. Many physicians have interpreted the scans using the predetermined criteria described above. This study reflects the overall diagnostic ability of the ^{99m}Tc-pertechnetate scan.

An abnormal brain scan is highly diagnostic of intracranial pathology (Table 1). The accuracy of brain tumor identification at various research centers has varied from 65 to 93% (*5*). In our study, overall correct correlation was obtained in 64% of the cases. Figure 3 shows the percentage of positive lesions identified. Seventy-five percent of the primary neoplasms were identified by the scan. In our study, there were only eight cases of primary neoplasms. During the study period of 3 years, however, many primary tumors were correctly identified and surgically removed; these cases were not included since autopsy confirmation was not obtained. The eight cases are not a realistic indication of the incidence of primary neoplasms in a large Veterans Administration Hospital (1,000 beds).

The overall incidence of false-negative scans in our study was 33%. Most such cases were due to vascular lesions, the remainder to metastatic tumors. Two of the eight primary tumors (25%), five of the sixteen metastatic tumors (31%), and 21 of the 37 vascular lesions (57%) were false-negatives (Fig. 3). It is suggested that a latent period is associated with vascular lesions prior to the appearance of scan abnormalities. In one reported series, some vascular

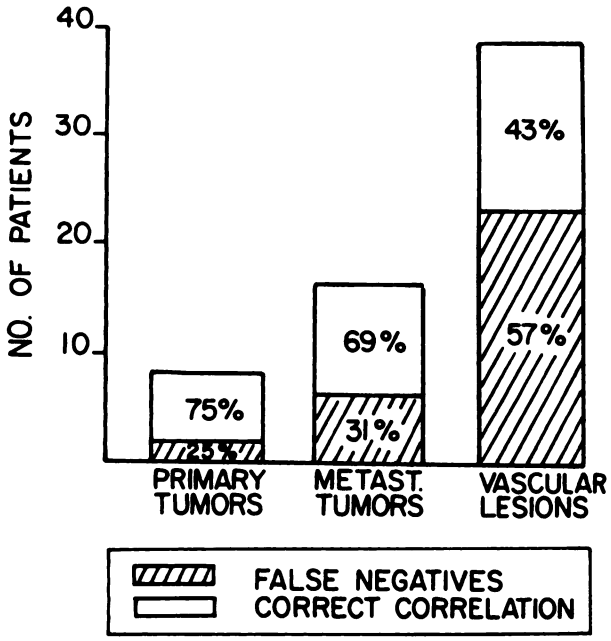

FIG. 3. Brain scan and autopsy correlation of primary and metastatic tumors and vascular lesions. Note high incidence of false-negative scans in vascular lesions.

lesions did not become demonstrable for as long as 10 weeks after the onset of symptoms (*7*). Molinari, et al reviewed 20 patients with cerebral infarctions caused by thrombosis or embolism (*8*). They observed that only 25% of the brain scans were abnormal in the first week (i.e., 75% of the early scans were false-negatives). Subsequent brain scans of these same patients performed during the second and third week after the onset of symptoms increased the incidence of abnormal brain scans to 67%. The incidence of false-negative brain scans in vascular lesions in our study is quite high (57%), reflecting the limitations of brain scanning in the diagnosis of cerebrovascular disease in the early stage (Fig. 3).

Size is an important factor in the detection of brain lesions by scan. It is expected that lesions larger than 2 cm will be readily delineated. Of the 33 positively correlated cases, only one lesion was less than 2 cm. Nevertheless, in about 50% of the false-negative scans, lesions were more than 2 cm in size (Table 2). This category, it should be noted, included mainly vascular lesions and metastatic tumors. Thus not only the size but also the duration, site, and pathology of the lesion are important factors. Most false-negative scans are caused by lesions situated in the temporal region or the midline (Table 4). Temporal lobe lesions are probably obscured by temporalis muscle or choroid plexus radioactivity. Potassium perchlorate may not adequately block choroid plexus uptake in all patients. Midline lesions are probably beyond the focal plane of the collimator. In primary tumors, the greater the degree of malignancy, the greater the chance that the scan will be positive. In one reported series, only 53.3% of the Grade I, but 96.4% of the Grade IV, astrocytomas were detected by scan (*9*).

Since most false-negative scans involve vascular lesions, cerebral perfusion studies performed at the time of static studies are most important. In the usual clinical situation, it is impractical to wait 2 or 3 weeks to demonstrate a vascular lesion. In many cases, there may be no opportunity to repeat the brain scan. In recent months, we have been performing ^{99m}Tc perfusion studies with the scintillation camera routinely in all patients suspected of having vascular lesions. In many instances, the perfusion study has been abnormal, the static study normal.

The disparity in the identification of primary tumors (75% positive) and of vascular lesions (43% positive) requires further explanation. At least two phenomena may account for the increased radioactivity observed in abnormal brain areas: (A) the presence of radioactivity in the new vascular network after breakdown of the normal blood-brain barrier, and (B) active radionuclide uptake by tumor cells. It is possible that both are responsible. The highest percentage of abnormal scans in vascular lesions is found in the third or fourth week of the recovery phase. Since new capillaries are formed at this time, it is possible that the blood-brain barrier may be immature or incomplete, and thus may allow the radionuclide to concentrate at the site of the vascular lesion (*10*). In primary neoplasms it appears that the radionuclide is taken up by the tumor cells. Baum has shown very clearly by autoradiography that glioma tumor cells in the mouse and acoustic neurinoma cells in humans accumulate ^{99m}Tc (*11*). This hypothesis is supported by other workers who have observed tumor localization of radioactive substances (*12,13*). The scan appearance of primary neoplasms and vascular lesions is therefore the result of different pathophysiologic mechanisms. One can at present draw no definite conclusions as to the pathophysiology of metastatic tumors.

In this study left-sided lesions were observed to be almost twice as numerous as right-sided lesions (Table 5). The reason is not clear. It is possible that, since left-sided lesions are in the dominant hemisphere, they produce more clinical signs and symptoms, thereby alerting physicians to the possible presence of intracranial pathology.

The correct prediction as to the pathologic nature of the lesion can be made in up to 64% of abnormal brain scans (Table 6). This observation is contrary to the results of studies done with ^{203}Hg-chlormerodrin (*14*). Waxman, et al studied 27 patients and

concluded that cerebrovascular disease could not be differentiated from cerebral tumors. There is no ready explanation for this disparity, although it may be related to the less advantageous radiopharmaceutical agent employed in their study. We feel that an attempt should be made to predict the basic nature of the lesion. This will certainly help the clinician in the management of the patient.

CONCLUSIONS

The diagnostic ability and limitations of the ^{99m}Tc brain scan were evaluated in 84 cases. In every case an autopsy was performed. Scan-to-death intervals were 6 weeks or less. It is concluded that: (A) an abnormal scan is highly diagnostic of intracranial pathology; (B) overall false-negativity is 33% (25% of primary neoplasms, 31% of metastatic tumors, and 57% of vascular lesions give false-negative results when the scan is done within a week of the onset of clinical symptoms); (C) the majority of false-negative scans are either in the midline or in the temporal region; and (D) when clinical information is considered, the basic nature of the lesion is predicted in 64% of the abnormal scans. It is suggested that cerebral perfusion studies may increase diagnostic sensitivity for vascular lesions in the early stages of evolution.

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