PRELIMINARY REVIEW ON BRAIN TUMOUR

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Abstract

This paper presents a basic review on the anatomy of brain tumour and certain causes for its formation and proliferation. A brain tumour (sometimes referred more commonly as brain cancer) occurs when a group of cells within the brain turn cancerous and grow out of control, creating a mass. There are two main types of tumours: malignant (cancerous) tumours and benign (non-cancerous) tumours. These can be further classified as primary tumours, which start within the brain, and secondary tumours, which most commonly have spread from tumours located outside the brain, known as brain metastasis tumours. All types of brain tumours may produce symptoms that vary depending on the size of the tumour and the part of the brain that is involved. The symptoms that exist, they may include headaches, seizures, problems with vision, vomiting and mental changes. Other symptoms may include difficulty in walking, speaking, with sensations, or unconsciousness. The cause of most brain tumours is unknown, though up to 4% of brain cancers may be caused by CT scan radiation. Uncommon risk factors include exposure to vinyl chloride, Epstein–Barr virus, ionizing radiation, and inherited syndromes such as neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau Disease. Studies on mobile phone exposure have not shown a clear risk. Possibly, prolonged use of mobile phones may cause brain tumour as indicated by some experts. The most common types of primary tumours in adults are meningiomas (usually benign) and astrocytomas such as glioblastomas. Among children, the most common type is a malignant medulloblastoma.

Keywords: Brain Tumour, Brain Metastasis, Meningiomas, Glioblastomas

1. Introduction

Mostly brain cancer occurs as metastasis due cancer from other parts of the body. Fig. 1 shows brain metastasis in the right cerebral hemisphere from lung cancer, shown on magnetic resonance imaging.

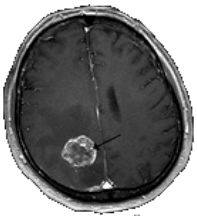

Fig. 1: MR Image

Symptoms vary depending on the part of the brain involved, like headaches, seizures, problem with vision, vomiting, mental changes. The brain tumour may be malignant or benign. Causes for this brain tumour are unknown. In general, the risk factors are neurofibromatosis, exposure to vinyl chloride, Epstein–Barr virus, ionizing radiation. Usually, the diagnosis is carried out by medical examination along with computed tomography (CT) or magnetic resonance imaging (MRI). The result is then often confirmed by a biopsy. Based on the findings, the tumours are divided into different grades of severity. The treatment could be invasive surgery, radiation therapy, chemotherapy, to name a few. Anticonvulsants, dexamethasone, furosemide are used for medication.

Treatment may include combination of surgery, radiation therapy and chemotherapy. If seizures occur, anticonvulsant medication is needed. Dexamethasone and furosemide are medications that may be used to decrease swelling around the tumour. Some tumours grow gradually, requiring only monitoring and possibly needing no further intervention. Treatments that use a person's immune system are being studied. Outcomes for malignant tumours vary considerably depending on the type of tumour and how far it has spread at diagnosis. Although benign tumours only grow in one area, they may still be life-threatening depending on their size and location. Malignant glioblastomas usually have very poor outcomes, while benign meningiomas usually have good outcomes. Secondary, or metastatic, brain tumours are about four times as common as primary brain tumours, with about half of metastases coming from lung cancer.

The signs and symptoms of brain tumours are quite broad. People may experience symptoms regardless of whether the tumour is benign (not cancerous) or cancerous. Primary and secondary brain tumours present with similar symptoms, depending on the location, size, and rate of growth of the tumour. For example, larger tumours in the frontal lobe can cause changes in the ability to think. However, a smaller tumour in an area such as Wernicke's area (small area responsible for language comprehension) can result in a greater loss of function.

'Headaches' as a result of raised intracranial pressure can be an early symptom of brain cancer. However, isolated headache without other symptoms is rare, and other symptoms including visual abnormalities may occur before headaches become common. Certain warning signs for headache exist which make the headache more likely to be associated with brain cancer. These are defined as "abnormal neurological examination, headache worsened by Valsalva maneuver, headache causing awakening from sleep, new headache in the older population, progressively worsening headache, atypical headache features, or patients who do not fulfill the strict definition of migraine". Other associated signs are headaches that are worse in the morning or that subside after vomiting.

2. Anatomy of Human Brain and Location Specific Symptoms

Before getting into further details, let us have a brief idea about the anatomy of human brain. Fig.2 shows the basic anatomy of human brain.

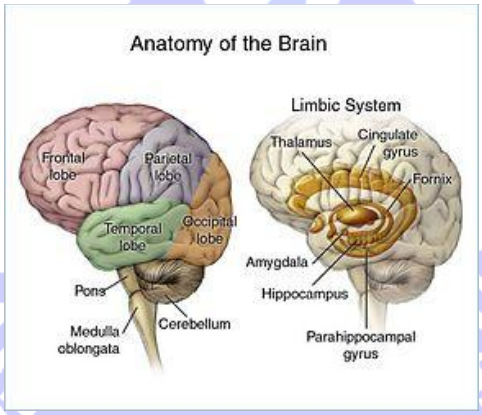

Fig. 2: Main areas of the brain and limbic system

With reference to Fig. 2, the brain is divided into lobes and each lobe or area has its own function. 'Location-specific symptoms' are as follows: A tumour in any of these lobes may affect that area's performance. The symptoms experienced are often linked to the location of the tumour, but each person may experience something different.

1. **Frontal lobe:** Tumours may contribute to poor reasoning, inappropriate social behavior, personality changes, poor planning, lower inhibition, and decreased production of speech (Broca's area).
2. **Temporal lobe:** Tumours in this lobe may contribute to poor memory, loss of hearing, and difficulty in language comprehension (Wernicke's area is located in this lobe).
3. **Parietal lobe:** Tumours here may result in poor interpretation of languages, difficulty with speaking, writing, drawing, naming, and recognizing, and poor spatial and visual perception.
4. **Occipital lobe:** Damage to this lobe may result in poor vision or loss of vision.
5. **Cerebellum:** Tumours in this area may cause poor balance, muscle movement, and posture.
6. **Brain stem:** Tumours on the brainstem can cause seizures, endocrine problems, respiratory changes, visual changes, headaches and partial paralysis.
7. **Leptomeninges:** Tumours that spread to the leptomeninges, the lining of the brain, may cause cranial nerve palsies such as facial paralysis, abnormalities of eye movement, abnormalities of facial sensation or swallowing difficulty, depending on which cranial nerves are involved.

Behaviour Patterns

A person's personality could be altered due to the tumour-damaging lobes of the brain. Since the frontal, temporal, and parietal lobes control inhibition, emotions, mood, judgement, reasoning, and behavior, a tumour in those regions can cause inappropriate social behavior, temper tantrums, laughing at things which merit no laughter, and even psychological symptoms such as depression and anxiety. More research is needed into the effectiveness and safety of medication for depression in people with brain tumours. Personality changes can have damaging effects such as unemployment, unstable relationships, and a lack of control.

Causes of brain cancer

1. A known cause of brain cancers is ionizing radiation. Approximately 4% of brain cancers in the general population are caused by CT-scan radiation. For brain cancers that follow a CT scan at lags of 2 years or more, it has been estimated that 40% are attributable to CT-scan radiation. The risk of brain cancer is dose dependent, with the relative risk increasing by 0.8 for each 100 gray of ionizing radiation received. At this dose, approximately 6391 people would have to be exposed to cause 1 case of brain

cancer. Ionizing radiation to the head as part of treatment for other cancers is also a risk factor for developing brain cancer.

2. Mutations and deletions of tumour suppressor genes, such as P53, are thought to be the cause of some forms of brain tumour. Inherited conditions, such as Von Hippel–Lindau disease, tuberous sclerosis, multiple endocrine neoplasia, and neurofibromatosis type 2 carry a high risk for the development of brain tumours. People with celiac disease have a slightly increased risk of developing brain tumours. Smoking may increase the risk, but evidence of this remains unclear.
3. Although studies have not shown any link between cell-phone or mobile-phone radiation and the occurrence of brain tumours, the World Health Organization has classified mobile-phone radiation on the IARC scale into Group 2B – possibly carcinogenic. The claim that cell-phone usage may cause brain cancer is likely based on epidemiological studies which observed a slight increase in glioma risk among heavy users of wireless phones. When those studies were conducted, GSM (2G) phones were in use. Modern, third-generation (3G) phones emit, on average, about 1% of the energy emitted by those GSM (2G) phones, and therefore the finding of an association between cell-phone usage and increased risk of brain cancer is not based upon current phone usage.

Pathophysiology: Meninges

The meninges lie between the skull and brain matter. Tumours originating from the meninges are meningiomas. Human brains are surrounded by a system of connective tissue membranes called meninges that separate the brain from the skull. This three-layered covering is composed of (from the outside in) the dura mater, arachnoid mater, and pia mater. The arachnoid and pia are physically connected and thus often considered as a single layer, the 'leptomeninges'.

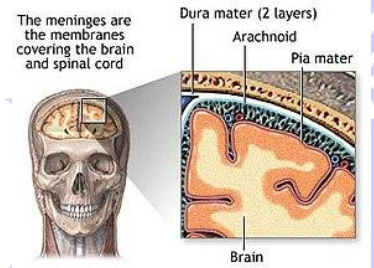

Fig. 3: Meninges in a human brain

Between the arachnoid mater and the pia mater is the subarachnoid space which contains cerebrospinal fluid (CSF). This fluid circulates in the narrow spaces between cells and through the cavities in the brain called ventricles, to support and protect the brain tissue. Blood vessels enter the central nervous system through the perivascular space above the pia mater. The cells in the blood vessel walls are joined tightly, forming the blood–brain barrier which protects the brain from toxins that might enter through the blood. Fig. 3 shows meninges in a human brain. Tumours of the meninges are meningiomas and are often benign. Though not technically a tumour of brain tissue, they are often considered brain tumours since they protrude into the space where the brain is, causing symptoms. Since they are usually slow-growing tumours, meningiomas can be quite large by the time symptoms appear.

Brain matter

The three largest divisions of the brain are the cerebral cortex, cerebellum and the brainstem. These areas are composed of two broad classes of cells: neurons and glia. These two cell types are equally numerous in the brain as a whole, although glial cells outnumber neurons roughly 4 to 1 in the cerebral cortex. Glia come in several types, which perform a number of critical functions, including structural support, metabolic support, insulation, and guidance of development. Primary tumours of the glial cells are called gliomas and often are malignant by the time they are diagnosed. The thalamus and hypothalamus are major divisions of the diencephalon, with the pituitary gland and pineal gland attached at the bottom; tumours of the pituitary and pineal gland are often benign, that is noncancerous. The brainstem lies between the large cerebral cortex and the spinal cord. It is divided into the midbrain, pons, and medulla oblongata.

Diagnosis

Fig. 4 shows a posterior fossa tumour leading to mass effect and midline shift. There are no specific signs or symptoms for brain cancer, but the presence of a combination of symptoms and the lack of alternative causes may indicate a brain tumour. A medical history aids in the diagnosis. Clinical and laboratory investigations will serve to exclude infections as the cause of the symptoms. Brain tumours, when compared to tumours in other areas of the body, pose a challenge for diagnosis. Commonly, radioactive tracers are up taken in large volumes in tumours due to the high activity of tumour cells, allowing for radioactive imaging of the tumour. However, most of the brain is separated from the blood by the blood–brain barrier (BBB), a membrane that exerts a strict control over what substances are allowed to pass into the brain. Therefore, many tracers that may reach tumours in other areas of the body easily would be unable to reach brain tumours until there was a disruption of the BBB by the tumour. Disruption of the BBB is well imaged via MRI or CT scan, and is therefore regarded as the main diagnostic indicator for malignant gliomas, meningiomas, and brain metastases.

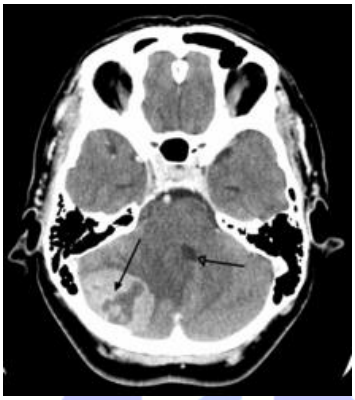

Fig. 4: Posterior fossa tumour

Imaging

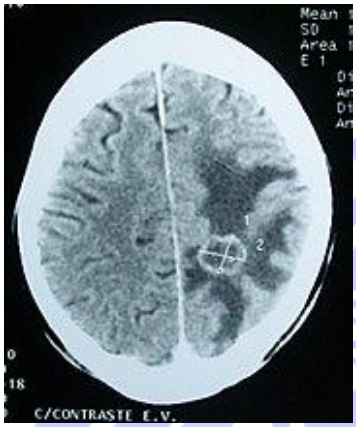

Fig. 5: CT scan of brain tumour

Fig. 5 shows a CT scan of a brain tumour, with its diameters marked as an X. There is hypoattenuating (dark) *peritumoural edema* in the surrounding white matter, with a "finger-like" spread. Medical imaging plays a central role in the diagnosis of brain tumours. Early imaging methods – invasive and sometimes dangerous – such as pneumoence-phalography and cerebral angiography have been replaced by non-invasive, high-resolution techniques, especially magnetic resonance imaging (MRI) and computed tomography (CT) scans. MRI with contrast enhancement is the preferred imaging test in the diagnosis of brain tumours. Glioblastomas usually enhance with contrast on T1 MRI weighted MRI imaging, and on T2 with FLAIR imaging showing hyperintense cerebral edema. Low grade gliomas are usually hypointense on T1 MRI, and hyperintense with T2 with FLAIR MRI. Meningiomas are usually homogenously enhanced with dural thickening on MRI. Treatment with radiation can lead to treatment induced changes in the brain, including radiation necrosis (death of brain tissue due to radiation treatments) visible on brain imaging and which can be difficult to differentiate from tumour recurrence.

Different Types of MRI and Other Scans

Magnetic Resonance Angiography (MRA) – looks at the blood vessels in the brain. In the diagnosis of brain tumour, MRAs are typically carried out before surgery to help surgeons get a better understanding of the tumour vasculature. For example, a study was done where surgeons were able to separate benign brain tumours from malignant ones by analyzing the shapes of the blood vessels that were extracted from MRA. Although not required, some MRA may inject contrast agent, gadolinium, into the patient to get an enhanced image

Magnetic Resonance Spectroscopy (MRS) – measures the metabolic changes or chemical changes inside the tumour. The most common MRS is proton spectroscopy with its frequency measured in parts per million (ppm). Gliomas or malignant brain tumours have different spectra from normal brain tissue in that they have greater choline levels and lower N-acetyl aspartate (NAA) signals. Using MRS in brain tumour diagnosis can help doctors identify the type of tumour and its aggressiveness. For example, benign brain tumours or meningioma have increased alanine levels. It can also help to distinguish brain tumours from scar tissues or dead tissues caused by previous radiation treatment, which does not have increased choline levels that brain tumours have, and from tumour-mimicking lesions such as abscesses or infarcts.

Perfusion Magnetic Resonance Imaging (pMRI) – assess the blood volume and blood flow of different parts of the brain and brain tumours. pMRI requires the injection of contrast agent, usually gadopentetate dimeglumine (Gd-DTPA) into the veins in order to enhance the contrast. pMRI provides a cerebral blood volume map that shows the tumour vascularity and angiogenesis. Brain tumours would require a larger blood supply and thus, would show a high cerebral blood volume on the pMRI map. The vascular morphology and degree of angiogenesis from pMRI help to determine the grade and malignancy of brain tumours. For brain tumour diagnosis, pMRI is useful in determining the best site to perform biopsy and to help reduce sampling error. pMRI is also valuable for after treatment to determine if the abnormal area is a remaining tumour or a scar tissue. For patients that are undergoing anti-angiogenesis cancer therapy, pMRI can give the doctors a better sense of efficacy of the treatment by monitoring tumour cerebral blood volume.

Functional MRI (fMRI) – measures blood flow changes in active parts of the brain while the patient is performing tasks and provides specific locations of the brain that are responsible for certain functions. Before performing a brain tumour surgery on patients, neurosurgeons would use fMRI to avoid damage to structures of the brain that correspond with important brain functions while resecting the tumour at the same time. Preoperative fMRI is important because it is often difficult to distinguish the anatomy near the tumour as it distorts its surrounding regions. Neurosurgeons would use fMRI to plan whether to perform a resection where tumour is surgically removed as much as possible, a biopsy where they take a surgical sampling amount to provide a diagnosis, or to not undergo surgery at all. For example, a neurosurgeon may be opposed to resecting a tumour near the motor cortex as that would affect the patient's movements. Without preoperative fMRI, the neurosurgeon would have to perform an awake-craniotomy where the patient would have to interact during open surgery to see if tumour removal would affect important brain functions.

Diffusion Weighted Imaging (DWI) – a form of MRI that measures random Brownian motion of water molecules along a magnetic field gradient. For brain tumour diagnosis, measurement of Apparent Diffusion Coefficient (ADC) in brain tumours allow doctors to categorize tumour type. Most brain tumours have higher ADC than normal brain tissues and doctors can match the observed ADC of the patient's brain tumour with a list of accepted ADC to identify tumour type. DWI is also useful for treatment and therapy purposes where changes in diffusion can be analyzed in response to drug, radiation, or gene therapy. Successful response results in apoptosis and increase in diffusion while failed treatment results in unchanged diffusion values.

Computed Tomography (CT) Scan – uses x-rays to take pictures from different angles and computer processing to combine the pictures into a 3D image. A CT scan usually serves as an alternative to MRI in cases where the patient cannot have an MRI due to claustrophobia or pacemaker. Compared to MRI, a CT scan shows a more detailed image of the bone structures near the tumour and can be used to measure the tumour's size. Like an MRI, a contrast dye may also be injected into the veins or ingested by mouth before a CT scan to better outline any tumours that may be present. CT scans use contrast materials that are iodine-based and barium sulfate compounds. The downside of using CT scans as opposed to MRI is that some brain tumours do not show up well on CT scans because some intra-axial masses are faint and resemble normal brain tissue. In some scenarios, brain tumours in CT scans may be mistaken for infarction, infection, and demyelination. To suspect that an intra-axial mass is a brain tumour instead of other possibilities, there must be unexplained calcifications in the brain, preservation of the cortex, and disproportionate mass effect.

CT Angiography (CTA) – provides information about the blood vessels in the brain using X-rays. A contrast agent is always required to be injected into the patient in the CT scanner. CTA serves as an alternative to MRA.

Positron Emission Tomography (PET) Scan – uses radio-labelled substances, such as FDG which taken up by cells that are actively dividing. Tumour cells are more actively dividing so they would absorb more of the radioactive substance. After injection, a scanner would be used to create an image of the radioactive areas in the brain. PET scans are used more often for high-grade tumours than for low-grade tumours. It is useful after treatment to help doctors determine if the abnormal area on an MRI image is a remaining tumour or a scar tissue. Scar tissues will not show up on PET scans while tumours would.

Pathology

Maximal safe surgical resection (to preserve as much neurological function as possible) and histologic examination of the tumour is also required to aid in the diagnosis. Cancer cells may have specific characteristics. Atypia: an indication of abnormality of a cell (which may be indicative of malignancy). Significance of the abnormality is highly dependent on context. Neoplasia: the (uncontrolled) division of cells that is characteristic of cancer. Necrosis: the (premature) death of cells, caused by external factors such as infection, toxin or trauma. Necrotic cells send the wrong chemical signals which prevent phagocytes from disposing of the dead cells, leading to a buildup of dead tissue, cell debris and toxins at or near the site of the necrotic cells. Local hypoxia, or the deprivation of adequate oxygen supply to certain areas of the brain, including within the tumour, as the tumour grows and recruits local blood vessels.

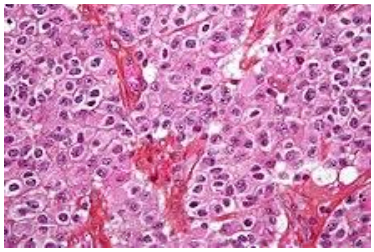

Fig. 6: Micrograph of a type of brain cancer

Tumour Classification

Tumours can be benign or malignant, can occur in different parts of the brain, and may be classified as primary or secondary. A primary tumour is one that has started in the brain, as opposed to a metastatic tumour, which is one that has spread to the brain from another area of the body. The incidence of metastatic tumours is approximately four times greater than primary tumours. Tumours may or may not be symptomatic: some tumours are discovered because the patient has symptoms, others show up incidentally on an imaging scan, or at an autopsy. Grading of the tumours of the central nervous system commonly occurs on a 4-point scale (I-IV) created by the World Health Organization in 1993.

Grade I tumours are the least severe and commonly associated with long-term survival, with severity and prognosis worsening as the grade increases. Low-grade tumours are often benign, while higher grades are aggressively malignant and/or metastatic. Other grading scales do exist, many based upon the same criteria as the WHO scale and graded from I-IV.

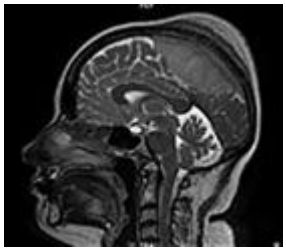

Fig. 7: Meningeoma

Primary tumours

Fig. 7 shows meningioma of the middle third of the sagittal sinus with large hyperostosis. The most common primary brain tumours are: Gliomas, Meningiomas, Pituitary adenomas, Nerve sheath tumours. These common tumours can also be organized according to tissue of origin.

Secondary tumours

Secondary tumours of the brain are metastatic and have spread to the brain from cancers originating in another organ. Metastatic spread is usually by the blood. The most common types of cancers that spread to the brain are lung cancer (accounting for over half of all cases), breast cancer, melanoma skin cancer, kidney cancer and colon cancer.

Behavior of tumours

Brain tumours can be cancerous (malignant) or non-cancerous (benign). However, the definitions of malignant or benign neoplasms differ from those commonly used in other types of cancerous or non-cancerous neoplasms in the body. In cancers elsewhere in the body, three malignant properties differentiate benign tumours from malignant forms of cancer: benign tumours are self-limited and do not invade or metastasize. Characteristics of malignant tumours include: (i) uncontrolled mitosis (growth by division beyond the normal limits), (ii) anaplasia: the cells in the neoplasm have an obviously different form (in size and shape). Anaplastic cells display marked pleomorphism. The cell nuclei are characteristically extremely hyperchromatic (darkly stained) and enlarged; the nucleus might have the same size as the cytoplasm of the cell (nuclear-cytoplasmic ratio may approach 1:1, instead of the normal 1:4 or 1:6 ratio). Giant cells – considerably larger than their neighbors – may form and possess either one enormous nucleus or several nuclei (syncytia). Anaplastic nuclei are variable and bizarre in size and shape.

Invasion or infiltration:

Invasion or invasiveness is the spatial expansion of the tumour through uncontrolled mitosis, in the sense that the neoplasm invades the space occupied by adjacent tissue, thereby pushing the other tissue aside and eventually compressing the tissue. Often these tumours are associated with clearly outlined tumours in imaging. Infiltration is the behavior of the tumour either to grow (microscopic) tentacles that push into the surrounding tissue (often making the outline of the tumour undefined or diffuse) or to have tumour cells "seeded" into the tissue beyond the circumference of the tumourous mass. metastasis (spread to other locations in the body via lymph or blood).

Genetic behaviour

The WHO restructured their classifications, in 2016, of some categories of gliomas to include distinct genetic mutations that have been useful in differentiating tumour types, prognoses, and treatment responses. Genetic mutations are typically detected via immunohistochemistry, a technique that visualizes the presence or absence of a targeted protein via staining. Mutations in IDH1 and IDH2 genes are commonly found in low-grade gliomas. Loss of both IDH genes combined with loss of chromosome arms 1p and 19q indicates the tumour is an oligodendroglioma. Loss of TP53 and ATRX characterizes.

Cancer treatment preliminaries

Many meningiomas, with the exception of some tumours located at the skull base, can be successfully removed surgically. Most pituitary adenomas can be removed surgically, often using a minimally invasive approach through the nasal cavity and skull base (trans-nasal, trans-sphenoidal approach). Large pituitary adenomas require a craniotomy (opening of the skull) for their removal.

Radiotherapy, including stereotactic approaches, is reserved for inoperable cases. Postoperative radiotherapy and chemotherapy are integral parts of the therapeutic standard for malignant tumours. Multiple metastatic tumours are generally treated with radiotherapy and chemotherapy rather than surgery and the prognosis in such cases is determined by the primary tumour, and is generally poor. The goal of radiation therapy is to kill tumour cells while leaving normal brain tissue unharmed. In standard external beam radiation therapy, multiple treatments of standard-dose "fractions" of radiation are applied to the brain. This process is repeated for a total of 10 to 30 treatments, depending on the type of tumour. This additional treatment provides some patients with improved outcomes and longer survival rates. Radiosurgery is a treatment method that uses computerized calculations to focus radiation at the site of the tumour while minimizing the radiation dose to the surrounding brain. Radiosurgery may be an adjunct to other treatments, or it may represent the primary treatment technique for some tumours. Forms used include stereotactic radiosurgery, such as Gamma knife, Cyberknife or Novalis Tx radiosurgery. Radiotherapy is the most common treatment for secondary brain tumours. The amount of radiotherapy depends on the size of the area of the brain affected by cancer. Conventional external beam "whole-brain radiotherapy treatment" (WBRT) or "whole-brain irradiation" may be suggested if there is a risk that other secondary tumours will develop in the future. Stereotactic radiotherapy is usually recommended in cases involving fewer than three small secondary brain tumours. Radiotherapy may be used following, or in some cases in place of, resection of the tumour. Forms of radiotherapy used for brain cancer include external beam radiation therapy, the most common, and brachytherapy and proton therapy, the last especially used for children. People who receive stereotactic radiosurgery (SRS) and whole-brain radiation therapy (WBRT) for the treatment of metastatic brain tumours have more than twice the risk of developing learning and memory problems than those treated with SRS alone. Postoperative conventional daily radiotherapy improves survival for adults with good functional well-being and high grade glioma compared to no postoperative radiotherapy. Hypofractionated radiation therapy has similar efficacy for survival as compared to conventional radiotherapy, particularly for individuals aged 60 and older with glioblastoma. Patients undergoing chemotherapy are administered drugs designed to kill tumour cells. Although chemotherapy may improve overall survival in patients with the most malignant primary brain tumours, it does so in only about 20 percent of patients. Chemotherapy is often used in young children instead of radiation, as radiation may have negative effects on the developing brain. The decision to prescribe this treatment is based on a patient's overall health, type of tumour, and extent of cancer. The toxicity and many side effects of the drugs, and the uncertain outcome of chemotherapy in brain tumours puts this treatment further down the line of treatment options with surgery and radiation therapy preferred.

Non-invasive detection

Efforts to detect and monitor development and treatment response of brain tumours by liquid biopsy from blood, cerebrospinal fluid or urine, are in the early stages of development.

3. Conclusions and Future Perspectives

In this paper, preliminary details of brain cancer and its causes have been discussed. As a future perspective, one can look into the possibilities of developing techniques for processing MRI scans, which are essentially three-dimensional images in order to extract hidden features.

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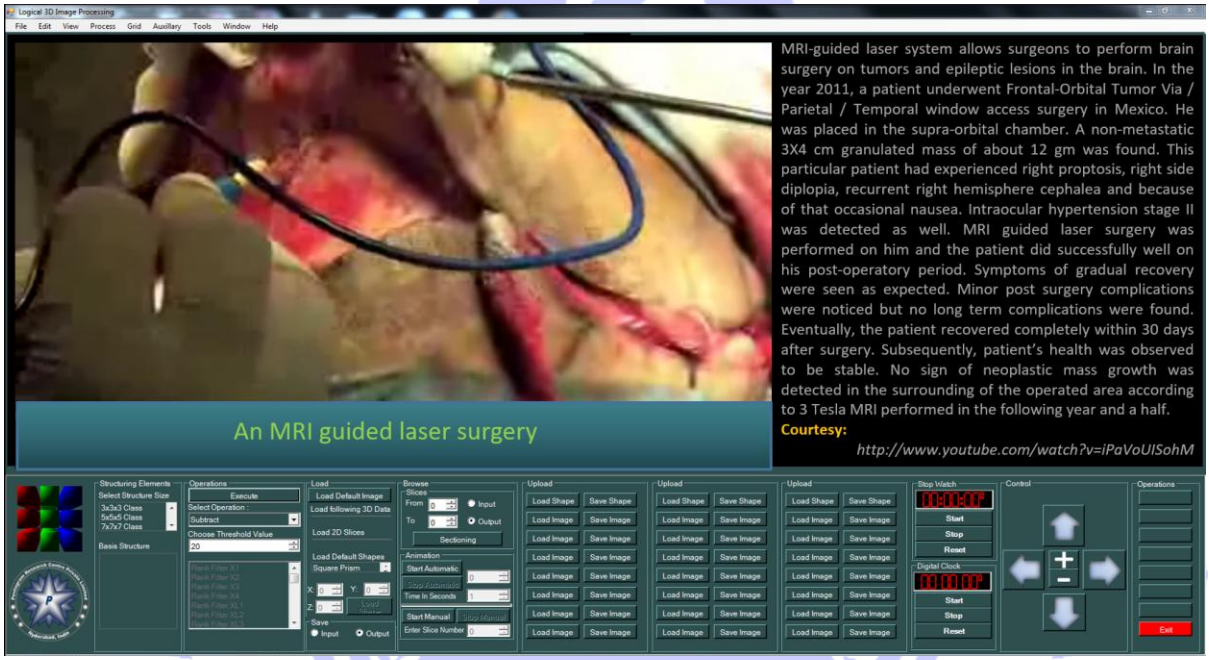

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