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METASTASIS OF MALIGNANT NEOPLASMS TO THE BRAIN

A study of incidence, diagnostic effort and trial in therapeutic assessment.

Setiono Diran and Asmino

Department of Radiology

Dr. Soetomo Hospital

Airlangga University

Surabaya Indonesia

22 patients were identified to have metastasis to the Brain from various primary locations. Most of them were from lung cancer (12 patients) then 5 patients having primary from the breast cancer. There were several patients with unidentified primary cancer. Several meningeal involvement were identified from the infiltration of leukemia and nasopharyngeal cancer.

Diagnosis were established by means of clinical, laboratory examinations and carotic angiography, later on additional computerized tomography examination has been included.

Most of the patients came in critical conditions, but after therapy by means of surgery, radiation and cytostatic agents, they showed some improvement.

Name of Registered Participant who will be presenting the paper: Setiono Diran

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METASTASIS OF MALIGNANT NEOPLASMS TO THE BRAIN
A study of patients, histologic effects and
management of metastasis

Setiono Diran and
Department of Pathology
Dr. Soetomo Hospital
Airlangga University
Surabaya, Indonesia

30 patients were admitted to lowland to the brain from

MILIK
PERPUSTAKAAN
"UNIVERSITAS AIRLANGGA"
SURABAYA

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with primary location
(13 patients) from 5
cases. There were

cases. Several members of the

admission of leukemia and carcinoma of breast

Diagnosis were established by review of clinical, histologic

examinations and certain radiologic data on additional

computerized tomography examination has been included.

Most of the patients came in critical condition, but after

therapy by means of surgery, radiation and systemic agents

they showed some improvement.

METASTASIS OF MALIGNANT NEOPLASM TO THE BRAIN *
 A study of incidence, diagnostic efforts and trials
 in therapeutic assessment.

Setiono Diran, Asmino, Sayid Darmadipura

Department of Radiology, Dr. Soetomo Hospital,
 School of medicine, Airlangga University, Surabaya.

It is very hard to detect metastasis of malignant neoplasm to the brain in early stage whereas most of the patients came in a late stage. Carotis angiography, lumbar puncture examination and electroencephalogram do not always give a positive finding. New non invasive procedures have been introduced quite recently with better results by means of computerized tomography of the skull, magnetic resonance and digital angiography.

Therapy is also another aspect of problem due to the difficult localization of metastasis even worse due to the critical condition of most of the patients.

There are three organs with metastasis on which there is a kind of " tabu " to treat it. Those are the brain, the lungs and the liver, because those are critical organs to irradiate without producing radiation side effects and surgery usually is beyond consideration whenever metastasis is involved.

Cytostatics are the only choice of treatment but usually the response is limited.

Miquel de Cervantes in his book " Don Quixote " cited : While there's life, there's hope (chapter 3, page 463).

MATERIALS AND METHOD.

Twenty seven were selected for metastasis to the brain is rare, but once found it will become quite a problem.

Previously the diagnosis was established by means of clinical history and cerebral manifestation like headache, disorientation, visual problems and peripheral paralysis and also by confirmation with EEG and arteriography.

Recently, CT examination is available and metastasis to the brain is readily recognized with less invasive method but with high accuracy, even though it still is a rather

* PRESENTED IN

The 7th ASIA - PACIFIC
 CANCER CONFERENCE

J A K A R T A, 16 - 20 S E P T E M B E R 1985

METASTASIS OF MALIGNANT NEOPLASMS TO THE BRAIN

A study of incidence, diagnostic efforts and results in therapeutic assessment.

Setiono Diran, M.D., Department of Radiology, Dr. Sardjito Hospital, School of Medicine, Airlangga University, Surabaya.

It is very hard to detect metastasis of malignant neoplasms in the brain in early stage whereas most of the patients come in a late stage. Carotid angiography, lumbar puncture examination and electroencephalogram do not always give a positive finding. However, in some cases of metastasis have been introduced with better results by means of computerized tomography of the skull, magnetic resonance and digital angiography.

Therapy is also another aspect of problem due to the difficulty of location of metastasis even worse due to the physical condition of most of the patients. There are three organs with metastasis on which there is a high "take" to treat it. Those are the brain, the lung and the liver. Because those are critical organs no therapy without producing maximum side effects and surgery usually is beyond consideration whenever metastasis is involved. Cytotoxic are the only choice of treatment but usually the response is limited. Miguel de Guzman in his book "New Methods" (page 463) stated: "While there is life, there is hope" (chapter 3, page 463).

MATERIALS AND METHOD

Twenty seven were selected for metastasis to the brain in various once found it will become quite a problem. Presumably the diagnosis was established by means of clinical history and cerebral manifestation like headache, disorientation, visual, auditory, and gait abnormality and also by confirmation with EEG and angiography. Of examination is available and metastasis to the brain is slightly recognized with less invasive method but with high accuracy. even though it still is a tough task.

RESULTS

The first case - PROPHET. J. A. K. A. ... S. E. P. T. E. M. R. K. 1983

expensive, but CT does not always requires hospitalisation and produces less complications than the carotis angiography. Sixteen patients were diagnosed to have brain metastasis by carotis angiography and 9 patients be means of CT examinations and only 3 patient were diagnosed by clinical and laboratory examinations.

Another aspect of problem is treatment, because some people think that with metastasis to the brain, any effort is worthless. But we do not share that opinion our neurosurgeons still consider, that craniotomy followed by wide extirpation of the tumor mass still can be performed, most of them even toto extirpation of the mass. External decompression is being done to function as a safety valve.

External irradiation is then performed with care and accuracy. Three patients received whole brain irradiation because of leukemic infiltration and uncertain location of metastasis. Twenty five patients were irradiated to the localized area of metastasis. It is preferable to use high energy photons like cobalt-60 or linear accelerators of 6 - 10 Mev.

Treatment dose planning should be used to give maximum accuracy and to give optimum dose distribution is improved by combining with high LET electron beam for the peripheral located tumors and rotation treatment for deep located ones. Fourteen patients received complete radiation of 40 - 60 Gy. Another 14 patient received only a small dose, mostly due to poor general condition of the patients.

Beside the metastasis the primary tumor should also be given irradiation.

Cytostatics play an important role in those cases with wide spread metastasis. Combined cytostatics were applied depending on the nature of the primary tumor, such as Cyclophosphamide, Methotrexate, Doxorubicin, -fluoronocil etc

Result and Discussion.

Table 1. The incidence of brain metastasis from various primary neoplasm.

Lung cancer	12 (43%)
Nasopharynx ca.	3
Breast cancer	2
Skin cancer	1

..... Fibro Sarcoma

expensive, but it does not always require hospitalization and produces less complications than the classic angiography. Sixteen patients were diagnosed to have brain metastasis by orbital angiography and 9 patients by means of CT scanning. Only 3 patients were diagnosed by clinical and laboratory examinations.

Another aspect of problem in treatment, because some people think that with metastasis to the brain, any effort is worthless, but we do not share that opinion. Our research work still consider that craniotomy followed by wide excitation of the tumor mass will can be performed, most of them even also excision of the mass without decompression is being done to function as a safety valve.

External irradiation has been performed with care and accuracy. Three patients received whole brain irradiation because of leukemia infiltration had uncertain location of metastasis. Twenty five patients were irradiated to the localized sites of metastasis. It is preferable to use high energy photons like cobalt-60 or linear accelerators of 30-100 kVp. Treatment dose planning should be used to give maximum accuracy and to give optimum dose distribution to involved by comparing with high intensity beam for the peripheral located tumor and rotation treatment for the located case. Localized patients received curative radiation of 40-60 Gy. Another 16 patient received only a palliative dose, mostly due to poor general condition of the patients.

Before the metastasis the primary tumor should also be given irradiation. In some cases, the primary tumor should also be given Cytosaric, may an important role in these cases with wide extent metastasis. Combined cytotoxic drugs applied according to the nature of the primary tumor, such as Cyclophosphamide, Methotrexate, Fluorouracil, Mitomycin, etc.

Result and Discussion

Table 1. The incidence of brain metastasis from various primary neoplasm.

Primary Neoplasm	Number of Patients
Lung cancer	12 (75%)
Esophagus ca	3
Breast cancer	2
Skin cancer	1

Fibro Sarcoma	1
Leukemia	2
Unknown	7

Lung cancer had the highest frequency to develop brain metastasis ($12/28=43\%$). The number of patients suffering from lung ca between 1980 - 1984 were 192, or an incidence of $12/192$ ($6,3\%$).

H.C. Berry (6) found that the frequency of lung ca which developed brain metastasis among other primary carcinomas was 30%. That's why lung ca has become a point of interest in term of diagnosis and treatment in preventing brain metastasis. Nasopharyngeal ca invades into the base of the skull more often than cerebral metastasis.

It is obvious that cerebral metastasis was suspected on clinical examinations, confirmed by carotis angiography and CT examination. Carotis angiography shows indirectly vascular deflection of the space occupying lesion, while CT scan shows directly location, size and nature of the lesion. Brain scan using Technitium pertechnate-99m also has been used, but was lacking sensitivity and specivicity. Recent development in digital angiography promises a simple. less invasive method and reveals sufficient resolution of the picture.

It is also more economical because no hospitalisation is needed, less film is used, less contrast is needed and less risk of developing side effects of the contrast media and catheterisation (8,12,14).

Even more promising in the recent development of diagnostic imaging is the magnetic resonance with the advantage of better anatomic delineation with various direction of cut and with no X-ray exposure to the patient : (4, 13).

Table 2. Initial clinical symptoms.

Headache	6
Vomiting	1
Collaps	1
Disorientation	5
Convulsion	3
Hemiparesia	11
Visual disturbance	1

.....Table 3. .

Table 3. Interval between the finding of primary tumor and development of brain metastasis.

At almost the same time	9 (30%)
Less than 6 months	3
6 - 12 months	3
More than 12 months	4 (14%)
Unrecorded	9

Hemiparesis was the most frequent early symptoms of brain metastasis. The earlier the first detection of metastasis the better was the result.

Because of hemiparesis, usually the patient came to see the neurologists or neurosurgeons. And that's why patients were operated upon because of brain tumors, where as pathologic examination revealed metastasis and later or almost at the same time a small primary tumor also was found (9 patients, all of them were lung ca as a primary site).

H.C. Berry (6) in his research found that 39% of his patients developed brain metastasis 12 months after the primary ca has been diagnosed in our experience it was 14 %. Thomas Doyle (7) found that 20% - 30% of lung ca developed brain metastasis at the time lung ca were found, which was similar with our experience.

Table 4. Location of the cerebral metastasis.

Frontal area	6
Parietal area	6
Temporal area	8 (29%)
Occipital area	2
Unidentified	6



The temporal area was the most frequent site of brain metastasis which coincided with the early findings of the clinical symptoms (hemiparesis). There were 5 females and 23 males in this case.

Table 5. Pathologic findings of the lesions.

Epidermoid ca	14 (50%)
undifferentiated	8
differentiated	6

Table 3. Interval between the finding of primary tumor and development of brain metastases

Unrecorded	9
More than 12 months	4 (100%)
6 - 12 months	2
Less than 6 months	3
At least the same time	8 (100%)

Metastases were the most frequent early symptoms of brain metastases. The earlier clinical detection of metastases the better was the result. Because of metastases usually the patient came to see the neurologist or neurosurgeon and that a way patients were treated was because of brain tumors, where as pathologic examination revealed metastases and later or almost at the same time a small primary tumor also was found. In patients with brain metastases found that 30% of the patients developed brain metastases 12 months after the primary ca has been diagnosed in our experience. It was in Thomas Boyle (7) found that 20% - 30% of lung ca developed brain metastases at the time lung ca was found, which was similar with our experience.

Table 4. Location of the cerebral metastases

Unidentified	5
Cerebellar area	8
Temporal area	8 (100%)
Parietal area	8
Frontal area	8

The temporal area was the most frequent site of brain metastases, which coincided with the early findings of the clinical symptoms of brain metastases. There were 2 patients and 33 cases in this series. Table 5. Pathologic findings of the metastases as seen in Ependymoma ca. The result of improvement of the metastases followed by wide differentiation.

Adeno carcinoma	11
undifferentiated	3
differentiated	8
Leukemia	2
Fibrosarcoma	1
Undifferentiated ca	11 (39%)

Epidermoid ca was the most common pathologic finding in lung (50%), followed by undifferentiated ca (39%), in which the small cell ca type is the most common type of lung ca metastasizing to the brain.

Thomas Doyle (7) found 28% of small cell lung ca developed brain metastasis and John I. Nugent (24) found 49%.

H.C. Berry (6) reported that 58% of his cases were poorly differentiated from various origin.

When the early signs of metastasis is observed, the diagnosis is established and the exact location of the lesion is defined, then surgery should be performed as soon as possible. Our neurosurgeons finds operation of metastasis to the brain to be easier than that of primary tumors the first is a well defined space occupying lesion while the second is rather infiltrative and undefined.

The response of operation is immediate as the the patients are being relieved and quickly improved from distress. But again it depends on the degree of the nerve damage and the interval between the finding of early brain symptoms and the time of operation.

Table 6. Interval between diagnosis of brain metastasis and operation.

Less than 1 month	1	
2 - 4 months	9	(32%)
5 - 12 months	7	
Unclear duration	9	
Inoperable	3	

Only 1 patient responded readily to have an operation done, but most of them delayed their decision for an operation. This consequently influenced the result of improvement. The operation consisted of trepanation, followed by wide

..... extirpation

The technique of operation of most of the cases were more
 simple than that of the primary gliomas of the brain.
 The lesion usually were well delineated and the excitation
 mostly could be done in toto.
 Asher and Hapner (2) used CO-2 laser beam for the
 treatment of neurosurgical diseases like gliomas, meningiomas
 and metastatic disease to the brain. They found that detri-
 mental effects to the patients were minimal like blood loss,
 less irritation and transtension, postop-operative edema
 and pain, less scarring. Furthermore, it could be performed
 with the utmost precision in small operating fields.
 There were 20 patients considered to be operable and only 3
 patients were inoperable due to poor general conditions
 and wide spread of the disease, while 5 patients refused
 operation. The nature of certain disease such as leukemia
 made operation impossible.
 External irradiation were performed in our operable cases
 as a mean of sterilization of the operative area and as a
 palliative procedure in inoperable cases. Localized irradi-
 tion was given to 25 patients and whole brain irradiation to 3
 patients.
 Thomas Doyle (7) applied prophylactic whole brain irradiation
 especially on patients suffering from small cell lung ca,
 which proved to be effective in preventing brain metastasis.
 showed by the decrease in incidence of brain metastasis from
 lung ca, which dropped from 40% to 2%.
 However, in general the survival of the patients appeared not
 to be prolonged due to wide spread activation of the disease.
 High energy photon irradiation like 6 Mev linear Accelerator
 was preferred rather than Cobalt-60, due to superficial
 irradiation with effects. Computerized dose treatment
 planning showed that complication with high LET 12 Mev
 electron beam increased the effectiveness of the peripheral
 brain tissue as revealed in the dose distribution percentage.
 Removal of the bone flap for external decompression improved
 the efficiency of the radiation due to the elimination of
 bone absorption, beside the fact that it acted as a safety
 valve in case the intracranial pressure increases at any
 time. Further investigation proved that higher particle beam
 like neutron beam will improve the result especially in cases

of radio resistant tumors.

Neutron beam therapy has been used for treatment of large epidermoid ca and resistant tumors of head and neck and cervical ca, adenocarcinoma of gastrointestinal tract, radio-resistant tumors like bone sarcoma, malignant melanoma and tumors of the central nervous system and showed better results than by using high photon energy. The radiation injury by neutron beam is about 3 times higher than by high photon energy (CO-60, 4 Mev) with the same dose of irradiation Neutron beam therapy is being used in several institutions like : Hammersmith, RTOG, EORTC, Fermi-Lab, Hamburg-Eppendorf, CHIBA, etc. (3).

Various cytostatics had been used to brain metastasis but the result of treatment was not so positive compared to the primary carcinoma or metastasis elsewhere, due to the phenomenon of Blood Brain Barrier.

John L.Nugent (24) tried to give intrathecal methotrexate combined with prophylactic cranial irradiation in preventing cerebral metastasis of small cell cancer of the lungs and reported a slight improvement in the incidence and some prolonged survival of those who had metastasis (3-5 months) H.C Berry (6) reported that the average survival of untreated intracranial metastasis was about 1 month, while the treated group, either with single or multiple metastasis, was about 4, 8 months,

Table 7. Survival (periode from the cranial operation till last control).

1 month or less	5
2 - 3 months	4
5 months	4
7 months	4
9 months	4
11 months	3
Unknown	3

Average survival 5,48 months.

When the tumor was inoperable or only partly extirpated the response of radiation and cytostatics was limited : There were 3 patients with such situation with only 1 month survival. Most of the patients completed treatment showed

..... deterioration.

of radio resistant tumors. Neutron beam therapy has been used for treatment of large epidermoid and resistant tumors of head and neck and cervical esophagus. The effectiveness of radio-resistant tumors like bronchomas, malignant melanomas and tumors of the central nervous system and showed better results than by using high photon energy. The radiation injury by neutron beam is about 3 times higher than by high energy (100-500 eV) with the same dose of irradiation. Neutron beam therapy is being used in several institutions like: Hannover with RIK, BOSTON, Fermilab, Lawrence Livermore, ORNL, etc. (3).

Various cytotoxic drugs had been used to brain metastases but the result of treatment was not so positive compared to the primary carcinoma or metastasis elsewhere due to the predominance of blood brain barrier.

John D. Gelber (2) tried to give intrathecal methotrexate combined with procarbazine cerebral irradiation in preventing cerebral metastases of small cell cancer of the lung and reported a slight improvement in the incidence and some prolonged survival of those who had metastases (3-5 months). H. E. Perry (6) reported that the average survival of untreated intracranial metastases was about 1 month while the treated group, either with single or multiple metastases, was about 4-8 months.

Table 7. Survival (months) from the cerebral operation till last control.

1 month or less	2
3 - 3 months	4
5 months	4
7 months	4
8 months	4
11 months	3
Unknown	3
Average survival: 7.42 months	

When the tumor was inoperable or only partly excised the response of radiation and cytotoxic was limited. There were 3 patients with such situation with only 1 month survival. Most of the patients completed treatment showed

deterioration of their general condition due to wide spread metastasis to other organs in conclusion, it has been proven that those is a necessity of combined treatment to achieve a better palliation and prolonged survival. Furthermore earlier diagnosis of metastasis, quick action of treatment and better knowledge of treatment technology could improve results.

Acknowledgment :

This paper has been made with the scientific support of Department of neurosurgery.

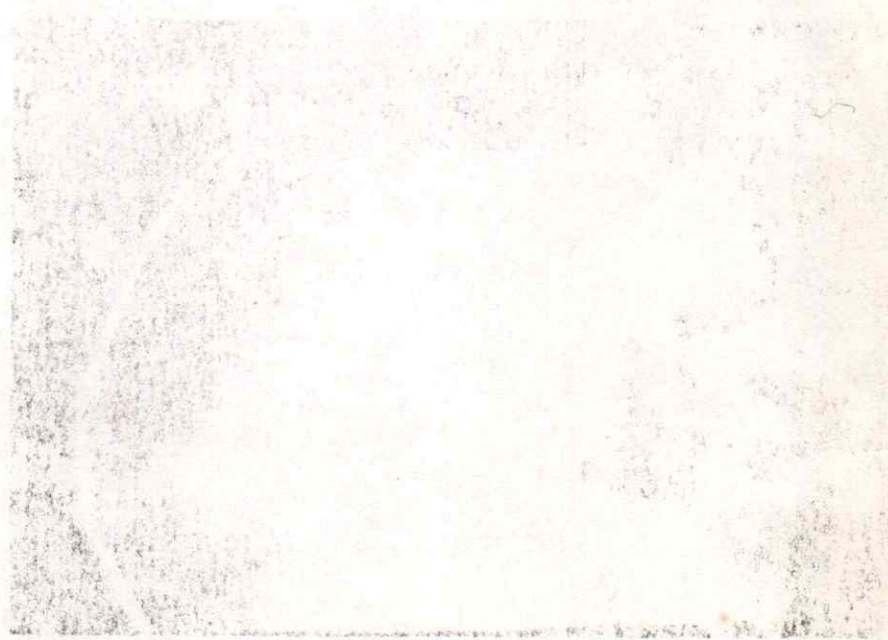
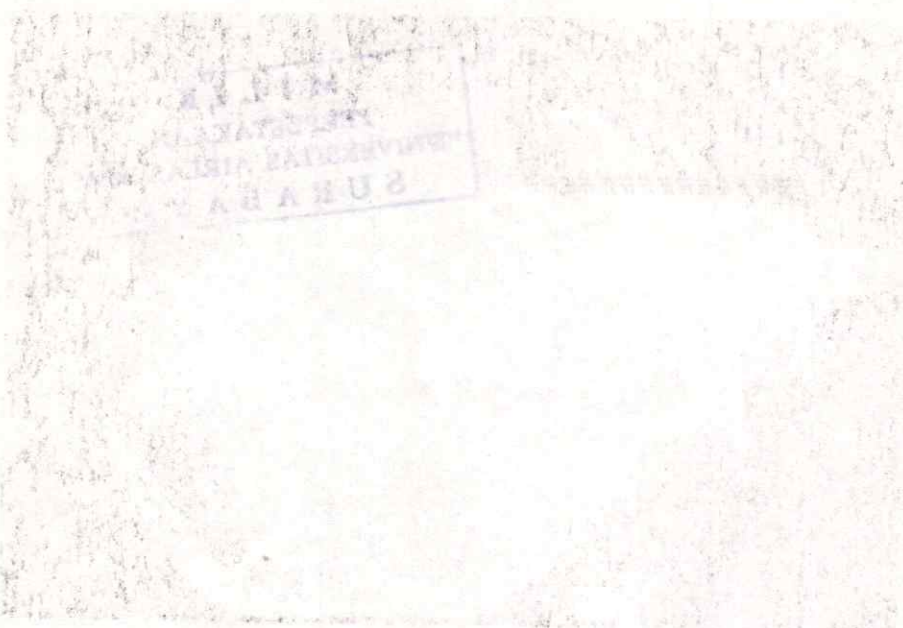
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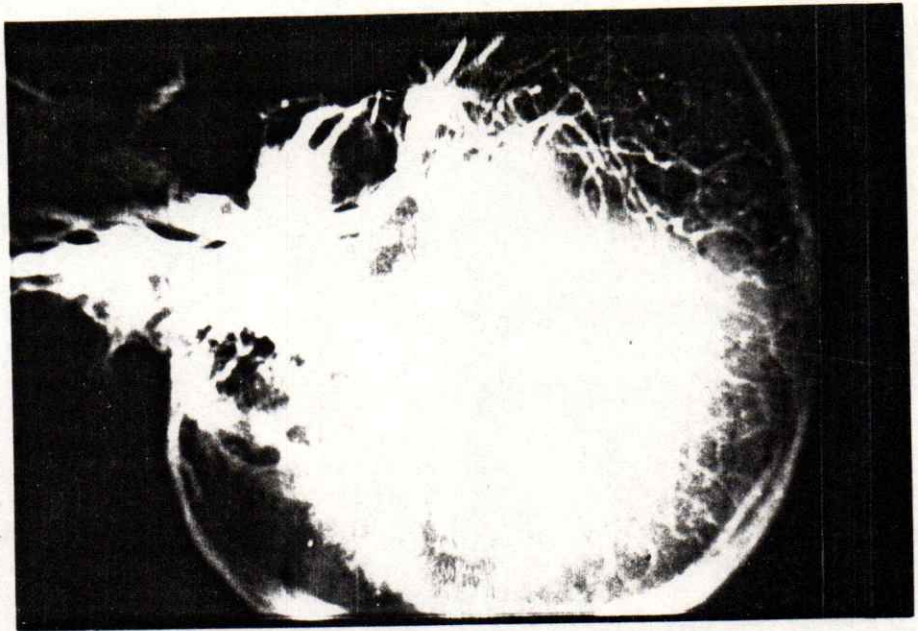
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...and better knowledge of treatment...
...could improve results

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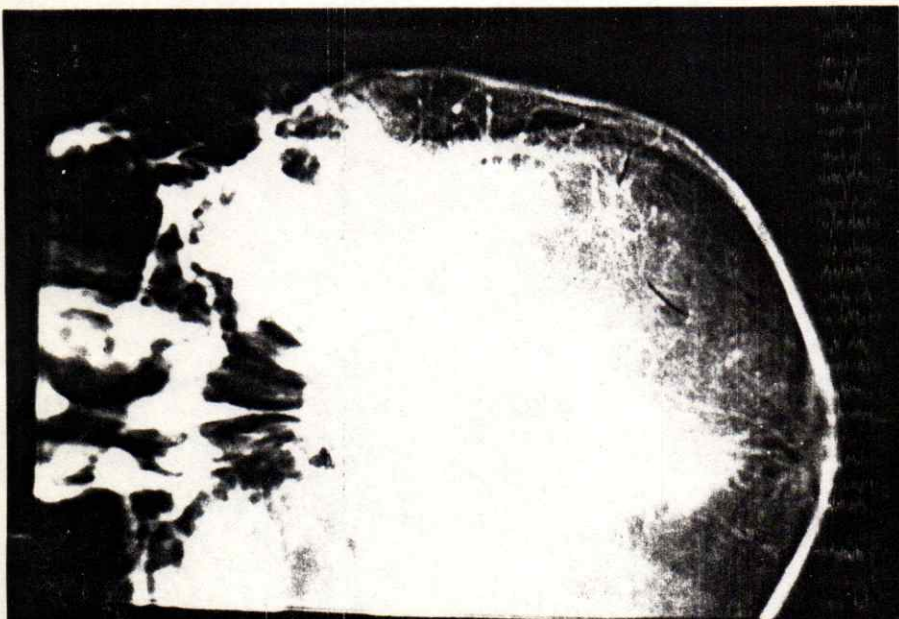
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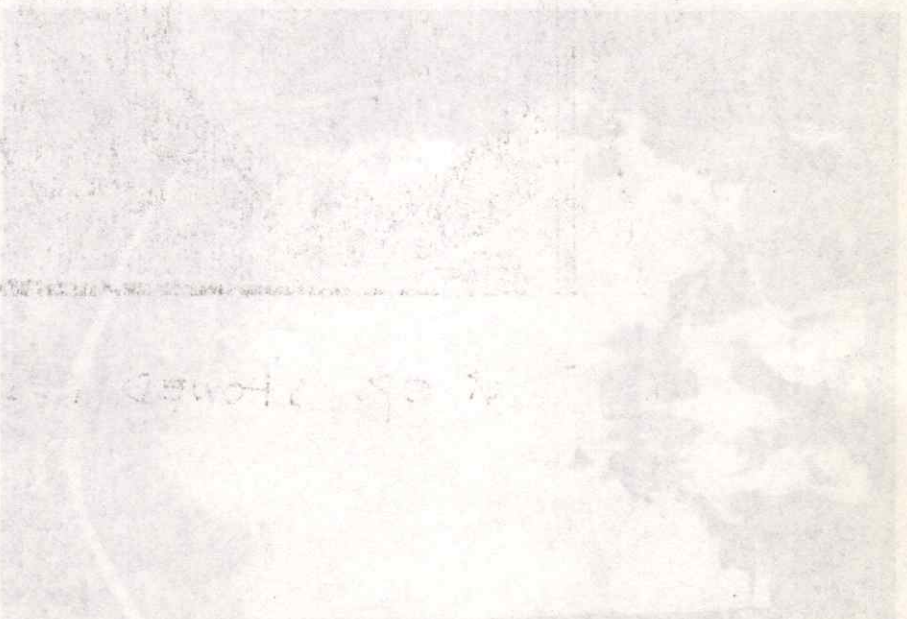
METASTASIS TO THE
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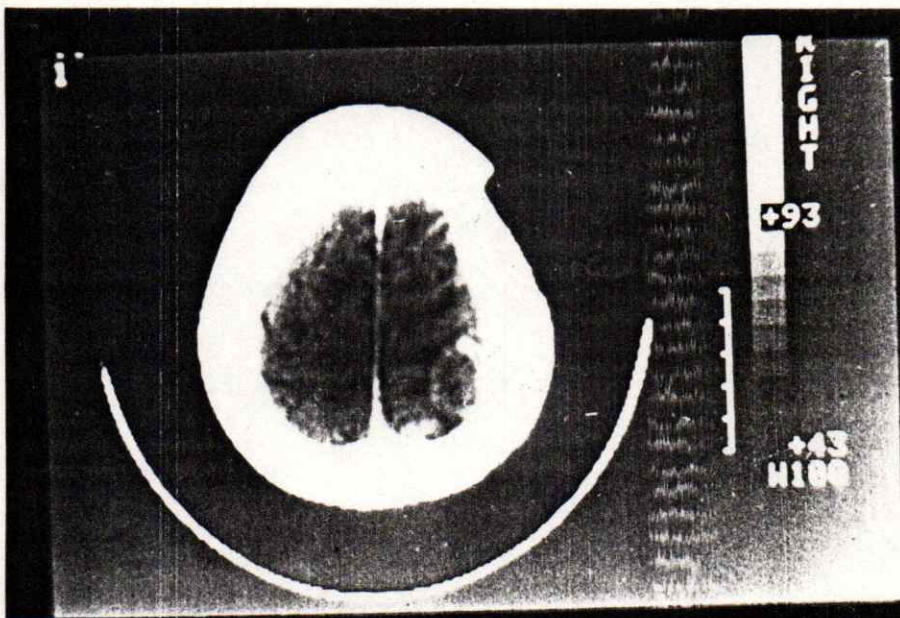
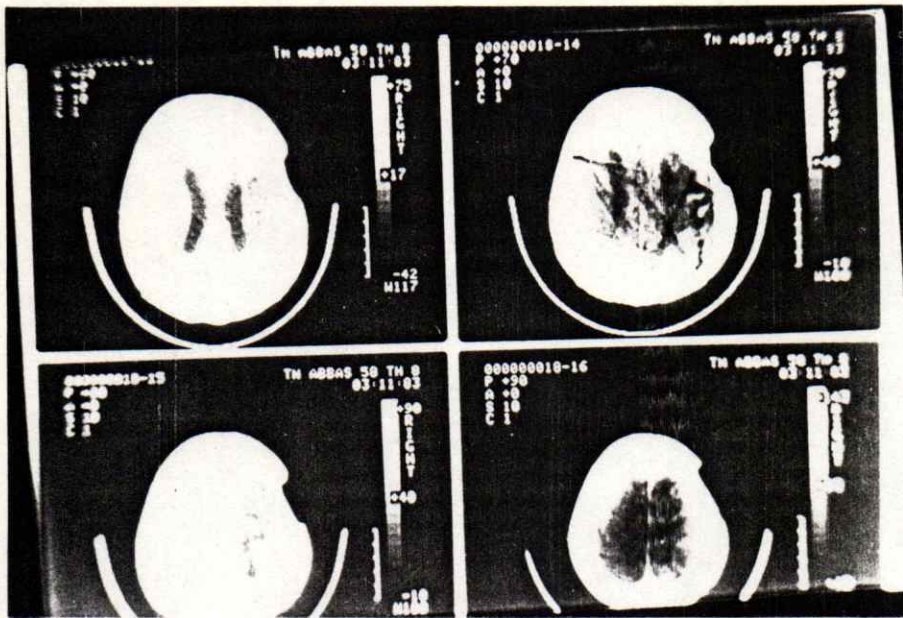
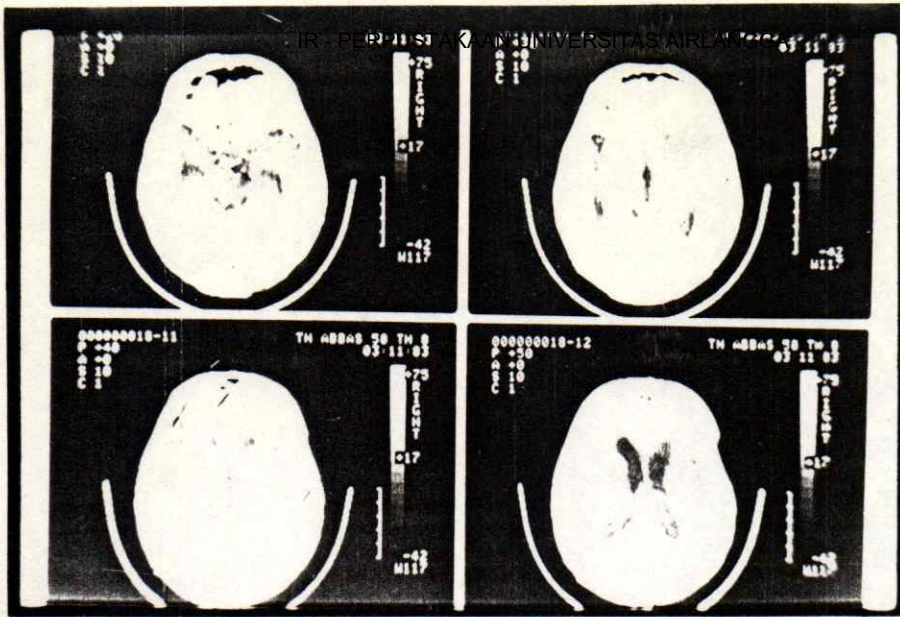


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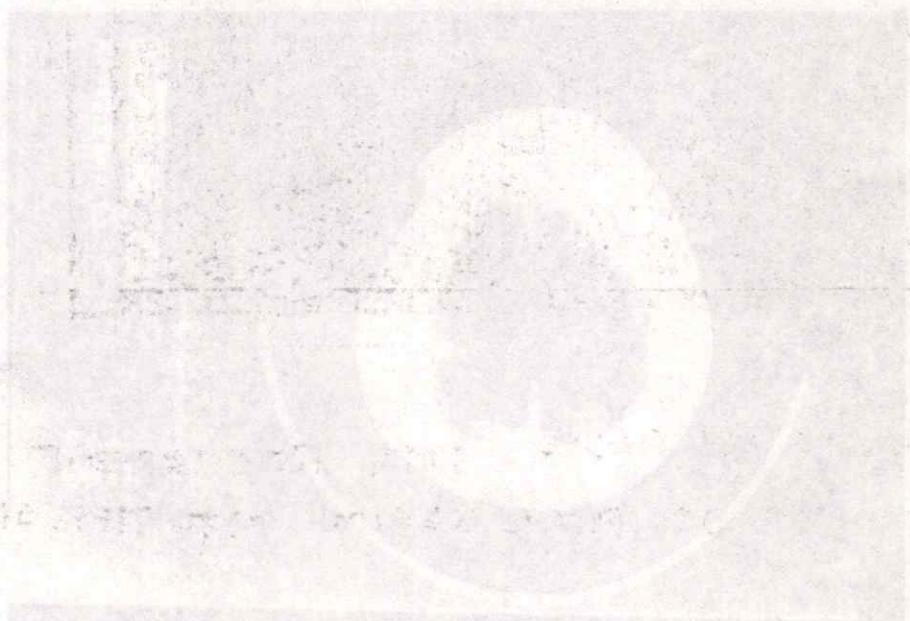
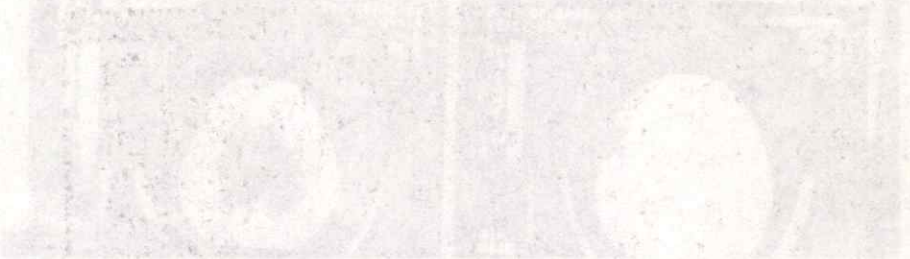
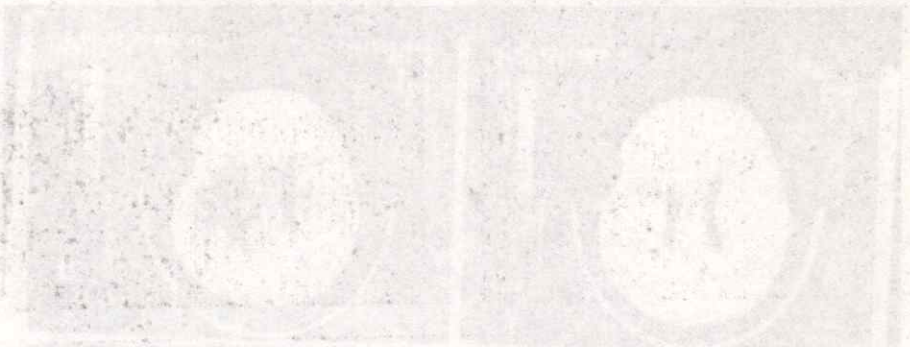
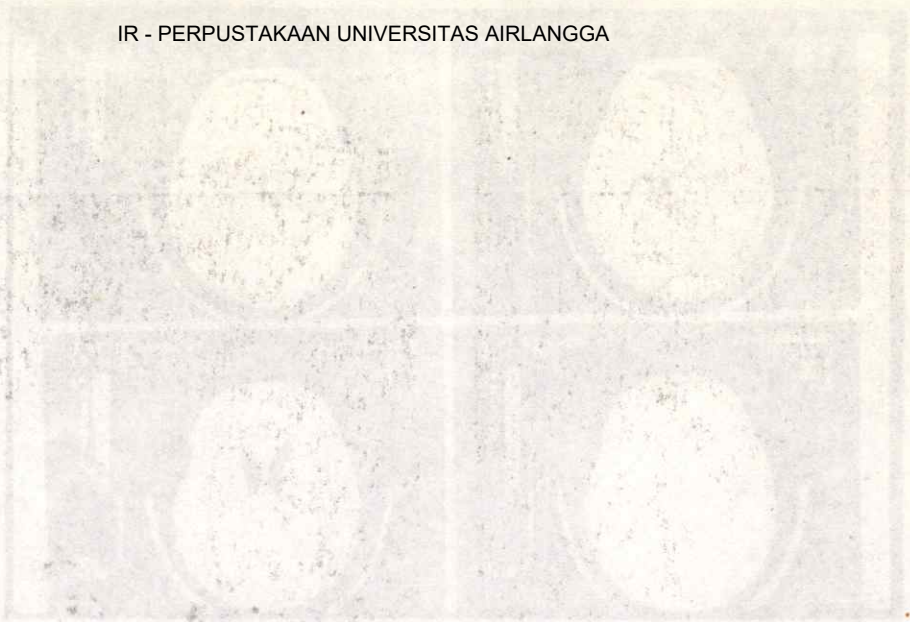


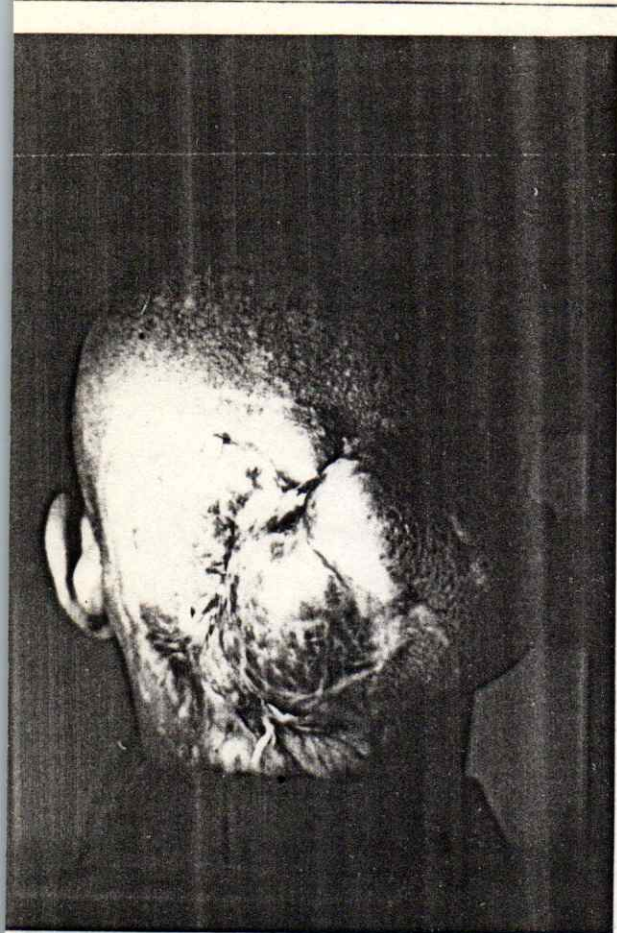
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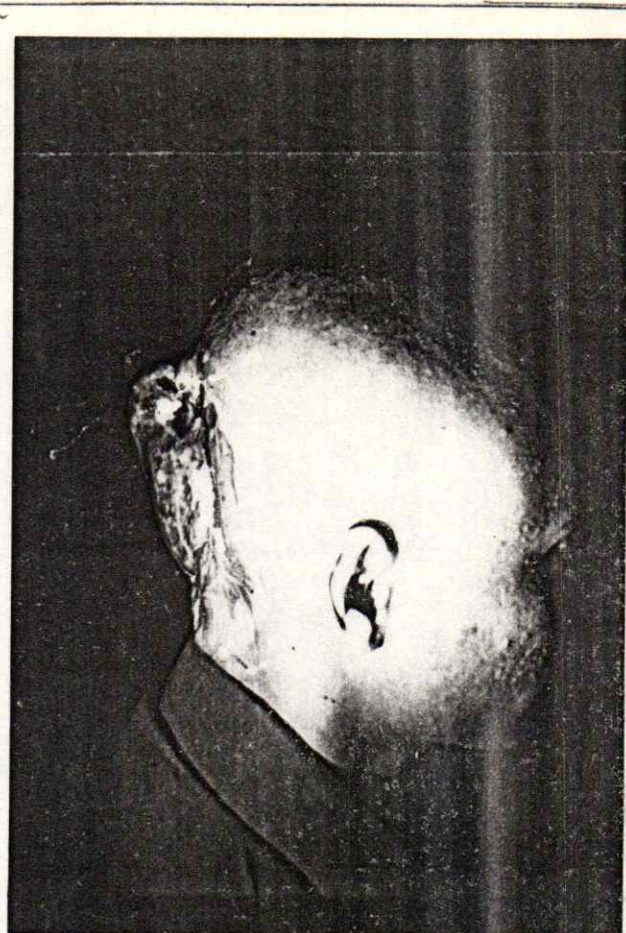


CT post op. showed residual mass

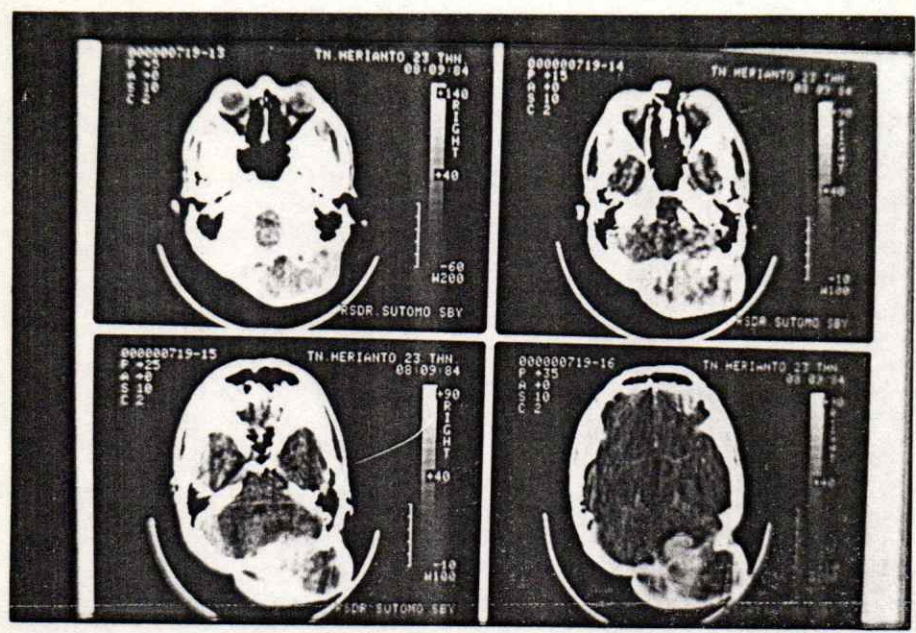




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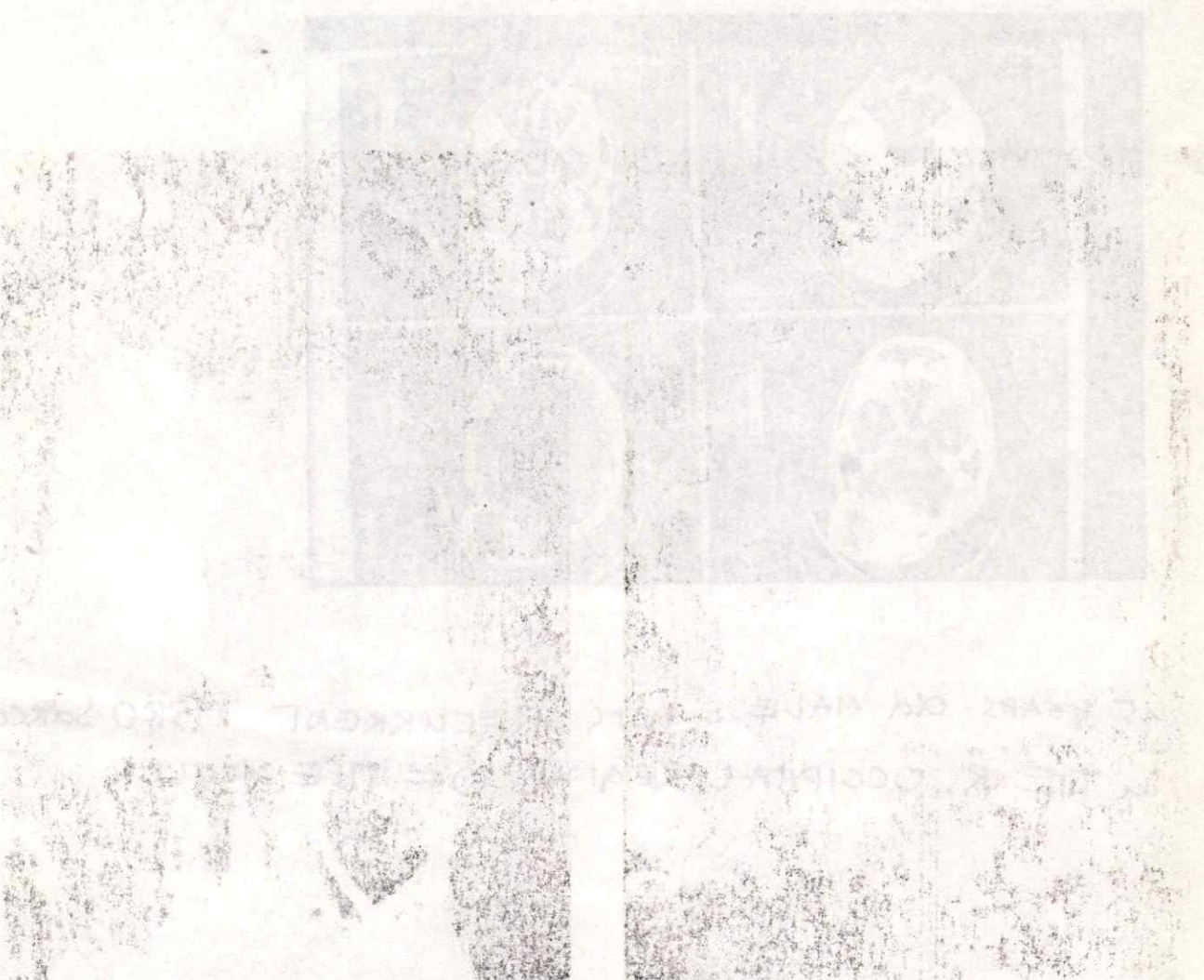
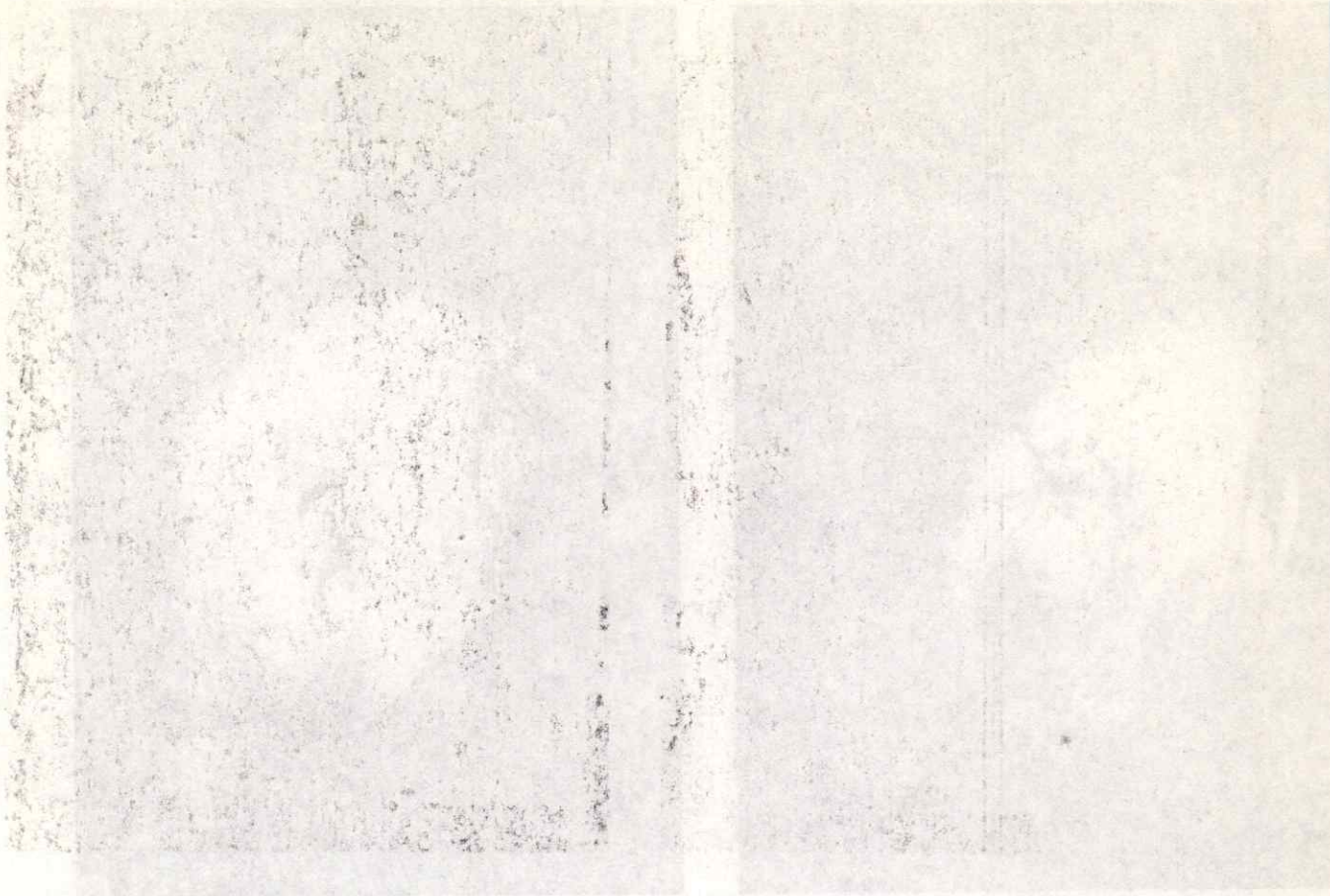


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25 YEARS old MALE . WITH RECURRENT FIBRO SARCOMA
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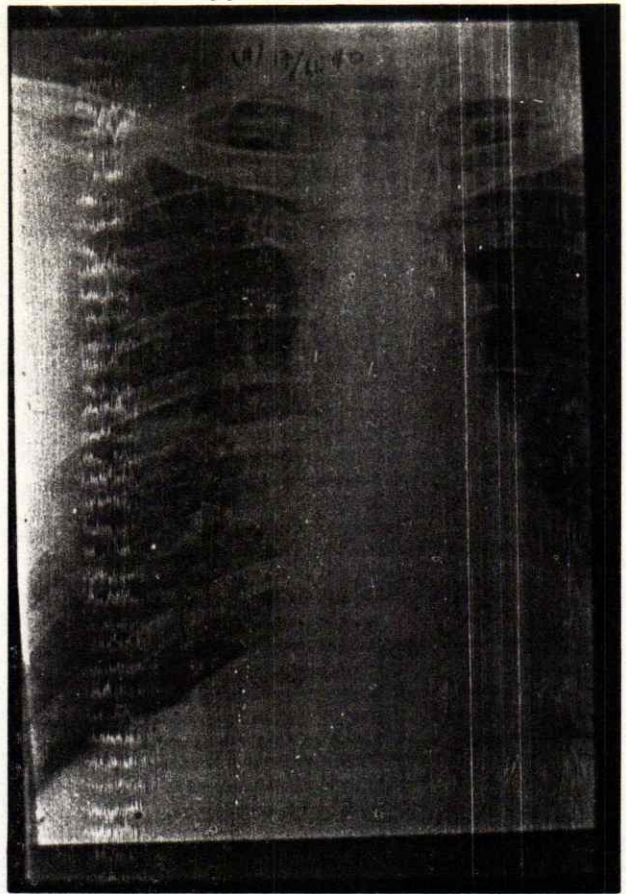
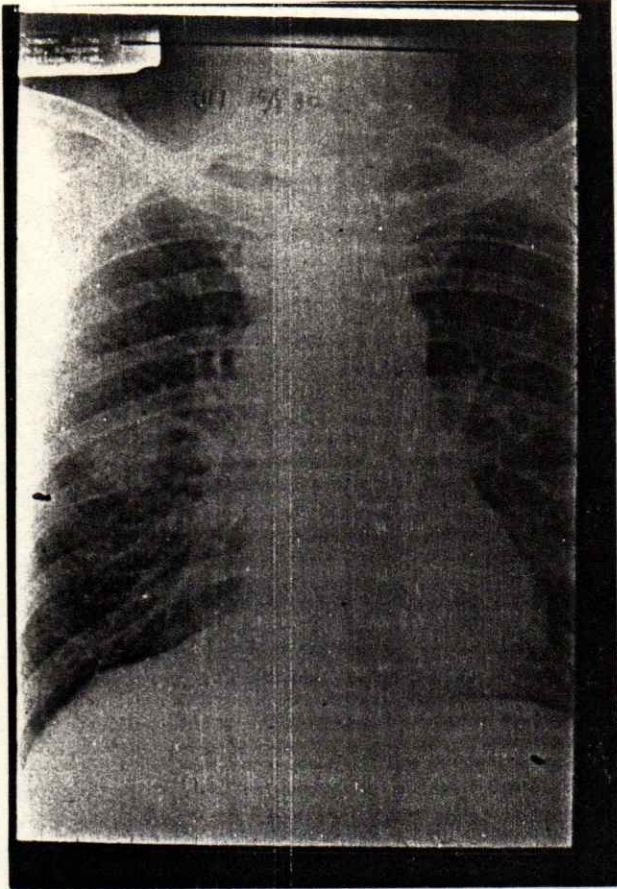


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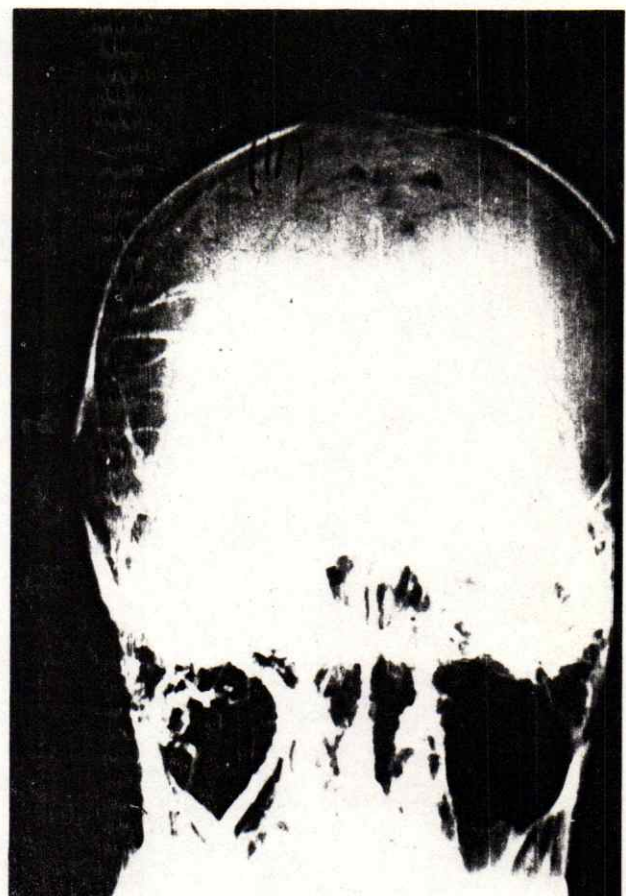
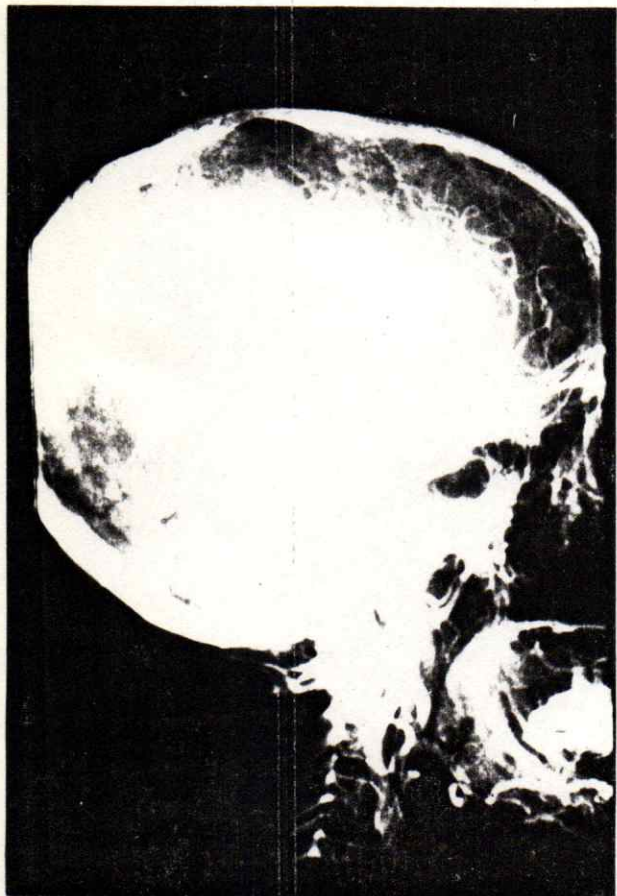
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R. LUNG CA . DETECTED AFTER CEREBRAL METASTASIS DEVELOPED.



CER. ANGIO . SHOWED A METASTASIS TO THE R TEMPORAL AREA OF THE BRAIN

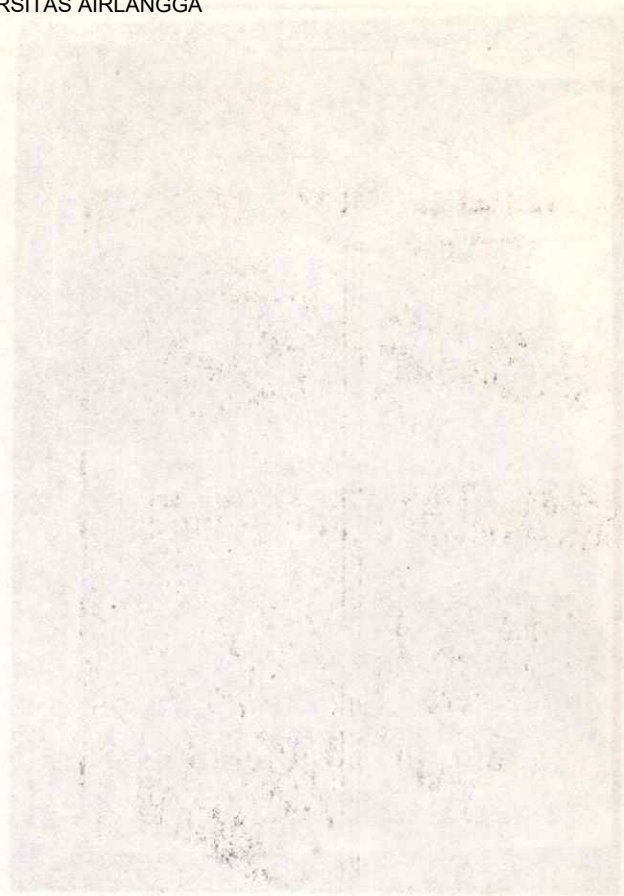
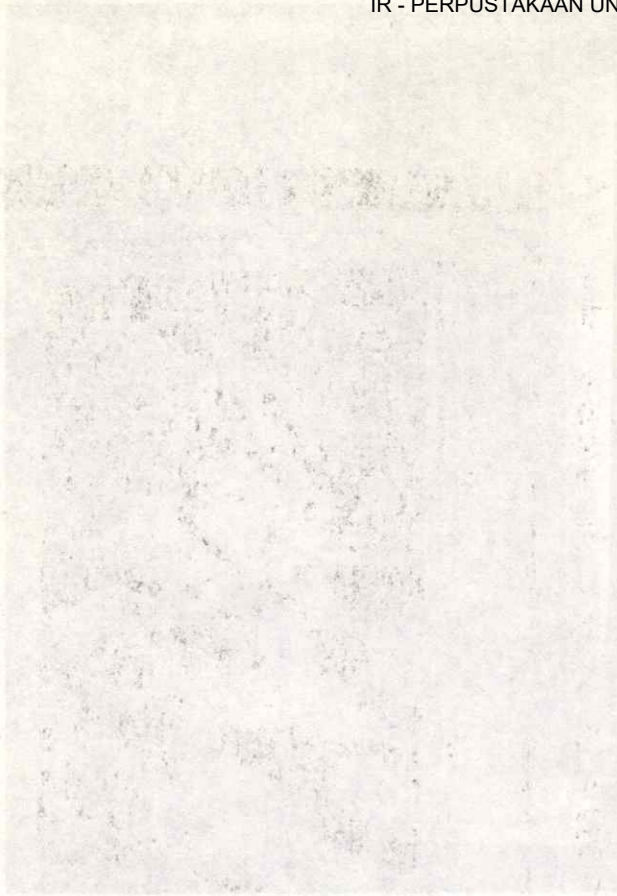


Fig. 1. (Left) Normal brain tissue. (Right) Brain tissue showing metastatic neoplasms.

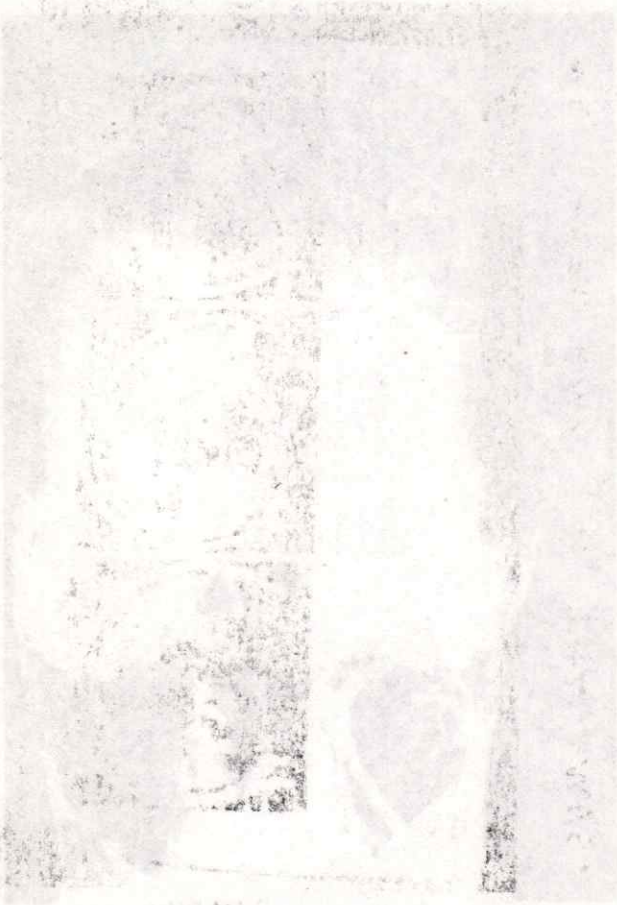
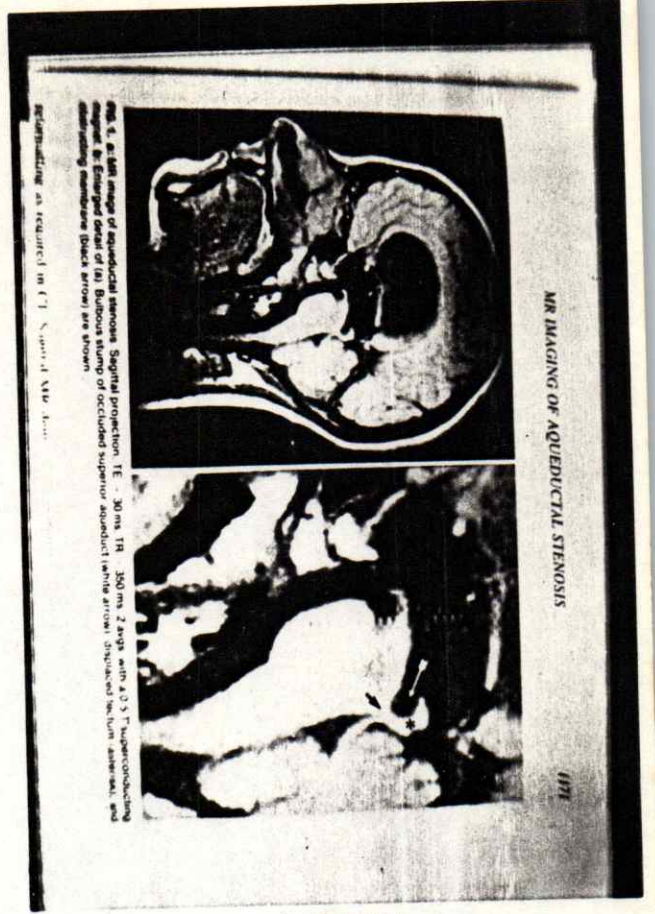


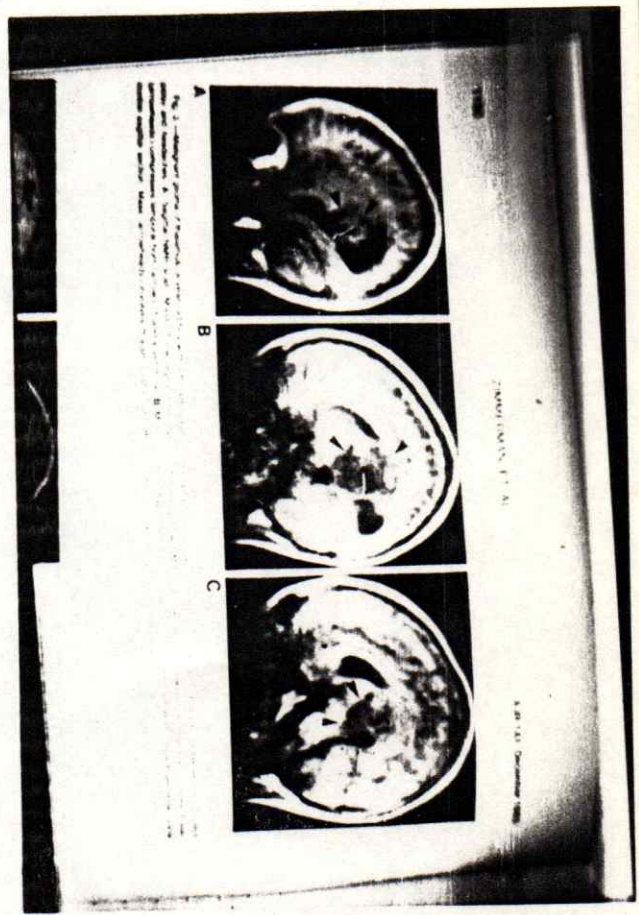
Fig. 2. (Left) Normal brain tissue. (Right) Brain tissue showing metastatic neoplasms.

MRI OF AQUA-DUCTAL STENOSIS

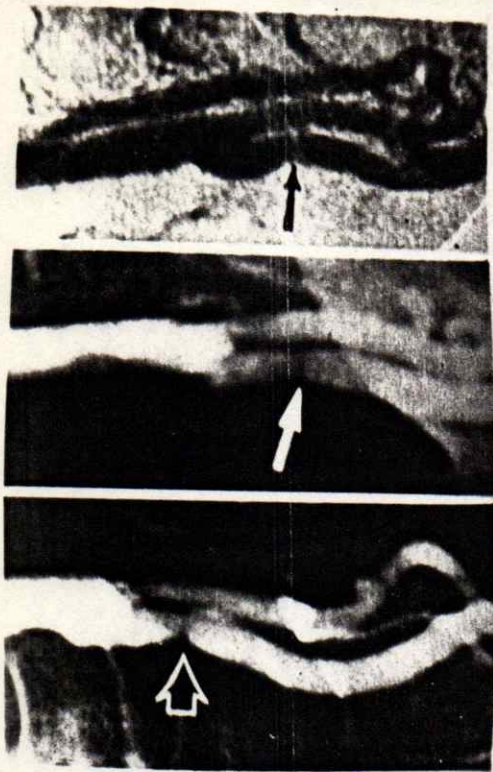


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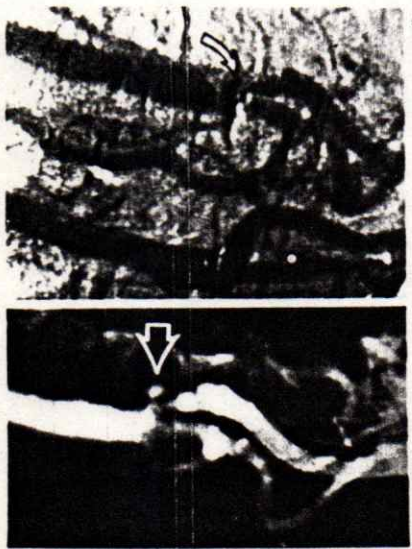
MRI SHOWED A MASS IN THALAMUS.



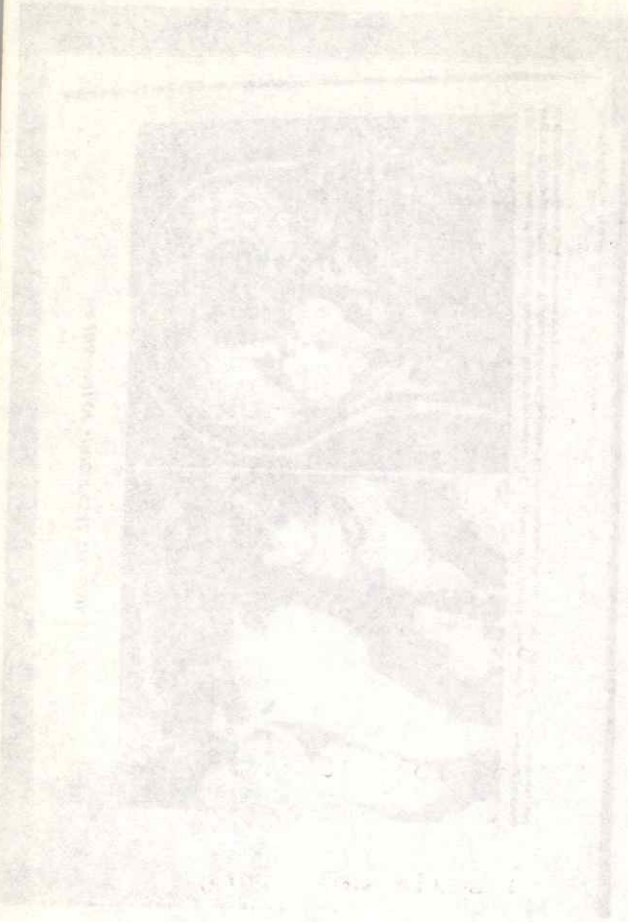
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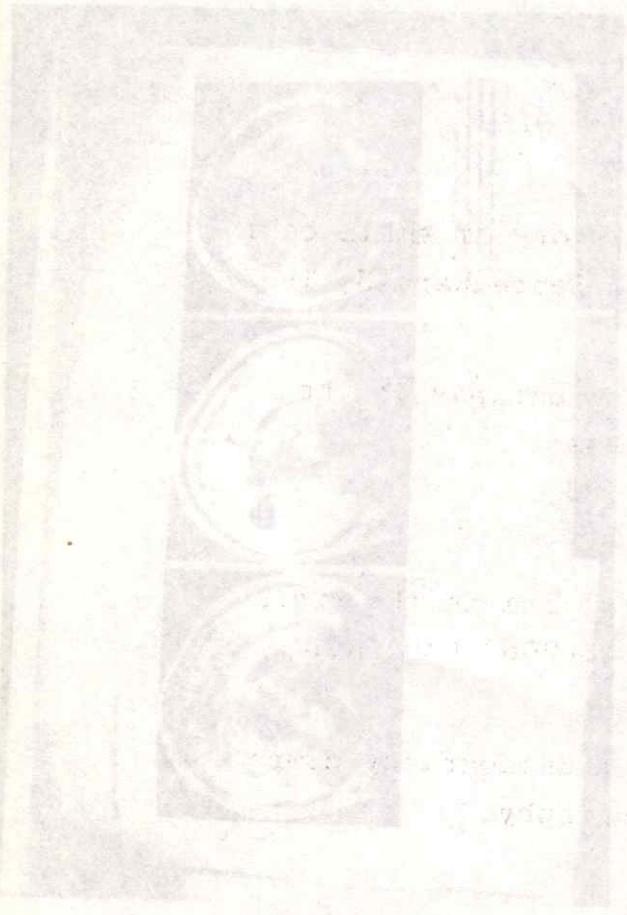
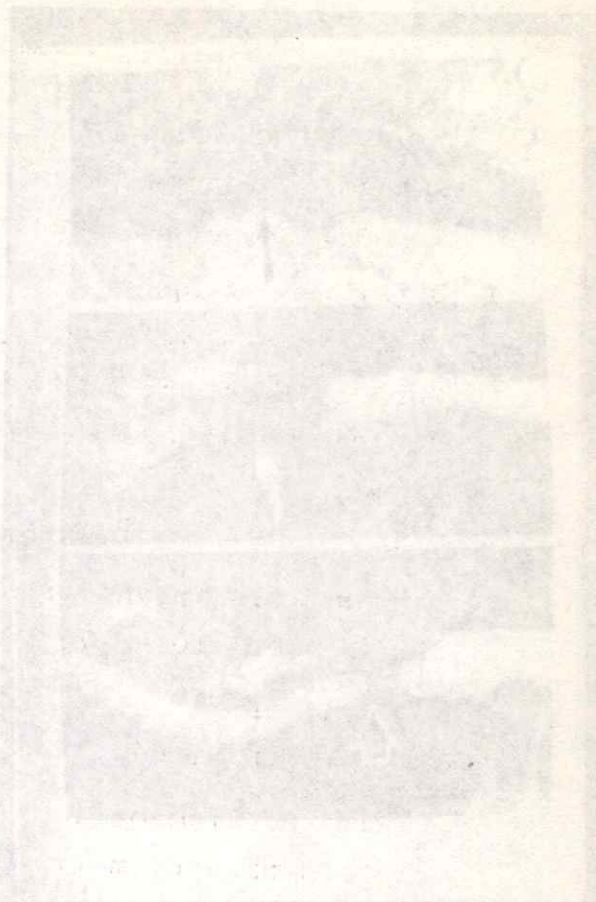
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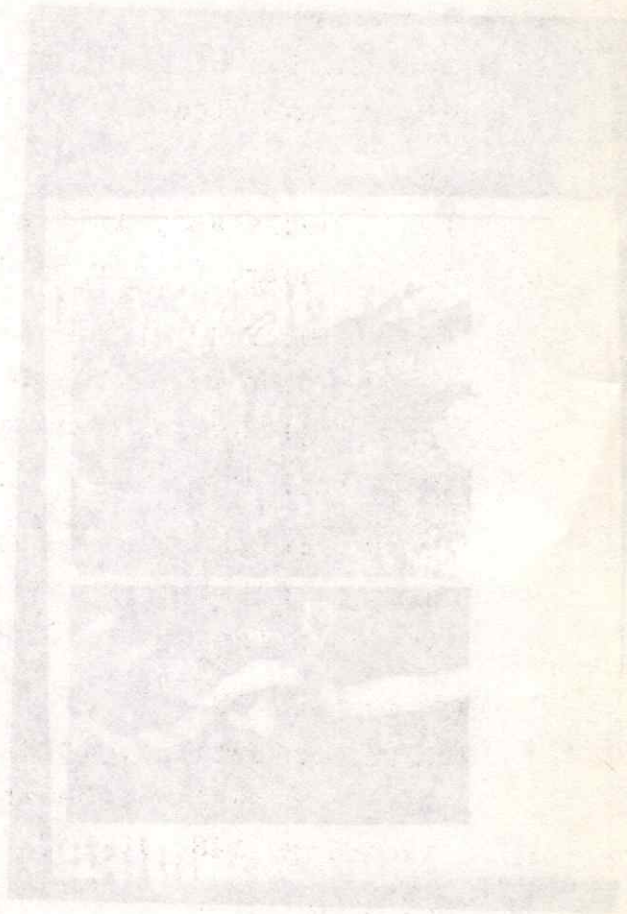
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MR. OF YOUNG DOCTOR J. STENOZ



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