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THE USE OF BRAIN SCANNING IN THE DIAGNOSIS OF INTRACRANIAL TUMORS

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Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska February 1, 1966 Omaha, Nebraska

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Introduction

The rose of scintillation scanning for the detection and localization of intracranial neoplasms has, in recent years, become an increasingly important one in medical centers throughout the country. However, this roke has been a varied one as a diagnostic procedure due to the different methods of detection and recording, the wide variety of radioactive materials employed, and the differences in interpretation of scans. The results of scintillation scans have, in some instances, been used as correlative information, along with pneumoencephalography and arteriography, and clinical information, in arriving at tentative diagnoses. In other cases, the information obtained by scanning has been sufficient to warrant operative procedures in the presence of strong clinical findings.

In an attempt to make an evaluation of the accuracy of brain scanning generally, and to assess the role of the various methods and agents used, a number of reported series of scans are reviewed herein.

In each series, the materials and methods will be rewiewed and the accuracy, advantages, disadvantages and implications will be discussed and compared, and an overall analysis of all cases in these series will be pre-

(1)

sented. Emphasis will be placed on the definitions of positive and negative scans and the criteria for such designations, and upon the incidence and meaning of false positive and false negative scans.

History and Principles of Brain Scanning

Brain scanning, as with other scintillation scanning, is carried out in most instances with rectilinear scanning devices. Basically, a rectilinear scanner consists of a collimator which allows passage of gamma rays from a sharply defined region in the patient to the detector, the detector which gives electrical evidence that gamma rays have reached it, the spectrometer which sifts out information deemed desirable and a recording device. Tracer substances employed must be of higher energy level than used in scanning other organs because they must penetrate the skull, or else be limited to use at operation. To be pharmacologically ideal, they should accumulate in the tumor with good count rate differential between normal and abnormal tissue.(1)

Brain scanning has been carried out since World War II. The first compound used was dilodo-131-flouroscein by Moore in 1947. (2) Geiger-Muller detectors, mounted on the two sides of the head for count rate comparison

(2)

were used by his group. Later, radioiodinated serum albumin was found to be more pharmacologically suitable and has continued to be quite popular. The development of rectilinear scanners and improved collimators made the procedure easier to perform, requiring less time for scanning and obviating many technical problems in mounting the Geiger-Muller detectors.

In 1959, Blau and Bender introduced Hg-203 chloromerodrin which has a short biological half-life and is rapidly excreted by the kidneys, and makes scanning possible soon after injection, and later Hg-197 chloromerodrin which has an even shorter biological half-life. (3) Other substances such as P-32 and K-52 were tried and found to be unsuitable for routine scanning. P-32 does not penetrate the skull and K-52 has high energy gamma rays which lead to technical difficulties. (4)

A mechanical dot recorder to indicate the level of gamma radiation detected was devised by Cassen in 1951.(5) Later, Horwitz and Lofstrom introduced a method of photographic recording, (6) and Herring combined mechanical and photographic techniques to make routine scanning feasible.(7) Indeed, early scanning procedures were considered by some to be not helpful enough, prior to 1959, to warrant their continued use.(8) The same workers,

(3)

using the techniques of Blau and Bender, have since foung it to be a welcome adjunct to other methods and in some cases, they are willing to operate without further contrast studies on the basis of brain scans alone.

In order to localize brain tumors, both lateral and anterior projections should be obtained. In addition, posterior projections are desirable when lesions of the posterior fossa are suspected. In the lateral projections, the area of normal brain appears as a light area of low count rate surrounded by vascular structures which appear darker because of high count rate. A peripheral rim of increased count rate appears at the margin of the head becoming wider posteriorly. This is due to the scalp, underlying calvaria, and the superior sagittal sinus. Just below the vertex, a linear area of activity is frequently seen where the superficial cerebral veins merge with the superior sagittal sinus. Inferiorly, increased count rate extends below a line from the nasion to the . external auditory meatus. This is due to the vascularity of temporal, orbital and facial muscles and the mucous membranes of the nasal cavities. There is also increased out 🗺 🖚 count rate below a line from the external auditory meatus to the inion due to muscles inserting into the base of the skull. The lateral dural sinuses also produce a ver-

(4)

scanned, 71 were subsequently proved to have intracranial tumors. The results of their scans are presented in Table I.

T	a	b	1	e	I
4.	CL,	0	-	U	

Diagnosis	Positive	Negative
Meningioma	13	0
Metastatic	16	3 (post. fossa)
Glioblastoma	5	2
Astrocytoma	44	
Glioma	4	2 (pontine)
Medulloblastoma	0	l (post. fossa)
Hemangioblastoma	0	l (post. fossa)
Acoustic Neuroma	l	0
Ecendymoma	l	0
Pituitary tumors	4	6
Uncertain	4	1
Tota	ls 52	19

In addition, this group had 16 scans which were read as positive in which the diagnosis was not brain tumor. Of these, 7 were encephalomalacia, 3 arteriovenous fistulas, 2 hematomas, and 4 others. Also, in this series of patients in which tumors were found, pneumoencephalograms and ventriculograms were obtained. Five of these did not reveal a localized mass by either of these methods.

(6)

In 4 of the 5, localization was achieved by scanning.

The method was successful in 70% of all intracranial lesions, with a success rate of 73% in detection and localization of intracranial tumors. It was felt that the advantages of the technique were it's freedom from discomfort and complications, the position and extent of lesions was accurately demonstrated, the methods does not depend on displacement, and that a localized scan almost always indicates the presence of an organic lesion-This group felt that other confirmatory procedures should be carried out. (10)

Group II - University of Michigan

The first intracranial scans at the University of Michigan Hospital using the methods of Blau and Bender (3) were carried out in December 1960. This method employs a universal recording system and radiomercury Hg-203 labeled chloromerodrin (Neohydrin.)

A dose of 10 microcuries per kg. with a maximum of 700 microcuries was used. Scans in the lateral and anterior-posterior projection were made. The physical halflife was found to be 47 days, the biological half-life to be 13 hours. Kidney dose may be up to 8 rads per 100 microcuries with a total body radiation of 300 millirads.

(7]

Results: A total of 74 scans was carried out. of these, 24 were read as positive for surgical lesions, 36 were read as negative, 9 equivocal. There were 5 scans which were false negatives and which proved to be avascular at operation. Fifteen of the 24 which were read as positive have been confirmed by operation or postmortem examination and 6 by positive arteriography, pneumography or both. Of the 15 tumors demonstrated by surger, 5 were glioblastomas, 4 meningiomas, 2 astrocytomas, 3 were metastatic and 1 was a dermoid cyst. Highest uptakes were in glioblastomas, meningiomas and adenocarcinomas. Current accuracy is approximately 80 %.

The reporter concludes brain scanning by this technique to be an effective method of tumor diagnosis which carries no risk whatsoever. The amount of radiomercury seems excessive, but the seriousness of the lesions under donsideration justifies any mild risk of radiation exposure to the kidneys. Arteriography rarely demonstrates the tumor itself and ordinarily merely demonstrates indirectly a surgical lesion by displacement of blood vessels. Pneumoencephalography also rarely demonstrates tumor and is an inditect method subject to misinterpretation. When a scan is positive, direct evidence of the exact location of the tumor is obtained, and a more

(8)

accurate surgical approach to the tumor can be planned. When unequivocally positive, even though neurologic findings are minimal, this group is willing to operate without further contrast studies should the symptoms and accessibility of the tumor warrant such a procedure. (11)

Group - Hahnemann Medical College

In this study, Hg-203 chloromerodrin was used according to the technique of Blau and Bender. One cc. of Neohydrin was given I. M. 24 hours prior to scanning as a blocking dose to the kidneys. Ten microcuries per kg. was used with a maximum dose of 700 microcuries. All patients had diagnostic studies such as cerebral arteriograms, ventriculograms and/or skull films. Lateral and anterio-posterior projections were obtained at $2\frac{1}{2}$, 5, 24, and 48 hours. Blood level radioactivity was measured during this time, and 24 hour urinary excretion was determined. There was no evidence of toxicity or untoward effects and no significant difficulty with scanning. Radioactivity at 24 hours was 17%, 4.2% at 48 hours. Physical excretion at 48 hours was 32%. Total body radiation dose is considered to be higher since there is significant retention of Hg-203 beyond 24 hours. Total radiation dose in 70 kg. man is 290 millirads, less thanthe 700 millirad dose with RISA. These workers felt

(9)

that a significantly shorter biological half-life makes this a safe compound.

Results: In 17 patients scanned 5 of 7 scans were read as positive, 2 as negative in patients which were subsequently shown to be intracranial tumors. In this series, all cerebral vascular accidents were read as negative. (12)

Group IV - Mayo Clinic

In conjunction with studies of the turnover of macromolecular substances at the Mayo clinic, investigation of polyvinyl pyrrolidone - I-131 was begun at that institution. It was the feeling of these workers that recent improvements in instrumentation and the improvement of accuracy with the mercury compounds gave the formerly disappointing technique of brain scanning a note of optimism. They also felt that certain properties of this macromolecular substance might offer some improvements two the technique. This report deals with the results obtained with the first 94 patients who were given brain scans in their investigation.

Methods: Patients with signs and symptoms suggesting intracranial tumors were studied. All but a few of them had not yet undergone contrast studies by anglography or pneumoencephalography. Five hundred microcuries of I-131

(10)

PVP was injected intravenously. The first patients were scanned on each of the succeeding 3 days until the time of optimal contrast between lesion and background was established. Subsequently each patient was scanned once. Scanning routinely was performed in anterio-posterior, postero-anterior and lateral projections. A mechanically tracking scintillation scanner was used and both photo scans and Telededtos-dot recordings were obtained. The masion, inion, and external auditory canals were marked on the films in appropriate projections for accurate superposition over the patients skull roentgenograms.

Results: The scans were evaluated in two ways. First of all, all scans were evaluated without any prior knowledge of the clinical situation on the part of the observer. They were then re-evaluated, seperately in the light of a review of the clinical history. Fortysix of the 94 patients were eventually shown to have brain tumors on the basis of histologic confirmation, angiography, pneumography or stron clinical evidence, or a combination of these criteria. Of the 46 patients, the tumors were located correctly in 36. Six were observed to have suggestive (indeterminate) scans in the presence of probable tumors and four, with proved brain tumors, gave negative scans. The scan method located

(11)

accurately 4 of 6 lesions in the posterior fossa and was suggestive in one more. No false positives were observed. In 25 of the 46 cases, histologic confirmation of the lesions was obtained. Correlation of the scan method with other diagnostic criteria is shown in Table II.

Table II

Correlation of scan method with other diagnostic criteria:

Criterion		<u>can</u> <u>result</u> negative	equivocal
Histologic confirmation			
Ažtrocytoma, Grades	1-4 9	3	0
Meningioma	6	0	0
Metastasis	l	0	1
Sur de Barcoma	l	0	0
Chondrosarcoma	1	0	0
Neurilemmoma	l	0	0
Medulloblastoma	2	0	0
Confirmation by contrast	study 8	1	0
Strong clinical evidence	7	0	5
Totals	36	4	6

When interpretation of the scans was carried out without knowledge of the clinical findings, the over-all accuracy was 78% and for tumors in the posterior fossa, accuracy was 66%. When available clinical data were taken into consideration, the accuracy increased to 84% and 83% and 83% respectively. The scan was negative in only 4 of the 46 cases of tumor, indicating the high degree of correlation between abnormal scans and the presence of tumor. The 48 hour delay necessary between injection of isotope and scanning may be criticized as a loss of vital time. However, the great majority of brain tumors do not present as surgical emergencies.

I-131 PVP does not accumulate in the cranial and suboccipital musculature, thus the contents of the posterior fossa may be studied. This is a distinct advantage. Interpretations by this method were difficult mainly when lesions were adjacent to the base of the skull where background radioactivity was relatively intense. Meningicmas produced more intense radioactive foci and all were localized correctly. Astrocytomas varied in density and this did not appear to be related to the degree of malignancy. The mechanism of tumor uptake of this material is not known. It is suspected that diffusion from vasculature takes place. (13)

Group V - W ashington University.

Workers at Washington University found the use of radio mercury labeled with chloromerodrin used with scanning scintillation detectors and photographic recordings to be a useful method in the localization of intracranial tumors in the majority of cases prior to using contrast studies. The isotope initially used was Mg-203 tagged to chloromerodrin. Later Hg-197 was used in this series because of the shorter physical half-life (65 hours) and the absence of beta ray emission which reduces the Ridney dose to 3.06 rads.

The dose used in this study was 700 microcuries of either isotope intravenously 3 to 5 hours before the scan. Head immobilization was required. The side suspected of harboring neoplasm was placed nearest the probe. Minimum examimation included 1 lateral and the anterior view. If a tumor was suspected in the posterior half of the head, the posterior aspect was scanned. All four views were required where localization was not evident clinically or where multiple lesions were suspected.

The scan was interpreted as positive only if 3 adjacent lines exhibited abnormal uptake in corresponding areas on two views. If such an area was present on only l view, the scan was read as equivocal. Twenty-five percent of patients scanned were scanned with both of the agents and results were satisfactory and comparable.

Results: A total of 67 patients were scanned, of which 31 had intracranial tumors as final diagnoses after

(14)

hospital evaluation. The results of the brain scans on these patients are shown in the following table, Table III.

Type of tumor	<u>00</u>	sitive scan	<u>negative</u> scan
Gliobla stoma	5	5 0	0
Metastatic		11	l
As troey toma		2	l
Astrocytoma, cystic		l	l
Meningioma		1	0
Oligodendroglioma		1	0
Acoustic neuroma		0	l
Medulloblastoma		1	0
Choroid plexus papilloma		1	0
Third Ventricle glioma		1	1
Undetermined		2	0
	Totals	26	5

Table III

These 26 patients who had positive localizing scans represent an accuracy of 84%. There were 7 scans with focal uptake without tumors. Six were from patients with cerebral infarctions and 1 had no demonstrable organic pathology and who had an angiogram on the day prior to scan. The main disadvantage as demonstrated in this series

(15)

is the demonstration of non-neoplastic lesions, and on this basis are "false positives". However, a scan showing focal increased uptake almost always indicates focal pathology. Sixteen scans on cerebral vascular accident patients showed that the positivity in cases where there is focal encephalomalacia may be useful in differentiating cerebral ischemia without infarction from cases with ischemic necrosis. (14)

McAfee and Taxdal (10) suggest that scans not be done for one week after anglography due to the possibility of false positive scans. The reporters of these cases place the accuracy of brain scans at 84%, increasing this to better than 90% if only lateral neoplasms within the cerebral hemispheres are included. This is especially significant when low rask, and application of the procedure to outpatients use are considered. Uptake is within the tumor and does not depend on displacement of vessels! In patients with metastatic disease, the demonstration of multiple lesions may relieve the need for further, more difficult studies. It is likely, in the view of these workers, that surgery may be done strictly on the basis of scan alone in some cases, including some posterior fossa tumors. Focal uptake in cerebral infarcts detracts from it's value in determining

(16)

the presence or absence of tumor. Chloromerodrin reduces the objectionable high renal dosage and makes the procedure attractive as a repeatable one. It was also felt that scanning may be useful in determining what study should be done, possible obviating need for other studies, particularly in metastatic lesions. (14)

Group VI - Hartford Hospital

One hundred cases are studied and reported from Hartford Hospital. Hg-203 labeled with chlormerodrin and radioiodinated serum albumin were used for brain scanning. A blocking dose of 1 cc. of mercuhydrin 2 to 24 hours prior to administration of radiomercury or 0.5 cc. of Lugol's solution 2 to 24 hours prior to the administration of RISA was given. The dose of the mercury compound was 700 microcuries given 1; hours prior to the scan. When RISA was used, 500 microcuries was given intravenously 24 to 48 hours prior to scanning. Dot and photo scans were used, la teral and A-P scans were taken routinely and an additional P-A view was taken if posterior fossa lesions were suspected. The final diagnosis was established in all cases under study. Scans were considered positive only when an increased uptake was shown in areas where normally there is no increase due to muscle or adfacent vasculature. In 25

(17)

patients in whom the diagnosis was intracranial tumor, the results are shown in table IV.

Table IV

Tumor	Posit	ive	Nega	tive	Equivocal	L
Glioblastoma	6		0		0	
Astrocytoma	2		0		0	
Astrocytoma,	cystic	1	1		٥	
Unclassified	glioma	2	0)	l	
Sarcoma	2		0)	0	
M ening <u>tio</u> ma	3		0	1	0	
Metastatic	5		0)	2	
Totals	21		1		3	

In this series, accuracy of brain scans was 84%, of arteriograms 92%, and pneumograms, 82%.

The Hartford group felt brain scanning to be a valuable aid in localization and defining the extent of tumors. They found it to be simple, safe, adaptable to outpatient use with only one trained technician. Limiting factors were that there must be differential uptake, the tumor must have a critical volume of 2 cc. or 2 cm. diameter to be detected, and deeper lesions must have an even greater volume. Immobilization may be impossible in restless or semicomatose patients. They felt that delineation of vessels, which scans fail to show, is of

(18)

some importance in surgical procedures. They noted that occipital lesions may be obscured by muscle mass and venous sinuses. Prediction of the nature of tumors was unsatisfactory and they theorized that the chronological appearance of increased uptake may be helpful in this respect, A-V fistulas and hypervascular lesions showing increased uptake almost immediately, meningionmes within 24 hours, and cystic and avascular tumors within 48 hours. They were willing to operate on the basis of scans alone when elinical signs warranted it, in other cases found them to be a useful adjunct to diagnosis. (15)

Group VII - Montreal, Quebec

In this report results of brain scanning in 2 consecutive series of brain tumors which were verified pathologically are summarized. In the first series, RISA labeled with I-131 was used, and in the second, radioneohydrin labeled with mercury 203 was used. Twin balanced scintillation detectors which simultaneously survey both sides of the head from front to back in a series of nine parasagittal concentric arcs are used. Background radioactivity and any differential uptake on either side of the head are registered on a semi-circular chart by suitable symbols. Results with RISA are shown in Table V.

(19)

Table V

Accuracy of a	scan using RISA	
Tunjor	Positive	Negative
Glioblastoma Mult	lforme 15	0
Oligodendroblas- toma	1	0
Oligodendrogliom	a 3	0
Astrocytoma	3	4
Meningioma	? ·	0
Hemangioblastoma	2	1
Metastatic	9	0
Totals	40	5

Results with radioneohydrin are shown in Table VI.

Table VI

Accuracy of scans u	<u>ising</u>	mercury	compounds
Tumor	+		Negative
Glioblastoma	22		0
Oligodendroglion	na 2		0
Astrocttomas, diffuse	4		2
Astrocytomas,			
gemistocytic	2		2
Glioma unclass.	3		
Meningioma	8		0
Metastatic cerci	m. B a		0

In In these two consecutive series of brain tumors, all were verified as to pathology. The first series consisting of 45 patients recieved scans using RISA labeled with I-131 and gave a detection rate of 88%. The second series was scanned with radioneohydrin and also gave a detection rate of 88%. All patients with meningloma, glioblastoma multiforme and metastatic neoplasms in both series showed a positive scan. In all of these a differential uptake as compared to normal regions of brain tissue of 15% or more was reported. The lowest differential uptakes and negative scans were reported in the low grade gliomas. Results were considered equally satisfactory with both materials. It was also noted by these workers that high differential uptakes can be obtained on brain scans of occlusive vascular lesbons which cannot be distinguished from neoplastic lesions of the basis of a single brain scan. Radioneohydrin labeled with mercury 197 was felt by these reporters as the most satisfactory radioisotope available at the present time. (16)

Compilation of Results

The statistical information to follow represents an attempt to compile the detection rates for all types of tumors reported by all of the workers whose cases are under review. It is to be borne in mind that several

(21)

techniques and several radioisotopes have been used, and furthermore, that some of the cases were read without prior knowledge of the clinical findings. In some, but not all of the cases, correlative procedures were carried out on the same patients. The final diagnosis in most cases was made on the basis of histological findings either by biopsy or post-mortem microscopic examination or on the basis of strong clinical evidence. Two of the groups of cases under review were not broken down as to the histological types of tumors and these will be donsidered as undertain or unclassified and are represented in the over-all accuracy of tumor detection by brain scanning.

The detection rate for meningiomas is 93% in all series reviewed, with 5 of the 6 groups reporting having a detection rate of 100%. The 3 cases in which the scans were reported as negative had tumors in the posterior fossa. Metastatic carcinoma was detected at the rate of 92%. The detection rate for glioblastoma multiforme was 96%. Accuracy for detection of astrocytomas was 60%; for gliomas, 63%; for medulloblastomas, 71%; for hemangieblastomas, acoustic neuromas and for ependymomas, 50%; for pituitary tumors, 40% for sarcomas, neurilemmomas oligodendrogliomas and for choroid plexus papillomas, 100%. These last 4 types of tumors were small in number. Uncertain or unclassifiedtumors had a detection

(22)

rate of 81%. Of 270 tumors under review, 222 were read as positive for an over-all detection rate of 82.2%.

Conclusions

1. Early attempts to detect and localize brain tumors by scanning the brain after administration of radioactive materials were unreliable and disappointing until the development of accurate collimation, mechanical and photographic recorders, and radioactive substabces with short biological half-lives. Since 1959, it has become a useful and dependable procedure. (1,2,3,5,6,7)

2. Brain scanning depends on the differential uptake of radioactive substances in the areas of tumor as compared to normal brain substance in which there should be virtually no uptake. Surrounding musculature and vasculature and bony structures represent normal areas of increased uptake. Tumor uptake is dependent in part on increased vasculature and in part on permeation of the blood brain barrier occasioned by the presence of abnormal cellular components in the tumor. (2,9)

3. Chloromerodrin (Neohydrin) labeled with Hg=203 or Hg=197 and RISA labeled with I=131 are considered at present to be highly suitable materials for brain scanning due to their relatively short biological half-lives.

(23)

There is, therefore, decreased hazard of total body radiation. The chloromerodrin compounds deliver considerable amounts of radiation to the kidneys, but not in quantities which are unjustifiable when the seriousness of lesions is considered. These compounds have greatly simplified the procedure of brain scanning because of the short pepiod of time between administration and scanning. (3,8,10,11)

4. Polyvinyl pyrrolidine labeled with I-131 is a macromolecular substance which offers some promise as a scanning material. It's main advantage is that it does not concentrate in muscles and vascudature. It's main disadvantage is the delay between administration and scanning. (13)

5. Contour scanning has the advantage that it does not foreshorten areas near the front and back of the skull and that it may pick up deep midline tumors because of the crossed axes of the projections of the two sides of the head in this area. (16)

6. Brain scanning as it is presently carried out is an innoccaous procedure which is adaptable to outpatients. (3,8,10,11,12,14,16)

7. The best results are obtained in meningiomas, metastatic neoplasms and glioblastoma multiforme. These

(24)

show high high differential uptake and are often parasagittal. Hemangioblastomas and other vascular tumors also show good uptake. (2,10,11,13)

8. Poorest results are with cystic and avascular tumors, such as cystic astrocytomas, and in tumors lying near the base of the brain, in the posterior fossa and in the pontine angle. Posterior fossa tumors may be picked up if additional P-A projections are made.(3,10, 11,13,15)

9. Brain scanning should usually be carried out prior to arteriography and pneumograph because it may obviate the need for these more noxious procedures, or it may give direction as to which procedures should be done next. Contrast studies done prior to brain scanning may interfere with tumor uptake. (14)

10. In the presence of strong clinical evidence the brain scan alone gives sufficient information in many cases to warrant surgical procedures. (3,12,14)

II. In other cases, it is a useful adjunct, especially in localizing and determining the extent of a tumor. It does not accurately delineate the vascular features of tumors as an arteriogram might do. (3,12,13,14)

12. There are virtually no "false positives" as the presence of increased uptake always means there is

(2)

an organic lesion. The most common non-neoplastic lesion picked up is the cerebral vascular occlusive disorder. It may prove to be a useful procedure in determining the extent of such lesions and in differentiating the cases of ischemia from encephalomalacia on the basis of serial scans.(13,14)

13. False negatives occur in those lesions which are small, which lie near the base of the brain, in the posterior fossa or near the midline. Many of these are read as equivocal. It is important to establish strict criteria of differential uptake and the number of lines of increased uptake in reading these scans. (3,8)

Summary

Several series of cases of brain tumors in which brain scanning has been carried out as a diagnostic and localizing procedures have been reviewed. The history of the development of the technique has been discussed and paralleled with the improvement in accuracy of the procedure. Those areas in which brain scanning are the most accurate and in which it offers the least have been discussed and some variations in results have been explained. Variations in methods and materials and their advantages and disadvantages have also been considered. The main purpose of this review has been to delineate and assess the current status and usefulness of scintillation scanning for detection and localization of brain tumors.

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