

A Perspective on Cancer: A Recent Update

Harshita Joshi*

Department of Biotechnology, Graphic Era University, Dehradun, Uttarakhand, India

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*For Correspondence

Harshita Joshi, Department of Biotechnology,
Graphic Era University, Dehradun, Uttarakhand,
India, Tel: +91 8126124888.

E-mail: harshitajoshi962@gmail.com

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ABSTRACT

A brain tumour occurs when abnormal cells starts to grow within the brain. Tumours are differentiated in two main categories i.e., malignant or cancerous tumours and benign tumours. Cancerous tumours can further be differentiated into primary and secondary tumours. Primary tumours growth starts within the brain while secondary tumours are the ones that have spread from somewhere else into the brain.

The symptoms of brain tumours depend on the part of brain in which it has infected. These symptoms may include headaches, seizures, vision problems, vomiting, mental issues, difficulty in walking, speaking and with sensations. The headaches occurring during brain tumours are rather worse than the normal ones and worsen during morning and goes away with vomiting. Brain tumour treatment can include surgery, radiation therapy, chemotherapy and in combinations. Secondary or metastatic brain tumours are more common ones. Annually, round 250,000 primary brain tumours occur globally.

INTRODUCTION

Cancer is a term which is used to refer to a condition where the body cell begins to grow and reproduce in an uncontrollable manner. These cells then due to their continuous growth destroy the other healthy cells, tissues and organs. Cancer usually begins at one part of the body before spreading to others. Cancer has now begun to be a major health issue in more of the population. It is known that more than one in three people will develop some form of cancer during their lifespan ^[1]. On development of cancer the orderly process of cell growth and division breaks down. When cells starts to become abnormal, the old or damaged cells survive instead of dying and new cells starts to form when not needed ^[2].

Oncogenes are the genes that have the ability to induce cancer. It is a gene in which the DNA sequence had been altered or mutated from its original form of proto-oncogene. Proto-oncogenes hold the role in the promotion of differentiation and proliferation of normal cells. Any change in the sequence of proto-oncogenes or in the amount of protein can lead to the irregular cellular regulation. When the cell growth becomes uncontrolled it results in the formation of cancerous tumor.

It is necessary that the parent cell produce exact duplicates of them as daughter cells. Sometimes due to mistakes in the duplication process or during distribution of the chromosome can lead to mutations but it needs to be controlled because this mutation can further pass on to a new cell produced from an abnormal cell. To prevent such an abnormal cell to divide, internal control mechanisms operate at three main cell cycle checkpoints i.e., G₁, G₂ and M.

These check points do not allow this abnormal growth to progress at high levels and thus it does not harm the human body and its systems. But when these checkpoints fail it leads to uncontrolled growth of such cells leading to cancerous cell growth.

Epidemiology of Cancer

Due to cancer, the death rate has tripled since 1950s. Earlier, heart diseases used to take the lives more often than cancer but from 2014 cancer have replaced heart diseases to be the leading cause of deaths worldwide. That's an enormously increasing range and it can happen that in coming years heart diseases would be replaced by cancer (**Figure 1**).

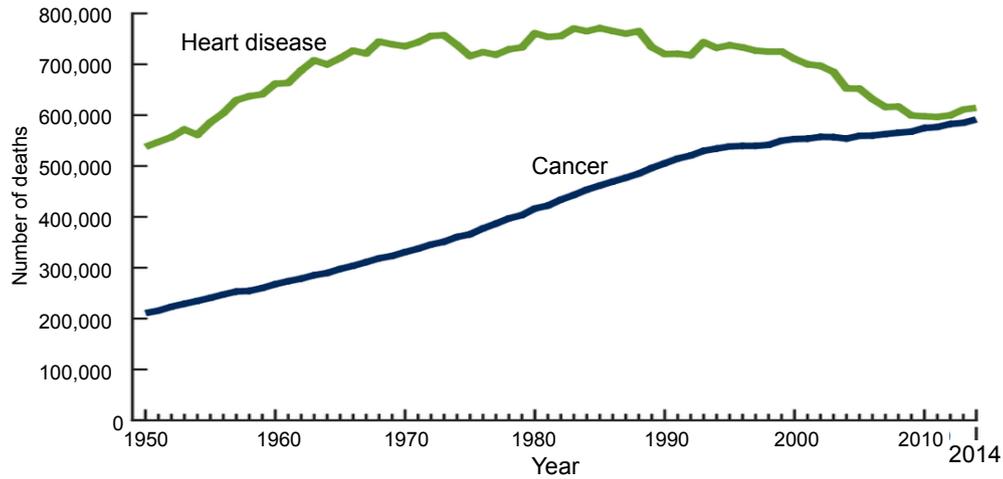


Figure 1. Graph showing increase in cancer deaths and decrease in heart diseases (Source: Cancer Surpasses CVD as Leading Cause of Death in 22 States).

It proves to be the in several high income countries where cancer deaths increasingly rising leaving behind the heart diseases. According to the American Cancer Society, the better detection of cancer can only be done if more cases can be diagnosed which may otherwise go unnoticed (**Figure 2**).

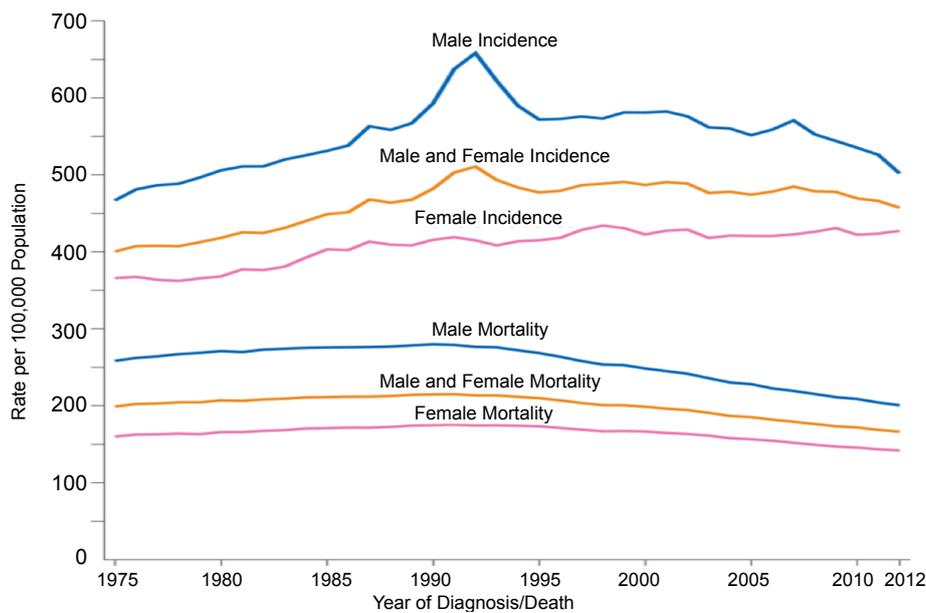


Figure 2. American Cancer Society trends in cancer incidence and death rates by sex, United States, 1975 to 2012 (Data source: Cancer statistics, 2016).

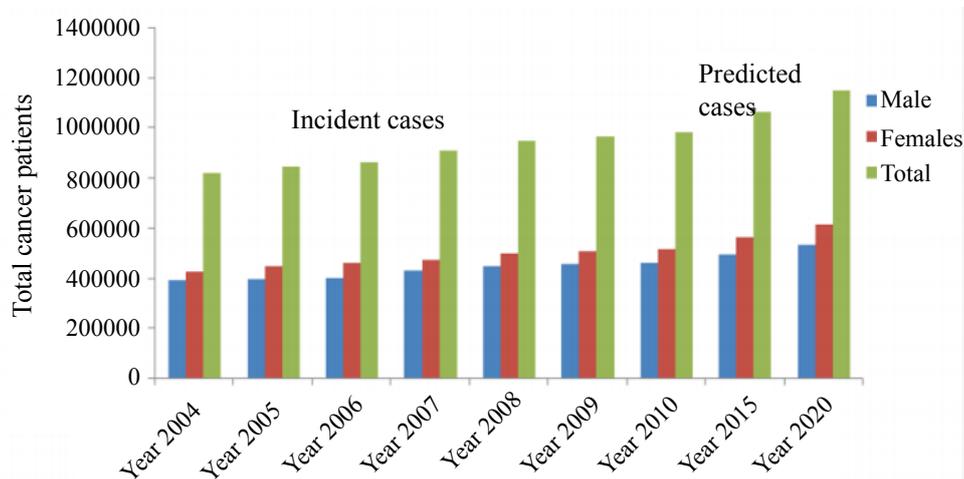


Figure 3. Year wise total cancer prevalence in India (Source: Cancer Scenario in India with Future Perspectives).

Figure 3 shows the cancer patients prediction from the end of 2015 to 2020 in India. The number of female patient is seen to be more than the males. According to the data by Indian Council of Medical Research (ICMR) the most common cancer types in male are moth/pharynx, oesophagus, stomach, lung/bronchi and in female are cervix, breast, moth/oropharynx and oesophagus. Carcinoma breast is more common in urban females and it is the leading cancer among females as registered in Mumbai, Delhi and Bangalore. India contributes about one-fifth of the burden on annual global increase in carcinoma cervix, i.e., 100,000 cases annually.

Types of Cancer

Tumours can be of two types i.e., benign and malignant. Cancer tumours are malignant i.e., they can spread into, or invade, nearby tissues while benign tumours usually don't grow back once removed except in the case to brain tumours which are life threatening ^[2].

Carcinomas are formed by epithelial cells; these are the cells that cover the outside and inside surfaces of the body. Carcinomas can be further differentiated based on their origins in different epithelial cell types. They are: - Adenocarcinoma form on the epithelial cells that produce fluids or mucus. These are also known as glandular tissues. Example: Breast, colon and prostate cancer.

Squamous cell carcinoma: form in the squamous cells that lie just beneath the outer surface of the skin. These are also known as epidermoid carcinomas. Transitional cell carcinoma forms in the transitional epithelium or urothelium. These cells are found in the linings of bladder, ureters, and part of the kidneys, and other organs. Sarcoma are the cancers that form in bone and soft tissues, muscle, fat, blood vessels, lymph vessels, and fibrous tissue are known as sarcoma. The most common cancer of bone is osteosarcoma.

Lymphoma: It begins in lymphocytes (T or B cells). Lymphomas are disease fighting white blood cells that are a part of immune system. Abnormal lymphocytes build up in lymph nodes and lymph vessels, as well as in other organs of the body. Lymphomas can be categorized as: - Hodgkin lymphoma which is usually formed from B cells. Patients with this disease have abnormal lymphocytes that are known as Reed-Sternberg cells. Non-Hodgkin lymphoma this starts in lymphocytes and is a large group of cancers. They form from B or T cells and can grow quickly.

Leukemia is the cancer that starts to begin in the blood-forming tissue of the bone marrow are called leukemia. Instead of forming solid tumors they form a large number of abnormal white blood cells which build up in the blood and bone marrow, crowding out normal blood cells making it hard for them to survive due to the low level of oxygen ^[2].

Brain and Spinal cord tumors: These are the cancers that have their origin in tissue of brain or spinal cords are called as central nervous system cancers. Primary brain tumors are the one that start in the brain. Such brain tumor can spread to other parts or remain intact at one place ^[3].

Generalized Sign and Symptoms of Cancer

These includes lump in the breast which is rapidly increasing in breast or somewhere else in the body ^[4]. Changes in bowel habits like Diarrhoea or constipation for no obvious reason, Persistent bloating, Blood in stools, Feeling of a filled bowel even after going to the toilet, coughing, chest pain and breathlessness ^[4,5]. Shortness of breath, Chest pain leading to pneumonia, Cough persisting for more than three weeks. Bleeding Blood from anus, Blood while coughing, Blood in vomit, Blood in urine, bleeding between periods. Moles which has more than one colored mole, Is bigger in size than 7mm in diameter, Has an irregular border with jagged edges, Has an irregular or asymmetrical shape, Is itchy, crusting or bleeding ^[4]. An unexplained or on-going pain that comes and goes for more than four weeks makes it urgent to visit your doctor ^[5]. On-going stress without any reason can also be associated with cancer ^[6].

General Causes of Cancer

Genetically some types of cancers run in some families but are not directly linked to the genes inherited by parents only a small portion of all cancers are inherited. The cause of most cancer formation is the gene change that starts in a single cell over the course of a person's life. Tobacco has been the major cause for cancer nowadays. Tobacco smoke is made up of 7,000 chemicals, including over 70 known to cause cancer and are called as carcinogens e.g.: nicotine, cyanide, formaldehyde, methanol, acetylene, ammonia, etc. Being overweight, usage of alcohol and unhealthy diet can have far-reaching health consequences, including raising the risk for certain types of cancers. Too much UV radiation from sun causes sunburn which can damage the genetic material in your skin cells. Enough damage over time can cause the cells to start growing out of control which can further lead to skin cancer ^[7]. Radiation can come from cosmic rays from our solar system or as radioactive elements present in soil. Both of these are the major contributors to worldwide radiation exposure. Other sources of radiation are x-rays, CT scans, Radiation therapies, nuclear weapon testing, etc.

General of Diagnosis Cancer

Imaging procedures include CT scans, nuclear scan, Ultrasound, MRI, PET scan; X-rays are various imaging procedures that

are used for cancer diagnosis^[8]. In some cases, biopsy is needed to be done for cancer diagnosis. It is a procedure in which the doctor removes a sample of tissue and then the tissue is looked under the microscope to see if it is a cancer or not. The sample removal is done in several ways like with a needle; with an endoscope and surgery is also an option^[9].

Possible Prevention

Reduce the intake of tobacco in any form. Smoking has led to a various type of cancer including lung cancer, mouth cancer, throat cancer, larynx cancer, bladder cancer, cervix cancer, pancreas cancer and kidney cancer. Even passive smoking can increase the risk of lung cancer. Quit tobacco should be the only motive if you need to lower the risk of above mentioned cancer types. Further a doctor's help can also be taken if someone really wants to quit smoking^[10]. Though healthy selection of food can't guarantee cancer prevention but it might help to reduce the risk of certain cancers. Certain guidelines are as follows:

Major diet of a person should rely on fruits, vegetables and other food from plant sources such as whole grains and beans^[10]. Choose low calorie food which includes refined sugar and healthy diet. Limited consumption of alcohol is seen to be beneficial for health^[11]. High consumption can lead to increased risk of tumors of cavity, pharynx, larynx, oesophagus, liver, colorectal and female breast. Processed meat is found to have an exogenous source of N-nitroso compounds because the food industry uses nitrite compounds. And such meat consumption is related to colorectal and lung cancers^[12]. A healthy weight should be maintained as obesity accounts for 14% of cancers in men and 20% of cancers in women^[11,12]. An exercise tends to decline ones chances of developing colon and breast cancer. 150 minutes a week should be surely dedicated to moderate aerobic activities or 75 minutes a week to vigorous aerobic physical activity. Sun rays are the major cause of skin cancer therefore; protective measures should always be used. Avoid sun during midday as at this time the rays are the strongest. If going out then cover exposed area, apply sunscreen^[13]. By getting some vaccinations the chances of cancer can be reduced. They are like Hepatitis B can increase the risk of developing liver cancer. This vaccine is recommended for certain high risk adults such as people who are public safety workers who might get exposed to infected blood or body fluids, people with sexually transmitted infection, etc. likewise, Human papillomavirus (HPV) is a sexually transmitted virus that can lead to cervical and other genital cancer as well as the squamous cell cancers of the head and neck. The vaccine is available for 11 to 12 year of person and also for people at age 26 or younger.

Brain Tumour

The growth of abnormally growing cells inside the brain is termed as brain tumour. Tumours can arise in brain from other existing cancer of body or can start in brain only. Such tumours that originate in brain only are termed as primary tumours^[14]. Tumours can spread at other areas too or remain localized at one place only. Tumours can be benign (non-cancerous) or malignant (cancerous). If there is a tumour in brain then it will definitely cause problems be it benign or malignant^[15].

The occurrence of brain tumour is not limited to any age group but it makes up to 20% of all childhood cancers. More than 1,200 new cases of brain tumour occur each year.

Epidemiology of Brain Tumours

Nearly 78,000 new cases of brain tumours are to be diagnosed this year which include the higher number of non - malignant tumours. Out of all the brain tumour types Gliomas accounts for more than 70% out of which glioblastomas are the most frequent ones. Primary brain tumours cause movement, speech and balance problems in patients. Many lifestyles, environmental and occupational factors are also responsible for increasing glioma risk. In US there are more than 600,000 people living with primary brain and CNS tumours. Astrocytomas occurs approximately about 75% of all gliomas^[16-18]. Survival rate after diagnosis of brain tumour is totally dependent on age, histology, tumour stage, tumour behaviour and molecular markers. A large number of primary brain tumours (36%) are located within the meninges.

Tumour Grades and Types

There are four grades of tumour i.e., I, II, III and IV. With increasing grade malignancy increases. Tumour grading helps the doctor in the treatment of tumour and also helps in predicting the outcomes. Grade I are slow growing cells which are least malignant and are associated with long term survival. These have a normal appearance under the microscope. Grade II are slow growing cells and looks slightly abnormal under the microscope. They can invade nearby tissues and recur, may be as a higher grade tumour. Grade III tumours are malignant and there is no wide difference between a grade II and grade III. Cells of this grade keep on reproducing abnormal cells, which grow in nearby brain tissue. These tumours tend to transform as grade IV tumours. Grade IV are the malignant tumours. They keep on producing abnormal cells which are very abnormal in appearance. They also have areas of dead cells in there centres.

Types of Primary Brain Tumours

Acoustic Neuroma: This is known by various names like vestibular schwannoma, schwannoma, or neurilemmoma. It mostly grows around the eighth cranial nerve and arises from cells that form a protective sheath around nerve fibres. Symptoms include dizziness, hearing loss, ringing in the ear, numbness in the face, walking problem, balance problem and lack of coordination. Treatment includes surgery id the basic treatment and focuses on complete removal of tumour without harming the seventh

cranial nerve. Radiosurgery can also be considered for some patients but these high-energy radiations do not always able to remove the complete tumor. Complete shrinkage of tumour may take several months or may not occur ^[19-22].

Chordoma: is a low grade tumour and occur very rarely. It generally originates from the cells left over from early foetal development and invades the bone and soft tissue. It occurs at the sacrum, near the lower tip of spine, or at the base of skull. Such type of tumours can recur or spread. Symptoms include double vision and headaches occur. Treatment include chordomas at the base of the skull are hard to remove rather the ones located in spine can be removed by surgical resection.

CNS Lymphoma: It is a very threatening tumour and develops in the lymphatic system. It is a common one in the people who have a weak immune system ^[23-25]. It can be of primary and secondary type. Occur in men more commonly than women. Symptoms include partial paralysis on one side of the body, speech disorders, headaches, vision problems and seizures. Treatment include common methods for treatment are radiation therapy, steroids and chemotherapy. Surgery is not considered good option because there are multiple lesions.

Craniopharyngioma: It occurs in areas at the base of the brain and near the optic nerves. It is of low grade and often accompanied by a cyst. It occurs in children and men and women in their 50s and 60s. Symptoms include headaches, weight gain, visual changes and delayed development in children. Treatment include surgery is the widely used treatment. Radiation therapy might be used.

Gliomas: Various types of gliomas are present which are described in the following section. Brain stem glioma is located at the base of the brain. This occurs mostly in children aged between three to ten years and is of low to high grade. Symptoms include nausea, speech or balance abnormalities, facial weakness, difficulty in swallowing, weakness or numbness of arms or legs and double vision are some frequent symptoms recorded. Treatment include surgery can't be considered in this case because brain stems cells can be easily damaged and can't be risked with surgery as it controls various vital body functions.

Ependymoma: It starts to develop from the cells that line the hollow cavities at the bottom of the brain which have slow or fast growth. These can block the ventricles causing the deposition of cerebrospinal fluid in the brain. It has a high occurrence frequency at the age of 5 and again at the age of 34. Symptoms include occurrence of severe headaches, difficulty in walking, neck pain, nausea and vomiting. Treatment include on determining if has spread to spinal cord or not surgery followed by radiation therapy is done. There is a need of a shunt to treat hydrocephalus caused by blockage of the ventricles. **Mixed Glioma:** it is a combination of an astrocytoma and an oligodendroglioma. It forms the most aggressive type of tumour cells and is common among both men and women in their 20s-50s. Symptom includes weakness or paralysis, visual problems, headaches, behavioural and cognitive changes. Treatment include they are treated for the most anaplastic type of cell found in the tumour. **Optic nerve glioma:** as per its name it is located near the path between the eyes and the brain. Most frequently occurs in infants and children, but can occur in adults too. Symptoms include they include headaches, progressive loss of vision and double vision ^[26-28]. Treatment include surgery is the basic treatment accompanied by radiation therapy or chemotherapy.

Subependymoma: It is a slow growing tumour usually located in the fourth and lateral ventricles and is more common in men than in women. Symptoms include nausea, headaches; loss of balance and in some cases no occurrence of symptoms. If tumour progresses than radiation therapy is used and surgery is done only when possible.

Medulloblastoma: It is a type of primitive neuroectodermal tumour which is generally located in the cerebellum or near the brain stem. There are chances that it can spread to spinal cord through the cerebrospinal fluid. Hydrocephalus can occur in this too. It is more common in men than female and often occurs in children under the age of 10. Symptoms include occurrence of early morning vomiting, sleepiness, headaches, double vision, lack of coordination, personality changes, sign of pressure are noticed behind the eyes when studies with an ophthalmoscope. Treatment includes chemotherapy and radiation both are the preferred treatment plan with surgery only if needed. Recurrence of this tumor is noticed if not treated properly.

Meningioma: Its growth is seen from the meninges. On growth it is seen that meningiomas compress adjacent brain tissue. These are classified into 3 grades namely: - Grade I: benign meningioma, Grade II: atypical meningioma, Grade III: malignant meningioma. These are common among women in rare cases occurrence of multiple meningiomas can also occur. Symptoms include vision changes, nausea, headaches, cognitive and behavioural changes, seizures and sometime no occurrence of symptoms. Treatment include in this case surgery is considered to be the standard treatment accompanied by radiation therapy. If the tumour is not completely removed than it can recur.

Metastatic brain tumour: They can originate in any part of the body but primarily it happens in the lung, breast, colon, kidney, or skin. Most people with metastatic tumour have multiple lesions. These tumours are located in cerebrum but can also develop in the cerebellum or brain stem and are common in middle-aged and elderly people. Symptoms include lack of coordination, behavioural and cognitive changes and headaches. Treatment include the standard treatment includes surgery and radiosurgery followed by whole brain radiation therapy (WBRT).

Oligodendroglioma: It can be of high or low grade and occurs in frontal or temporal lobes. More commonly occur in men than in women but can also occur in children. Symptoms include paralysis can happen, headaches, cognitive changes and seizures. Treatment include treatment options are totally dependent on the grade of tumour. If the tumour is of low grade and symptoms

are not that severe than surgery is done followed by keeping watchful eyes on the tumour growth through MRI. For the high grade tumour surgery is done followed by radiation and chemotherapy.

Pituitary tumours: These are located in the pituitary gland. These are specifically located at the centre of the brain and above the nose. Such tumours can cause excessive secretion of hormones and occurs in people in their 50s-80s. Symptoms include depression patients should be once analysed for these tumours; behavioural changes are seen, abnormal growth of hands and feet's, weight gain, nausea, and cessation of menstrual periods. Treatment include if the tumour is large than surgery is the standard treatment radiation and chemotherapy can also be used. Chemotherapy is also proven to be working properly in this case and the changes can be seen many a times through MRI scans.

Primitive neuroectodermal: They do not remain at one place instead spread throughout the CNS as they are highly aggressive and grow from undeveloped brain cells. They are Large in size. Symptoms include nausea, weakness, seizures, morning headaches, sleepiness or lethargy, behavioural changes, weight loss or gain. Treatment include surgery is the standard treatment followed by radiation therapy if needed.

Schwannoma: They mainly grow around the eighth cranial nerve and arise from cells that from a protective sheath around nerve fibres. Symptoms include hearing loss in the ear of the side of tumour; deficits depend on the nerve that is affected. Treatment includes surgery and radiotherapy is standard techniques tumour can recur if it is not completely removed.

Risk Factors in Brain Tumor

The basic cause of brain cancer is still not known but certain factors can relate to it for its cause, there is less risk factor known for causing brain cancer as compared to other cancers. The various known factors are listed below:-

There is no basic way of differentiating gender for getting brain cancer as some cancers, like medulloblastomas are more common in man and meningiomas are more frequent in females^[15,16]. People at any age can acquire brain cancer but its frequency increases with increasing age. Children could also acquire it but elders are at higher risk. The age factor keeps on varying with cell type and its location. There are no such evidence reported for brain cancers running in a family except in the case of certain diseases like Hippel-Lindau, neurofibromatosis, and Li-Fraumeni syndrome^[15,17]. The dietary N-nitroso compounds may raise the risk of childhood and adult brain tumor. It is seen after the studies that woman in her pregnancy having beer can also be a cause of this. History of any previous treatment of brain or head with ionizing radiations can lead to a further brain tumor.

Symptoms of Brain Tumour

Headache is a very common symptom in normal livelihood too therefore; tumor headaches can be differentiated with the normal headache as they have different pattern and different intensity of occurrence. A headache accomplice tumor is very severe and worsens in the morning^[26-28]. Loss of motor skill during a brain tumor certain areas of brain associated with motor functions are affected e.g. balance, co-ordination. Vision changes a tumor can lead to a blurred vision along with difficulty in watching or reading. Nausea it worsens in the morning if you are having a tumor. A feeling of being sick may rerun. Drowsiness as the tumor increases it may lead to more sleepy condition or sleep during daytime. Severe seizures and loss of consciousness should be directly taken to the doctor. Sometimes tumor in the frontal part of brain can lead to changes in behavior and personality.

Diagnosis of Brain Tumor

A neurological exam include hearing, vision, strength, balance, coordination and reflexes test along with knowledge about the family history to know about the cancer in detail. Imaging tests are the most widely used tool for diagnosis of brain cancer or for any other type of cancer. These tests have various other tests under them. They are: MRI, PET scan, CT scan, cerebral angiogram, Myelogram, Lumbar puncture. Biopsy is a procedure in which a small sample of tumor is isolated for examining it under microscope. Different types of biopsy are:-Needle biopsy,Stereotactic biopsy. In Electroencephalography process electrodes are attached to the outside of a person's head and the electrical activity of the brain is checked. It is used to analyse the seizures.

Treatment of Brain Tumor

Surgery acts as the basic step in the tumour treatment. In each case total removal of tumour is not possible but minor removal can help too as it can reduce the size of the tumour, relieve symptoms and help proceed towards other necessary treatments. Radiation therapy may stop or slow the growth of brain tumours. Tumours that are not removed completely or some leftover tumour cells can be removed through this therapy. A combination of radiation therapy and chemo therapy can also be used^[29-31]. New radiation techniques are now there which specifically focuses on the tumours and does not harm the other healthy cells around it. Photon therapy is basically focused on removal of tumours from highly sensitive areas (skull base and spine). It does not harm the nearby healthy cells. Drugs in chemotherapy can be consumed orally or through injections and can be given along with other treatments or individually.

Advanced Research for Cancer

Immunotherapy utilizes the immune system in the treatment of cancer by boosting the body's natural defense mechanism. It either utilizes materials made by the body or laboratory made material to restore immune system to fight cancer. The use of

antibody and antigen interactions can be utilized to treat cancer. Antibodies that can bind to tumour antigens help in treating cancer. Dendritic cells or vaccines can be used for this purpose while many other methods are under clinical trials. Vesicular stomatitis virus (VSV) is a non-segmented, negative-strand RNA virus with inherent oncolytic virus (OV) qualities. OV is an originating approach towards anti-cancer which utilizes viruses to infect and kill cancer cells. VSV belongs to the Rhabdoviridae family of virus [27,28]. It is found that strain of VSV are less toxic to cancer cells for a majority of brain tumour types. Retroviral replicating vector are the widely used tools for the delivery of material into host cells. These can deliver a gene which has a specific function to a cancer cell thus, attenuating the cell. The emerging usage of RRVs shows a terrific improvement in the development of new therapies for all types of brain cancer [29-31].

CONCLUSION

New antiangiogenic treatments are continuously changing the manners in which this disease is being treated. Bevacizumab is the only drug for now that has being approved by FDA as an angiogenesis inhibitor for brain cancer. Other drugs are under clinical trials and those which have passed the clinical trials are serving those patients who have stopped responding to the primary treatments. These antiangiogenic are providing improved treatment than the earlier used harsh and ineffective methods of treatment. A great aspect of precision medicines is yet to be derived. According to this concept every individual will be given treatments matching genetically to them and to their personal histories. In this way the therapies would me more effective and will cause few side effects. MSK scientists are already working on this concept of precision medicines for all kinds of cancer, both common and rare [32-35].

Another century old idea is to use a person’s own immune system to fight his or her cancer is known as immunotherapy. Two drugs (nivolumab and ipilimumab) are already being developed that boost the cancer-fighting powers of immune system’s T cells. These drugs belong to a class of immunotherapy treatments called checkpoint inhibitors, which work by emphasising on immune system and helping it work better. So far they have prodeuced remarkable results by eliminating cancer completely in some patients with advanced melanoma. These therapies do not work yet in everyone but research is on-going for its maturation process. In addition to drugs like ipilimumab and nivolumab, another immunotherapy strategy is utilised in which a patient’s own T cells are manipulated to attack cancer cells. T cells are collected from a patient’s blood stream and are genetically engineered to recognize certain proteins on cancer cells and are then infused back into the patients’ bloodstream [36-40].

Therapies that can block the tumour growth by blocking blood vessels of it are providing a ray of hope in patients for further treatment and removal of the entire tumour. Tumour treatments can be very destructive but it needs a patient to be adjusting according to the doctor’s plan of treatment [41].

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