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RESEARCH ARTICLE

CLINICAL STUDY OF CANCER TUMORS SIZE AND STAGES

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ABSTRACT

Cancer is dangerous disease that is result of out-of-control growth of DNA damaged cell. Death rate due to cancer is very high. More than hundred types of cancers are possible among that mortality rate of lung cancer, breast cancer, prostate cancer, brain tumor is very high. Early detection of cancer and proper treatment plan improves the survival rate of cancers. In clinical environment medical imaging modalities like Computed Tomography, Magnetic Resonance Imaging, Positron Emission Tomography, Ultrasound and others play a crucial role in early detection of cancers with use of various image analysis algorithms. Selection of modality and imaging algorithms depends on type and nature of cancer. TNM staging play a vital role in treatment plan. This paper discusses the major types of cancers, their TNM staging and also the type of modalities that are used for early detection of specific type of cancer.

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INTRODUCTION

In normal functioning tissues cell divides into multiple cells, as cells becomes old they collapses. These two biological processes occur in every healthy tissue to keep the balance between healthy cells and unhealthy cells. Over time old damaged and DNA damaged cells are eliminated by process known as Apoptosis. Some failure in apoptosis, damaged cells may continue to accumulate, multiply and grows into precancerous cells. Accumulation of precancerous cells results in cancer. Cancer is uncontrolled growth of precancerous cells. Apoptosis also plays an important role in cancer progression. Apoptosis prevents invade of cancerous cell to other parts of the body via blood or lymphatic systems. Cancer is not a single disease, it takes year of time to develop. Fig 1 and Fig 2 shows the cell division in normal tissue and cell division in cancerous tissue. Fig 3 shows progression of cancer from original site to other parts of the body. Classification of Cancers is based on the type of cell or the organ in which they originate:

Carcinomas: More than 90% cancers are Carcinoma Cancers. These type of cancers starts in epithelial tissues that line internal organs like liver, kidney or in skin cells.

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It spreads to other parts of body, but not always. Carcinoma in situ means cancer remains in cells where it is started and have higher frequency of mutation. Common malignancies, such as breast cancer, colon cancer, and lung cancer, are almost always carcinoma. Common types of Carcinoma cancer are Basal cell carcinoma, Squamous cell carcinoma, Renal cell carcinoma, Ductal carcinoma in situ (DCIS), Invasive ductal carcinoma, Adenocarcinoma

Sarcomas: Sarcomas are uncommon type of cancer in human. Theses tumors start in mesenchymal tissues such as bone, muscle, connective tissue, cartilage, fat and blood vessels. Sarcomas most often occur in arms and legs but can be present in any part of the body.

Leukemias: Cancers that occurs in the blood cells and bone marrow is known as Leukemias.

Lymphomas: Lymphomas starts in lymphatic system and in cells of immune system.

Central nervous system cancers: Occur in the cells of the brain and spinal cord. Early detection of cancer increases a survival rate of patient. Once a cancer is diagnosed doctors uses cancer staging method to stage the cancer in order to get more information about the spread of cancer in the body and to plan treatment.

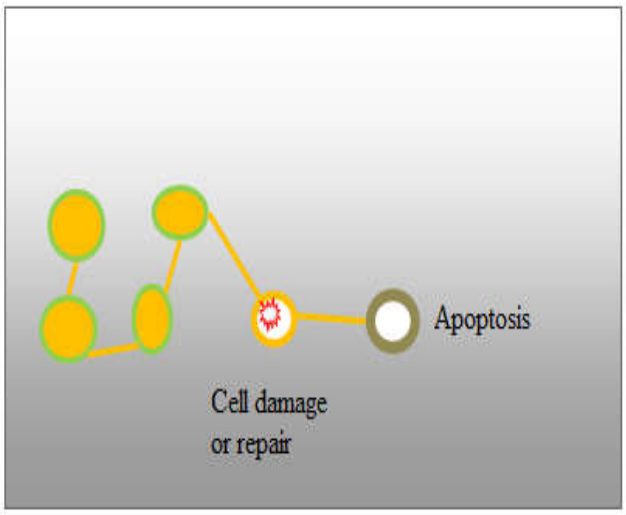


Fig. 1 Normal cell division

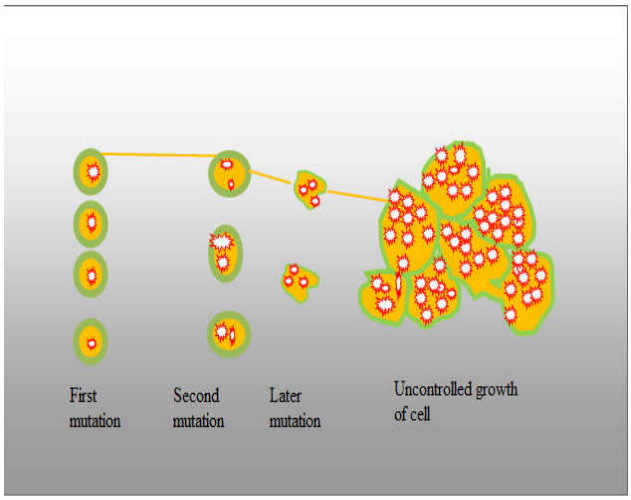


Fig. 2 Cancer cell division

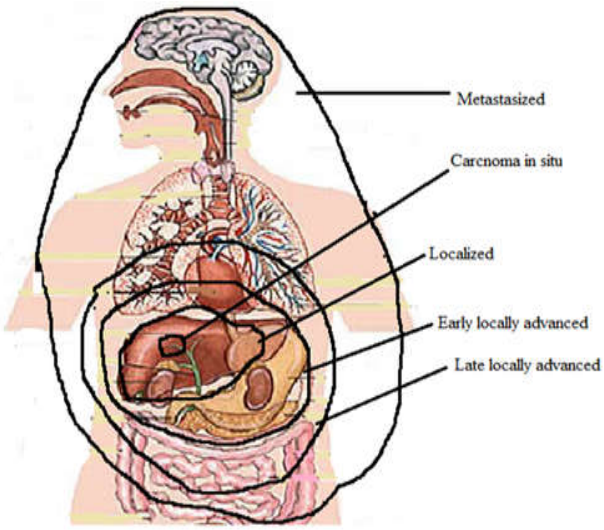


Fig. 3 Progression of Cancer

One of the standard staging tool is TNM staging developed by American Joint Committee on Cancer (AJCC) in collaboration with the Union for International Cancer Control (UICC). TNM (Tumor, Node, and Metastasis) staging is used for different kind of cancers to describe location, size, type, spread to nearby lymph node or to other part of body (metastasized). Table I provides information about TNM staging.

In clinical study percentage of patients survive at least five years from the time of cancer is diagnosed is knows five year survival rate of cancer. Clinical study of cancer disease shows that major types of cancers are lung cancer, breast cancer, prostate cancer, pancreatic cancer, brain tumor. Table II shows the survival rate and life time risk of above mentioned cancer types.

Lung Cancer

Lung cancer is carcinoma type cancer that is leading cause of death both in men and women worldwide, assassination of more than 161,000 per year due to lung cancer. Lung cancer is malignant tumor which is caused by uncontrolled division and growth of abnormal cells in lung. Initially accumulation of these abnormal cells results in pulmonary nodules which then becomes malignant lung cancer tumors. Major risk factors for lung cancer are Tobacco smoking, exposure to Radon gas, asbestos, air pollution and inherited genetic factors. Types of lung cancer are Small Cell Lung Cancer (SCLC) and Non Small Cell (NSCLC). Worldwide mortality rate of lung cancer is very high, early detection and diagnosis increases a survival rate of patients. In this aspect medical imaging modalities with advanced technologies play an important role in lung cancer detection, assignment of TNM staging and to assist doctors in treatment plan. Table III shows the TNM staging of lung cancer (Aminmohan Roozgard, 2012).

Imaging modalities in lung cancer detection

Computed Tomography –CT

CT is gold standard in lung cancer detection based on further assessment of the disease can be done. It. uses special type of x-ray which are more sensitive in finding lung cancer at earliest stage thus improves the survival rate. It takes many pictures by rotating around the patients, these pictures are combined by computer into image of slices. For a lung cancer and nodules detection Low Dose Spiral CT (spiral CT) is efficient modality. CT image of lung provides information about size, shape, position of all possible lung tumors. It provides the valuable information about large lung nodules with possibility of cancer that is metastasized nearby lymph nodes. CT guided needle biopsy helps the doctors to do a needle biopsy of suspected area with a deep lung cancer (Aminmohan Roozgard, 2012; Shiwen Shen *et al*., 2015)

Positron emission tomography –PET

PET modality uses FluoroDeoxyGlucose (FDG) a radioactive sugar while taking the image suspected cancer area. Cancer tumors absorb FDG very quickly and can be seen more clearly in special camera.PET/CT scan: PET is more efficient when it used with CT in lung cancer detection using same machine. In this combined modality area of lung containing cancer appears with higher radioactivity on PET scan and it appears as more detailed area on CT scan. Doctor uses this information for further assessment of cancer. Combined PET/CT modality is very useful in detection of early stage lung cancer, spread of lung cancer to nearby lymph nodes or other areas. This can also show metastasized state of cancer to liver, bones, adrenal glands, or some other organs. But doctors does not suggests PET/CT scan for routine follow up of lung cancer patients after treatment.

Table 1. TNM staging notation and meaning

T-Size and extent of the primary tumor	N-Number of nearby lymph nodes effected	M-Metastasized whether cancer has spread to other parts of the body
TX: Not possible to measure primary tumor	NX: Not possible to measure invaded cancer to nearby lymph nodes	MX: Not possible to measure metastasized cancer.
T0: No found of primary tumor.	N0: No cancer in nearby lymph nodes	M0: cancer is not metastasized to other parts of the body.
T with number indicates size and spread of primary tumor, higher number shows the severity of disease. Possible stages are T1, T2, T3, T4	N with number indicates location and number of lymph nodes infected with cancer. Higher value show that disease has invaded to more number of lymph nodes. Possible stages are N1, N2, N3	M with number indicates Metastasized state of cancer.

Table 2. Cancer types and five years survival rate

Cancer type	Five year survival rate	Life time risk
Lung cancer	17.4%	Men-1 in14, Women-1 in 17
Breast cancer	12.4%	Women-1 in 8
Prostate cancer	Metastasized is about 29%.	
Brain tumor	30.3%	

Table 3. TNM staging of lung cancer

Lung cancer stage	Description
Stage-0	Carcinoma in situ: Primary lung tumor start in lung.
Stage-IA	Lung Cancer tumor < 2 cm presents in the lung only.
Stage-IB	Lung Cancer tumor > 2 cm but ≤ 3 cm may grow larger in the lung, spread to the main bronchus and innermost layer of the pleura.
Stage-IIA	Lung Cancer tumor >3cm but less than 5cm has characters to spread to lymph nodes on the same side of the chest as the cancer.
Stage-IIB	Lung Cancer tumor >5cm but less than 7cm spreads to chest wall, diaphragm, pleura between the lungs, membrane around the heart and also to main bronchus.
Stage-IIIA	Lung Cancer tumor > 7 cm has spread to main bronchus, chest wall, diaphragm, pleura between lungs and to pericardium.
Stage-IV	Lung Cancer tumor of any size has spread to another lobe of same lung, to other lung and to other parts of the body.

Magnetic Resonance Imaging-MRI

MRI provides a detailed soft tissue images. It uses radio waves, strong magnate and contrast agent gadolinium. MRI images provide information of location of lung tumor, size, and its metastasized state. In very rare cases chest MRI is done for a lung cancer to check whether it has extended into central structures of chest.

MRI also helps for confirmation of spread of lung cancer to the brain or bones. DW-MRI detects the lung cancer accurately and structural changes in lung due to cancer causes in the early stages of the disease also.

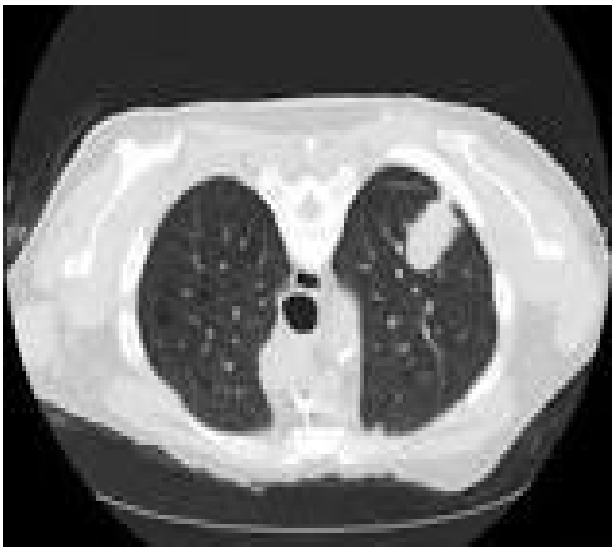
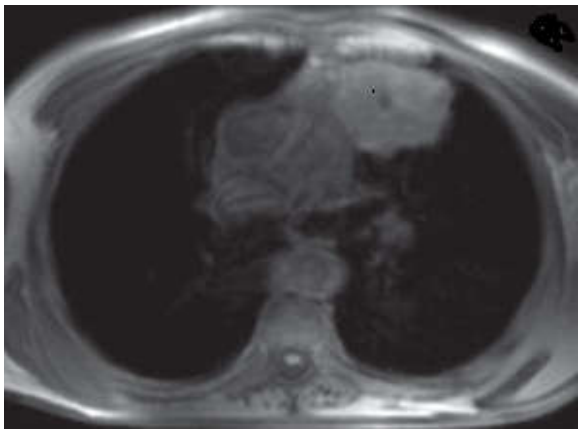
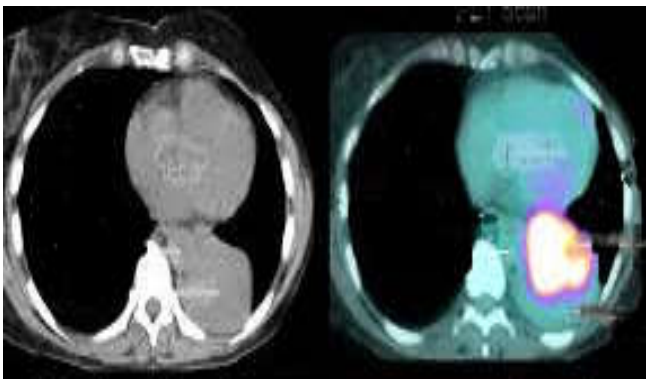


Fig 4.a. CT scan lung image



b. MRI pulmonary epidermoid carcinoma of lung



c. PET/CT scan of lung

Fig. 4a, b, c shows the CT scan, MRI scan and PET/CT scan of lung in different patient with lung cancer

Table 4. TNM staging of breast cancer

Breast cancer stage	Description
Stage 0:	Breast cancer in this stage is known as Ductal Carcinoma In Situ (DCIS), starts in milk glands.
Stage I	Breast cancer has spread to nearby tissues.
Stage IA	Invasion of cancer to fatty breast tissue.
Stage IB	Small Cluster is result of accumulation of cancer cells and has invaded too few lymph nodes.
Stage II	Cancer has grown and invaded to other parts of the breast and also to other breast also.
Stage IIA	Cancer tumor small in size with spread of few lymph nodes.
Stage IIB	Cancer tumor size as that of walnut or a lemon size. It may or may not spread in the lymph nodes.
Stage III	It is not metastasized yet to bones or other organs.
Stage IIIA	Tumor is comparatively bigger in size and has spread up to 9 lymph nodes.
Stage IIIB	The cancer tumor has spread into the chest wall, skin around breast and to lymph nodes.
Stage IIIC	Cancer tumor has been extended to more than 10 lymph nodes and to upper and lower part of collarbone.
Stage IV	Cancer tumor has metastasized too far away lymph nodes, bones, lungs, brain and liver

Cancer

Breast cancer is always caused by damage to a cell's DNA in breast tissues. Common most cancer in women is breast cancer and world wide it is second leading cause for cancer death. It is carcinoma type of cancer starts when cells in breast begin to grow out of control because of DNA damage in cells. Precise causes of breast cancer are unclear. Masses and microcalcifications in breast takes a years to become breast cancer. Major risk factors that cause breast cancers are mutation of BRCA1 and BRCA2 genes inherited from parents, overweight, obese, menstruation at an early age other lifestyle related factors such food diet.

Types of breast cancer

Ductal carcinoma: It is common type of breast cancer and begins in the cells of the milk ducts that carry milk to the nipple.

Lobular carcinoma: Cancer begins in glands that produce milk.

Inflammatory breast cancer: It is rare type of breast cancer, where breasts appear to be warm, red, and swollen.

Table IV describes the TNM staging of breast cancer. Higher number indicates more advanced cancer.

Imaging modalities in breast cancer detection

Ongoing research and improvements in imaging modalities have improved the early detection of breast cancer. Mammography is "GOLD STANDARD" for detection and diagnosis of breast cancer. MRI and Ultrasound imaging also play an important role in advanced stage of this cancer detection.

Mammography

Mammography is widely used imaging technique for breast cancer. Day by day mortality rate of breast cancer is reducing by usage of mammography in early detection of breast cancer since it is used to find tumors that are too small to feel.

Types of mammography

Screen Film Mammography (SFM)

It is gold standard for screening of breast cancer. It has a ability to provide adequate visualization of abnormalities in soft tissue, ability to depict subtle calcification, initial detection and follow up suspicious lesions. Disadvantages are limited dynamic range, contrast characteristic, fails subtle lesions in dense tissue very.

Full Field Digital Mammography (FFDM)

FFDM provides acquisition, display and storage of images. It provides facility to manipulate the contrast of lesions conspicuity. Images of FFDM have consistent image quality, better contrast, fewer artifacts, and slightly better lesions characterization as compared to other digital imaging for breast image, less processing time. It is better for breast cancer detection in women younger than 50, women with heterogeneous dense breast tissues.

Ultrasonography

Ultrasonography is major imaging technology to detect breast cancer. It is useful technology to differentiate benign or malignant solid breast tumor. It is also used to assist a doctor while performing interventional procedures (Sachin Prasad, 2007).

Tissue elastic imaging technology

Tissue elastic imaging technology is new imaging technology for breast diagnosis. The elasticity of malignant tissue is more that of normal tissue. It measures the tissue elasticity to diagnosis the disease.

Magnetic Resonance Imaging

MRI has high sensitivity in detection of breast cancer. Gadolinium contrast agent is used while taking image of breast. Dynamic contrast enhanced MRI is clinically proven imaging for breast cancer detection.

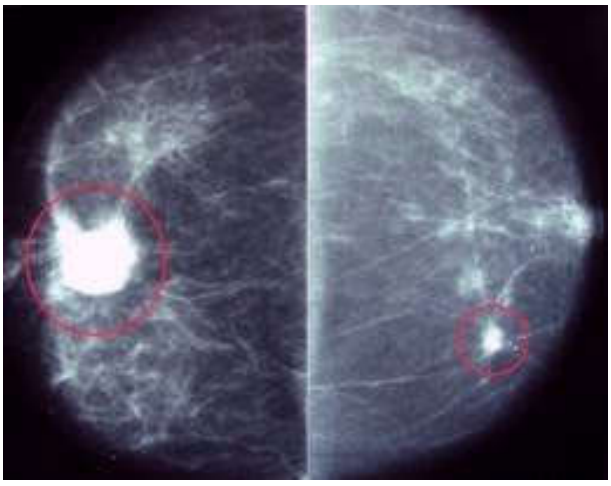
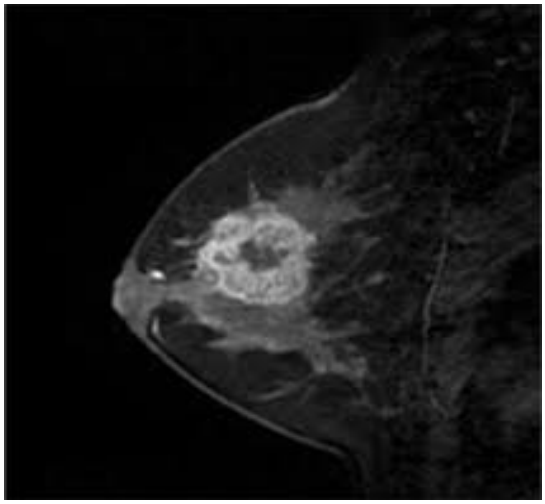


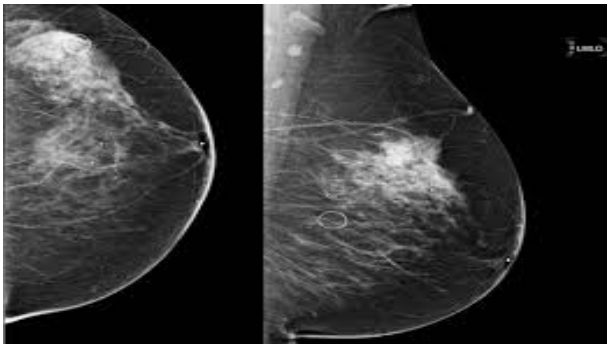
Fig5. a. Mammography breast image

This modality generates three dimensional images which contain volumetric anatomical and physiological information

that indicates increased vascular density and vasculary permeability changes associated with breast cancer infected tissues. Three different type of contrast are used detect to benign or malignant tumors in images. Type I is used for benign tumors. Type II is for malignancy tumors. Type III for indicates malignancy. The most significance of this modality is that it provides size of, extent of disease, muliticentricity and multifocality. It helps to differentiate between benign and malignant tumor (Gheoneo Ioana Andreea, 2011).



b. MRI breast image



c. Full Field Digital Mammography

Fig 5a, b, c are the Mammography, MRI and FFDM images of breast with breast cancer.

Prostate Cancer

Prostate cancer is most common cancer in men. Mutation in damaged cell's DNA causes uncontrolled division and growth cells of prostate. Accumulation of these abnormal cells results in prostate cancer. Cancer is classified based on nature of cancerous cells. Some cancer cells are limited only to prostate gland and grow very slowly. Some are grow very slowly and can be cured with minimal treatment. But cancers not belonging to first two mentioned cancers are more aggressive, spreads very quickly and needs more accurate treatment. Risk factors of prostate cancers are age, race, family history (men in family have had prostate cancer, BRCA1 or BRCA2), obesity. Men with prostate cancer have high PSA (Prostate-Specific Antigen) level. PSA is a protein produced by normal and metalized cells of the prostate gland. PSA level is measured as nanograms of PSA per milliliter (ng/mL) of blood. Rise of PSA in blood is indication of increased a number of benign nodules in prostate or prostate cancer. Continuous rise or Higher value of PSA in men blood sign of prostate cancer. The aggressiveness of prostate cancer is determined by grading system known as Gleason Score. This scoring system describes whether cells are normal (lower score) or abnormal (higher score) and helps to choose the appropriate treatment plan. Gleason score ranges from 6-10. The higher the score indicates more aggressive cancer that spreads quickly. The following tables TABLE V and TABLE VI describes the Gleason score and TNM staging of prostate cancer.

Imaging modalities in prostate cancer detection

Transrectal Ultrasound- Grey Scale Transrectal Utrasound (TRUS)

TRUS is very common imaging modality for screening of the prostate cancer, to guide needle biopsies, to estimate prostate volume accurately and to determine of PSA density. Specialty of this modality is that is cable to detect both hypoechoic and isoechoic prostate cancers. On TRUS prostate scanned images pprostate cancer appears as hypoechoic nearer to 1% and isoechoic nearer to 30%. But in most of the cases hypoechoic tumors are non cancereous. The Positive Predictive Value (PPV) of grey-scale TRUS is 52.7% and the Negative Predictive Value (NPV) is 72%. This shows that usage of TRUS in detection and localization of prostate cancer is limited.

Contrast-Enhanced TRUS (CEUS)

CEUS guided biopsy detects more prostate tumors as compared to traditional TRUS. CEUS uses microbubbles as contrast agent. The main advantages of CEUS are from the captured images it is possible for doctors to measure intraprostatic structures. The detection rate of this modality in prostate cancer (with diameter $\geq$ 5mm) detection is in the range 51% to 63%.

Computer-Aided Ultrasonography- HistoScanning

Malignancy of cancer results in disorganization tissue. Identification of malignant tumor can be achieved by disorganization behavior of infected tissue. This kind of disorganization of tissue due to malignant cancer can be obtained by imaging modality Computer-Aided Ultrasonography. The main advantage of this modality are finds the location of tumors, size with good accuracy, and scanned image also provides whether prostate is extended or not due to tumor. CT is not suitable modality in detecting and staging of prostate cancer.

Magnetic Resonance Imaging (MRI)

T2-Weighted Magnetic Resonance Imaging (MRI) is next modality option to detect prostate cancer but it is still under investigation and development. Significant Intraobserver variability is there in use of MRI for prostate cancer detection. The recent study shows that sensitivities of MRI to detect prostate cancer is between 37% to 96% and specificity ranges from 21% to 67%. MRI guided prostate biopsy is not recommended due it is time consuming, expensive and needs specific equipments. The recent study shows that MRI is useful during preoperative assessment prior to prostatectomy. Using Preoperative endorectal MRI images it is possible for surgeons to preserve neurovascular bundle during the surgery.

Table 5. Gleason score of Prostate cancer

Gleason score	Property of cancer cell
Gleason score<6	Structures of cancer cells looks like normal cells with slow growth.
Gleason score=7	Prostate is in aggressive stage
Gleason score>8	Prostate cancer spreads more aggressively to other parts and can be poorly differentiated.

Table 6. TNM staging and PSA level of prostate cancer

Prostate cancer stage	Description	PSA
Stage 0:		
Stage I	Presents only in prostate that too it involve partial part of one lobe of prostate.	PSA <10
Stage II	Tumor grows only within prostate, without extending outside the prostate.	PSA <20 or
Stage IIA	The tumor occupies more than one-half of only one lobes of the prostate.	PSA>=10<20
Stage IIB	The tumor presents in both lobes.	
Stage III	Spread of prostate cancer to nearby tissues, seminal vesicles but not to lymph nodes.	Any PSA
Stage IV	Prostate cancer has metastasized other parts of the body such as lymph nodes, bones, liver, lungs etc.	Any PSA

Table 7. Grade system of brain tumor

Grade	Description
Grade I	The tissues in tumors are benign. Tumors under this grade are known as Juvenile Pilocytic Astrocytoma (JPA) subependymoma. These are noninvasive, grow slowly and can be cured with surgery.
Grade II	The tissues in tumors are malignant. Tumors under this grade are known as Necrosis where so many abnormal cells present with absence actively dividing cells. Astrocytoma, Ependymoma, or Oligodendroglioma are grade II tumors. Tumor progress to higher grades of malignancy.
Grade III	Anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic ependymoma are Grade III tumors. Anaplastic astrocytoma contains dividing cells but no dead cells. Oligodendroglioma and Anaplastic ependymoma have dead cells.
Grade IV	Tumors under this grade are known as Glioblastoma. These types of tumors contain actively dividing cells. The tumor has blood vessel growth and areas of dead tissue.

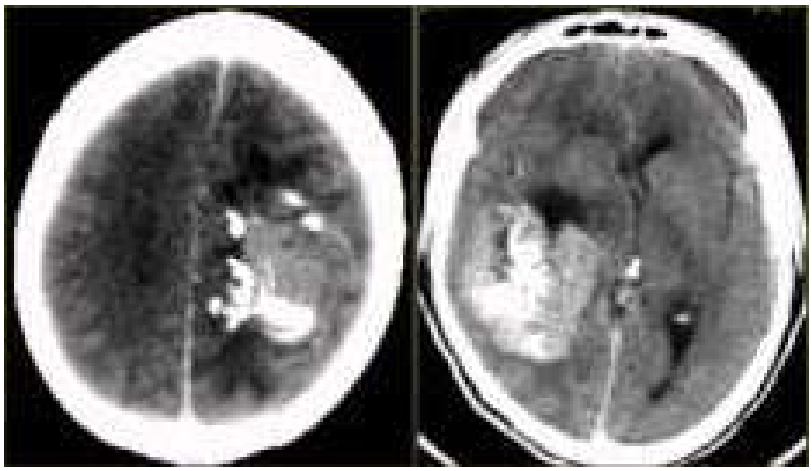
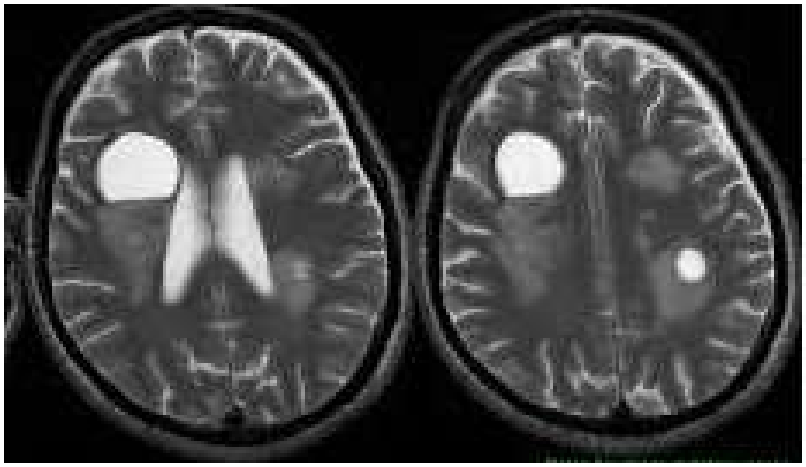


Fig.6.a. CT brain image Fig.6. CT brain image



b. MRI brain image

For staging of prostate cancer MRI is most precise imaging modality (Correas *et al*., 2013; Huge Hurvey and Nanditha M deSouza, 2016). Magnetic Resonance Spectroscopic Imaging (MRSI) is technology shows good specificity and sensitivity for metabolic profile of discreet voxel within MRSI image of prostate. MRSI is good in determining tumor aggressiveness as its sensitivity is higher. In prostate cancer detection MRSI sensitivity is good compared to T2-weighted MRI but specificity is less. Prostate cancer detection is more accurate when anatomic information from MRI and metabolic information from MRSI are combined. Various studies also showed that combined model of MRI and MRSI is more superior as compared with individual model. Clinical study shows that Dynamic Contrast-Enhanced MRI (DCE-MRI) also provides promising results in primary detection, localizing and staging of prostate cancer. DCE-MRI sensitivity is good compared to T2-weighted MRI in prostate cancer detection. Diffusion Weighted MRI (DW-MRI) is imaging modality to obtain molecular and cellular information about prostate. Combine model of DW-MRI/T2-WI is good in predicting recurrent of prostate cancer after radiation therapy (Yoursy, 2000; Tan, 2012).

Brain tumor cancer

Accumulation of abnormal cell in brain results in brain tumor. Cancerous brain tumor is either primary tumor that starts in brain or it is secondary that have metastasized from other part of the body. Risk factors for brain tumor are age, gender, home and work exposure, family history, exposure to viruses and infections, ionizing radiations etc. Behavior of brain cancer is different from other types of cancers such as breast cancer, lung cancer, and colon cancer. In some cases primary brain tumors spreads within the brain, in very rare conditions primary tumors get metastasized to other parts of the body. Grading system is used for brain tumor rather than staging system to determine spread of the tumor. Brain tumor grading system uses four distinct grades to grade the tumor. Factors used by grading system are size and location of tumors, type of tissue or cell affected recectability, spread of cancer with the brain or spinal cord and metastasized. Brain tumor cells are very aggressive in nature, based on this they are assigned with different grades. Brain tumor type and grade of the tumor both are necessary parameters to plan a treatment. Grade of brain tumor describes detailed features in the tumor such as if the growths of the tumors cells are very quickly are assigned with higher grade. Table VII provides grade description of brain tumor. Medical imaging with many technological advances has become crucial component in diagnosis, treatment planning and monitoring of disease response to treatment. CT and MRI are two most promising modalities for brain tumor diagnosis and to monitor the effect of therapy. Conventional non-invasive x-ray methods and Conventional invasive x-ray methods are currently not used in clinical practice for detection of brain tumor.

Computed Tomography

Technological improvements in CT made it as a clinical choice for choice for Brain tumor examination. Both Non-contrast enhanced CT and Contrast-enhanced CT imaging are used. Usage of contrast agents in CT (ionic, non-ionic, high osmolar, low osmolar, iso osmolar) depending on type of examination improves the detection rate of brain tumors. CT angiography is used to determine the relationship between the brain tumor and the blood vessels. CT-guided Stereotactic biopsy is useful in diagnosis of tumors.

Magnetic Resonance Imaging

MRI is valuable medical image modality for detection, treatment planning and follow up the therapy results of brain tumors. MRI uses the contrast materials (Gadolinium chelates) while taking the image of the brain that helps to differentiate between tumor and brain parenchyma. Different dose of contrast agent is required in MRI of brain tumor in different cases such delineation of extension of tumor, delineation of brain metastases. Traditional MRIs for brain tumors are Spin-Echo T1 Weighted Imaging (T1WI), Proton Density-Weighted Image (PDWI) and T2-Weighted Image (T2WI). As contrast agent dose increases cost of MRI also increases. This can be reduced by using standard dose Magnetization Transfer T1-Weighted image (MT T1WI). It provides accurate tumor classification and also information of residual tumor in postoperative patients which is not possible in traditional MRI. DW-MRI is valuable tool for description of brain neoplasm in which Apparent Diffusion Coefficient (ADC) of DW-MRI is used with tumor cellularity and grade. DWI is also useful for Lymphoma. Fig 6 a and b are CT and MRI images of brain with brain tumor (Antonios Drevelegas, 2011).

Conclusion

Every year death rate due to different types cancer is increasing all over the world both in men and women. Research is going on by many experts and researchers to reduce the mortality rate of cancer. Behavior of one cancer is different from other type. For a successful treatment doctors and also patients should know the characters of cancer tumors such as its size, location, metastasized state and TNM stage of tumor. All these characters depends on particular type of cancer and needs to be consider while treatment plan. Medical imaging modalities with advanced technologies are GOLD STANDADS for cancer detection and diagnosis. Use of image analysis algorithm with modalities as Computer Aided System it is possible to increase the survival rate of patients suffering from cancer.

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