CHAPTER 1

1.1 MEDICAL PERSPECTIVES

Even though reports of cranial surgery dates back to the B.C. era, modern intracranial tumor surgery commenced in the 1800’s. William Macewen removed the first intracranial meningioma in 1879[1] and in 1884 Rickman J. Godlee[2] performed the first resection of a glioma on a 25-year-old patient. Victor Horsley, Harvey Cushing and Walter Dandy later introduced the curved skin flap, various surgical approaches to anatomical structures of the brain and the pneumoencephalography[3]. In Norway, Vilhelm Magnus performed the first operation on a deep-seated tumor in the left cerebral hemisphere in 1903[4]. Magnus, being the only neurosurgeon in the country for 25 years carried out more than 200 intracranial procedures with a mortality rate of 8.1% [5].

Further development in the neurosurgical field included the stereotactic frame. The Horsley-Clarke frame[6] was introduced in the early 1900 for the purpose of animal research. In humans, stereotactic procedures were carried out after ventriculography was integrated with a frame system in 1947 by Spiegel and Wycis[7]. Though originally applied for lesion surgery on mental disorders and pain relief, stereotactic frame based biopsies of brain tumors were later established. The advent of computer tomography (CT) and magnetic resonance imaging (MRI) opened the possibility for frameless stereo-taxy using computers with pointing devices for pre – and preoperative planning and navigation. Frameless computer based neuro-navigation is now widely used in brain tumor surgery for biopsies, surgical approaches and resection of neoplasm’s.

The precise diagnosis of a brain lesion has always relied on microscopic examination of tissue. The historical path leading to modern histological techniques has been long and cumbersome: Problems with tissue fixation were overcome when formalin replaced alcohol in the mid 1800s. As to intra-operative diagnoses, frozen sectioning became greatly improved with the advent of the cryostat in 1938 enabling thin slices of tissue to be prepared [8]. Dudgeon and Patrick published a paper in 1927 describing the method of imprint cytology for fast diagnosis of tumors [9]. Today, these techniques are widely used for rapid diagnosis of tumors.
1.2 INTRODUCTION TO CANCER

Cancer is a genetic and vital disease. In last decade, many important genes responsible for the genesis of various cancers have been discovered their mutations precisely identified, and the pathways through which they act are being characterized. Mammography is the most common technique used by radiologists in the screening and diagnosis of the cancer cells. Although it is seen as the best examination technique early detection of cancer cells present a low accuracy in early prediction. Their interpretation requires skill and experience for proper diagnosis.

Computer aided diagnosis systems for detecting malignant texture have been investigated using several techniques. The existing computer aided diagnoses are generally categorized into two main categories namely Tumor mass detection and Cluster micro classification.

Cancer is the general name for over 100 medical conditions involving uncontrolled and dangerous cell growth. Scientists suggest that some cancer is caused by genetic factors, while other forms are caused by environmental conditions. In other words, one patient may already have a family history of brain cancer while another was exposed to a carcinogenic (cancer-causing) chemical in a factory. Both suffer from cancer--the only difference is the root mechanism which triggered the abnormal cell growth.

Cancer begins at the microscopic cellular level, the first signs of a malignant (actively cancerous) growth are nearly impossible to detect without special tests and training. In the case of pancreatic cancer, for example, there is little to no pain involved as the first malignant cells from around the organ [12]. As the tumor becomes more organized, new blood vessels may form to feed it directly or older vessels may be diverted. Meanwhile, the host body may only experience a few symptoms which resemble many other conditions besides cancer. Only after a sample of suspicious tissue has been removed and tested (biopsied) can many cancer forms be diagnosed.

One of the most insidious aspects of cancer is the way it grows. As the tumor outgrows the original organ, pieces of malignant tissue often break off (metastasize) and enter the bloodstream or lymph system. The cancer cells can then attach themselves to other vulnerable
organs and form new tumors. Thus a patient with pancreatic cancer may eventually suffer from lung, brain, kidney, and breast or colon cancer as well. This is why cancer specialists (oncologists) place so much emphasis on containing malignant tumors to their place of origin as proposed by Cigdem, D and Bullent, Y. [09].

Treatment for cancer ranges from rounds of powerful chemicals to focused burst of radiation to complete surgical removal of the tumor and surrounding tissue. Each treatment type brings a certain level of risk and pain to the patient, but cancerous cells left untreated will almost inevitably choke off vital organs and circulation. Chemotherapy introduces strong medicines which target fast-growing cells, but this also includes normal events such as hair growth and digestion as stated by Patrick J. Kelly, M.D., FACS [8]. Radiation treatments use heat energy to literally burn off malignant cells, but healthy tissue is also damaged. Surgical removal can lead to a permanent recovery, but undetected malignant cells may have already metastasized to other organs or be jarred loose by the surgery itself.

Curing cancer has been a major goal of medical researchers for decades, but development of new treatments takes time and money. Already there are many forms of cancer which are no longer considered untreatable. Some cancers, such as leukemia (blood cancer), can actually stop growing as suddenly as they started. This is called remission, and is often seen as a tremendous blessing for patients who have fought their conditions for years. Science may yet find the root causes of all cancers and develop safer methods for shutting them down before they have a chance to grow or spread as a part of Survey Results given in the Central Brain Tumor Registry of the United States (CBTRUS) in the year 2003[11].

1.3 MRI IMAGING TECHNIQUES

MRI has become the primary imaging modality for brain tumors and is now widely used in the pre–and postoperative evaluation of these patients.

Conventional MRI with or without contrast medium is the investigation of choice when suspecting a brain lesion. However, this imaging modality has limitations: The findings are often not specific as gliomas, metastasis, lymphomas, abscesses and infarction all may present ring-like contrast enhancement and surrounding edema. In addition, studies have demonstrated that the degree of contrast enhancement poorly correlates to the histologic grade of gliomas.
In a clinical setting this MRI technique alone has a limited diagnostic yield as proposed by Zhu H, Francis HY, Lam FK, Poon PWF in 1995[17].

**Perfusion MRI** measures blood flow to a tumor and the surrounding brain tissue. The most commonly used parameter is regional cerebral blood volume (rCBV) which evaluates the amount of blood passing through a specified region of the brain. The technique enables to a certain extent glioma grading, differentiation of metastasis and high-grade gliomas, selection of an appropriate target for stereotactic biopsy and definition of tumor margins as observed by T.K. Yin and N.T. Chiu [16]. Tissue concentrations of the metabolites choline, creatine and N-acetyl are estimated with MR spectroscopy. These concentrations are graphically displayed and ratios calculated relative to creatine. This MR modality opens the possibility of distinguishing between high-grade gliomas, solitary metastasis and even PNET. Radiation induced necrosis and recurrent GBM may appear similarly on MRI scans and represent a challenge even for perfusion MRI and MR spectroscopy.

**Positron emission tomography (PET)** can resolve part of this problem though the sensitivity is arguable. This technique measures metabolic activity in tumors and may even be used to trace the activity of genes introduced in GBM [17]. Most of these imaging studies are retrospective and designed to investigate threshold levels of specified parameters in order to attain an acceptable sensitivity and specificity. Even though various imaging modalities may be complementary and contribute to diagnosing a brain lesion, the clinical value is still partially undetermined for some of the techniques: A prospective clinical study on 100 patients with newly diagnosed brain tumors demonstrated that MR spectroscopy contributed in only 6 of these cases regarding the pre-operative diagnosis.

### 1.4 SURGERY ON BRAIN TUMORS

Basically, two types of surgery may be performed: Craniotomy or a stereotactic biopsy through a burr hole. In cases of glial tumors, controversy still exists whether resection of these tumors contributes significantly to overall survival. A number of studies with different end results have been performed over the past decades [15]. These investigations have been criticized because of their retrospective design and analytical flaws.

To date, no large, prospective, randomized trial has been carried out to investigate the role of surgical treatment in glioma patients. Similarly patients with a single brain metastasis
may benefit from cytoreductive surgery in combination with whole brain radiotherapy in terms of prolonged functionally independent survival though overall survival has not been shown to improve. Meningiomas represent the other end of the scale as these tumors often may undergo gross total resection with high rates of long-term survival.

Even though MRI and PET techniques are capable of distinguishing between several types of brain tumors, surgical intervention in order to obtain relevant tissue for histologic investigations remain the primary diagnostic modality. In cases of brain abscesses, puncture and culturing of sampled material provides a microbiological diagnosis. Stereotactic biopsies using frame-based systems are well documented in terms of precision, high diagnostic yield and low rate of complications. Stereotactic computers are now widely applied in neurosurgery after the introduction in the early 1990’s. These systems are considered as a helpful tool in pre-operative planning as well as assistance in placing a craniotomy, intra-operative navigation and defining resection borders of tumors.

In order to take full advantage of the navigational abilities, a skull-mounted guide system was developed at the department. This system is coupled with a stereotactic computer and permits puncture of intracranial mass lesions as well as introduction of ventricular catheters. The guide system was retrospectively evaluated and the results compared to stereotactic frames after application in 36 patients for a total of 39 procedures.[14]. The mechanical accuracy of the system was later studied on a phantom model using three different entry points to targets localized within a 3-dimensional co-ordinate system as shown in Fig 1.1.

![Figure 1.1: MRI of the Brain](image-url)
MRI provides an unparalleled view inside the human body. The level of detail we can see is extraordinary compared with any other imaging modality. MRI is the method of choice for the diagnosis of many types of injuries and conditions because of the incredible ability to tailor the exam to the particular medical question being asked. The representation of the tumor (dark white) is visible in Fig 1.2.

![MRI of Brain showing Tumor](image)

**Figure 1.2: MRI of Brain showing Tumor**

1.4.1 NEURO IMAGING BACKGROUND

The idea of localization of function within the brain has only been accepted for the last century and a half. Most of the information available on the human brain came from subjects who had sustained major head wounds, which influenced their behavior and capabilities. By determining the extent of the brain damage, and the nature of the loss of function, it was possible to infer which regions of the brain were responsible for which function [14,15,16].

With the development of the imaging techniques of computerized tomography (CT) and magnetic resonance imaging (MRI) it was possible to be more specific as to the location of damage in brain injured patients. Still the new era in the study of brain function came with the advents of the PET, SPECT, fMRI and MEG.

- a. PET – Positron Emission Tomography.
- d. MEG – Magneto encephalography.
1.5 fMRI DESCRIPTION

fMRI is based on the measurement of radio frequency electromagnetic waves as a spinning nucleus return to its equilibrium state. After the RF pulse is applied two effects are then measured, the longitudinal relaxation time (T1 – also known as spin-lattice relaxation time) and transverse relaxation time (T2 also known as spin-spin relaxation time). There is a third parameter - T2* which is like T2 except it takes into account the local in homogeneities too.

The fMRI is a method that is used in exploring the brain using the MRI principles. During an fMRI experiment, the subject is scanned repeatedly, usually using a fast imaging technique e.g. echo planar imaging (EPI). The subject is required to carry out some task consisting of periods of activity and periods of rest. During this activity the magnetic resonance (MR) signal from the region of the brain involved in the task normally increases due to the flow of oxygenated blood into that region. Signal processing is then used to reveal these regions [17].

1.5.1 THE WAY A SOURCE IS DETECTED IN fMRI

The brain like any other organ in the body requires a steady supply of oxygen in order to metabolize glucose to provide energy. This oxygen is supplied by the component of the blood called hemoglobin. It was demonstrated that the magnetic properties of hemoglobin depended on the amount of oxygen it carries. This dependency along with the following properties has given rise to measuring activation using MRI commonly known as functional MRI.

- High oxygen consumption – although the brain weight is only 2% of the body’s, its oxygen consumption rate constitutes 20% of the body’s oxygen consumption, and 15% of the blood flow.
- Blood flow – although the regional blood flow is poorly understood, it is known that neural activity results in a rapid selective increase in blood flow to that area.

1.5.2 THE BOLD MECHANISM

Since regional blood flow is closely related to neural activity, measuring the regional cerebral blood flow is useful in studying the brain function. One of the best contrast mechanisms used to measure blood perfusion with MRI in terms of sensitivity is the BOLD (Blood Oxygenation Level Dependent) mechanism, which depends on the blood oxygenation. The
mechanism behind the BOLD contrast are still to be determined, however there are hypotheses to explain the observed signal changes [13].

The time course for the bold signal changes is delayed from the onset of the neural activity by a few seconds, and is smooth, representing the changes in blood flow that the technique detects. Soon after the success in mapping the activity of the visual and motor parts using the BOLD technique, many fMRI experiments were conducted upon the visual and motor functions. Based on the function, the activity in the brain is visualized in the form of an image for further analysis.

1.6 STATEMENT OF PROBLEM

Human analysis on medical images is a difficult task due to very minute variations, due to co-resemblance between affected and original biological part, due to larger data set for analysis. This makes the biological analysis for prediction of affects in the tumor detection. The problem goes more complicated under cancer predictions basically in brain cancer. It is a challenging task to develop an automated recognition system which could process on a large information of patient and provide a correct estimation.

Brain cancer can be counted among the most deadly and intractable diseases. Tumors may be embedded in regions of the brain that are critical to orchestrating the body’s vital functions, while they shed cells to invade other parts of the brain, forming more tumors too small to detect using conventional imaging techniques. Brain cancer’s location and ability to spread quickly makes treatment with surgery or radiation like fighting an enemy hiding out among minefields and caves.

In recent years the occurrence of brain tumors has been on the rise. Unfortunately, many of the tumors are detected too late only after symptoms the appearance. It is much easier and safer to remove a small tumor than a large one. About 60 percent of glioblastomas(tumor) start out as a lower-grade tumor. But small tumors become big tumors. Low-grade gliomas become high-grade gliomas. Once symptoms appear, it is generally too late to treat the tumor.

This level of precision is reaching a point at which brain tumor that has spread beyond the margins of the tumor may become visible. Finding and removing these tumors could improve a patient’s chance of survival.
Early detection and complete removal is the best, if not only, proven method of treating deadly tumor growth. The only way to "cure" a cancer is to find and treat it early – before symptoms arise. Before it is too late.

To detect an early stage brain cancer automatically without human interaction. Detection of brain cancers at an early stage by human interaction may result in less interpretation as different types of cancers and their locations may not be predictive.

For the realization of such automated system for early prediction of cancer, the major problem is with the processing of MRI images for estimations of brain cancers. Noise, training of network, extracting the features of the brain samples, developing a neural network model to recognize and classify the different types of cancers/tumors using five different types of features.

For the first time in this thesis, the problem of Biological Early Brain Cancer Detection using Blind Source Separation is proposed and implemented.

1.7 OBJECTIVES OF THE STUDY

The main objective of the thesis is to develop an automated cancer recognition system from a given set of fMRI images. A Neural Network based BSS system is designed and implemented for the classification and estimation of cancer affect on given fMRI image. The performance of classification rate and the efficiency of tumor recognition is evaluated with number of samples taken as data set (fMRI images) are compared with the existing systems and sufficient results are obtained to prove the proposed system is better than the latter.

1.8 SCOPE OF THE STUDY

There is a growing consensus that brain cancer is a problem in need of a radically different solution, and that Early Detection of Brain Cancer fits the bill. This system could provide precision detection, targeted treatment, and real-time tracking that conventional technology lacks. For a disease in which only 5 percent to 32 percent of patients are likely to survive after five years, large hope is riding on the potential success of Early Detection of Brain Cancer technology[11].

This thesis implements an efficient system for the detection of cancer from a given brain fMRI and recognizes the extracted data for further applications. The implemented work finds
efficient usage under biomedical early cancer detection. The work can be efficiently used in the area of medical science such as Computer aided diagnosis & Mammography etc. The proposed work will be very useful under medicines for predicting early brain cancer cells using texture features and neuro classification.

1.8 ORGANIZATION OF THESIS

In Chapter 1, the based idea of deriving the problem is discussed. The problem identification, source of work and aim of the thesis is discussed. The dissertation of the thesis is also discussed. In Chapter 2, the different papers are reviewed with the problem and solutions in chronological order mentioning the pros and cons of the work already published. The problem is identified as goal of the thesis. In Chapter 3, the thesis is concerned with the study of the brain tumors at the early stages using blind source separation techniques based on the Blood Flow, De-oxygenation Contents in the Brain. In Chapter 4, different approaches for studying the Images of the Brain are proposed with the best techniques being considered as fMRI imaging system that is efficient and provide best results when compared to other existing techniques. In chapter 5, the major concern is analyzing the brain tumors in the fMRI Images in different stages and how they can be detected at early stages is discussed in detail. In Chapter 6, case study on every technique to blind source separation is discussed in detail. A new technique called “WAVELET PACKET” method is proposed and is implemented with satisfactory results followed by Conclusions and Future Research, References and Dissemination.

1.9 REFERENCES


16. Introduction to Neural Networks using MATLAB 6.0 by S.N. Sivanandam, S. Sumathi, S.N. Deepa, 2006