BIBLIOMETRIC ANALYSIS OF LIVER LESION AND LIVER TUMOR DETECTION WITH ARTIFICIAL INTELLIGENCE IN NUCLEAR MEDICINE

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Approval

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ABSTRACT

The ability to treat liver tumor metastases is highly depended on early detection. The use of AI in medicine has made significant progress. This study aims to evaluate different applications of AI algorithms in detecting liver lesions and tumor metastasis by using biomedical images from different diagnostic devices. This work evaluating AI models for the diagnosis of liver lesions and tumors published from 1st of January 2000 to 30th April 2021. Bibliometric analysis used 5251 articles from search PubMed, Scopus, Google scholar, IEEC, Springer Link and Science Direct. The biomedical imaging techniques are PET, SPECT and hybrid methods such as PET, SPECT and hybrid methods such as PET / CT, PET/MRI. This analysis found a global research situation that was dominated by studies from China, America, and Japan with 1380, 984, and 710 published articles respectively. The high-quality evidence, robust reporting standards with external validation and comparison to health-care specialists are recommended as first - line for AI-application in the medical domain.

Keywords: Artificial intelligence, liver lesion, liver tumor, liver lesion/tumor detection, nuclear medicine.

ÖZET

Karaciğer tümörü metastazının erken teşhisi, tedavi için esastır. Yapay Zeka (AI) tıp alanında önemli ilerlemeler kaydetti. Bu çalışmanın amacı, farklı tanı cihazlarından elde edilen biyomedikal görüntüler kullanarak, karaciğer lezyonlarını ve tümör metastazını tespit etmede AI algoritmalarının farklı uygulamalarını bibliyometrik olarak analiz etmektir. 1 Ocak 2000'den 30 Nisan 2021'e kadar yayınlanan karaciğer lezyonları ve tümörlerinin teşhisi için AI modellerini değerlendiren bu çalışma. Bibliyometrik analiz yöntemi ile PubMed, Scopus, Google Scholar, IEEC, Springer Link ve Science Direct'ten 5251 makale tarandı. Araştırmada kullanılan Biyomedikal görüntüleme teknikleri PET, SPECT ve PET, SPECT gibi hibrit yöntemler ve PET/CT, PET/MRI gibi hibrit yöntemlerdir. Bu çalışmanın uluslararası araştırma durumu, 1380, 984 ve 710 yayınlanmış makale ile çalışmaların çoğunlukla Çin, Amerika ve Japonya üzerinde yoğunlaştığını tespit etmektedir. Tıp alanında yapay zeka uygulaması için yüksek kaliteli kanıtlara, harici doğrulamaya sahip katı raporlama standartlarına ve sağlık bakım profesyonelleriyle karşılaştırmaya acilen ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Yapay zeka, karaciğer lezyonu, karaciğer tümörü, karaciğer lezyonu/tümör tespiti, nükleer tıp.

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LIST OF ABBREVIATIONS

AFP: Alpha Fetoproteins

AFP-3: Lens Culinaris- agglutinin reactive

AI: Artificial Intelligence

ANNs: Artificial Neural Networks

API: Application Programming Interface

BHs: Biliary Hamartomas

CNN: Convolutional Neural Network

CNNs: Convolutional Neural Networks

CRC: Colorectal Cancer

CT: Computerized Tomography

DBMs: Deep Boltzmann machines

DL: Deep Learning

DLS: Deep Learning Systems

DNN: Deep Neural Network

ES: Expert System

FDG: Fluorodeoxyglucose

FNH: Focal Nodular Hyperplasia

GHO: Global Health Organization

GLOBOCAN: Global Cancer Incidence, Mortality and Prevalence.

GPUs: Graphical Processing Unites

HCC: Hepatocellular Carcinoma

HTN: Hierarchical Task Network

IHHs: Infantile Hepatic Hemangiomas

KBS: Knowledge Base Systems

LSTM: Long Short-Term Memory

MRI: Magnetic Resonance Imaging

ML: Machine Learning

MLAA: Maximum- Likelihood reconstruction of Activity and Attenuation

mpMRI: Multiparametric Magnetic Resonance Imaging

MtL: Multitask Learning

NET: Neuroendocrine Tumor

NLP: Natural Language Processing

NM: Nuclear Medicine

PET: Positron Electron Tomography

PIVKA-II: Protein Induced Vitamin K Absence or Antagonist

RFA: Radiofrequency Ablation

RNN: Recurrent Neural Network

SPECT: Single Photon Emission Computerized Tomography

SVM: Support Vector Machine

TACE: Trans-Arterial Chemoembolization

UCSF: University of California San Francisco

US: Ultrasonography

VMCs: Von Meyenburg Complex

VGG: Visual Geometry Group

WHO: World Health Organization

CHAPTER 1 INTRODUCTION

1.1 Background on Liver Lesions and Tumors

The second leading cause of mortality worldwide is cancer (Wang et al., 2016). Liver lesions and tumors are classified as one of the deadliest worldwide (GHO, 2021) and in 2018 Primary Liver Cancer was diagnosed as the sixth most common cancer and the fourth cause of cancer death related worldwide, thus more than 800,000 cases and more than 700,000 deaths (Bray et al, 2018). Recently liver lesions and tumors are amongst the most common cancers and a third leading cause of deaths caused by cancer worldwide in a report GLOBOCAN/WHO International Agency in Cancer research, it is estimated that more than 19 million new cases and 10 million cancer deaths were recorded last year (Sung et al., 2021). All this makes liver lesion and tumors a serious health problem that if handled or taken care of with a lack of seriousness might result in more catastrophic outcomes or death. Liver lesions and tumors can be contained if handled with urgency and care, be it that there is treatment or not the best way to start the intervention is timely diagnosis. Like other diseases or disorders, liver lesion or tumors has diagnostic techniques that include a blood test, imaging test and biopsy (Ahn et al., 2020), (Russano et al. 2020), (Hu et al. 2019). Early liver lesions and tumors detection improve the survival rates of individuals suffering from liver lesion and tumors. Nuclear medicine is considered here, but its diagnosis is occasionally influenced by subjective experience, thus artificial intelligence may give a new diagnostic method. We search works based a deep learning system (DLS) in nuclear medicine and clinical data, including imaging and results from laboratory test. We aim to demonstrate the impact of the AI technique in the early detection of liver lesions and tumors. Liver lesions and tumors is a big issue worldwide. Detecting this in the early stage is a big relief to the response obtained when treatment is administered and also increase the rate of survival, but the issue is the early detection because an inadequate approach may result in a catastrophic or life-threatening condition (in some cases loss of lives). And in this case, we will not only turn to nuclear imaging techniques and human expertise that sometimes may be subjected to errors and time-consuming, but we will have to look up to the most recent and sophisticated digital approach.

1.2 Definitions of liver lesion and tumor

Lesion is a malady or trauma caused by any damage or abnormal alteration in an organism's tissue. Lesion is the result of "injury" Latin laesio. Both plants and animals could experience lesions. Lesions, masses, and tumors are defined in Taber's Cyclopedic Medical Dictionary as follows:

Lesion: a constricted area of tissue, wound or an infected patch of the pathologically altered tissue produced by skin disease. Examples of primary or early lesions include macules, vesicles, blebs and trabeculae, chancres, pustules, papules, tubers, wheals and tumors. Primary injuries lead to subsequent injuries. There will be crevices, excoriations, splits, scales, scars and sores. The result is a diffuse (a widespread lesion), a focal lesion (a lesion with a limited designated region) and a big lesion based on the surface covered (a lesion that is seen with naked eyes and does not necessitate a microscope). Lesions are not limited to the skin; vascular lesions are also common (vascular malformations of the venous, arterial, and lymphatic systems, i.e., infantile hemangiomas).

Mass: This is a collection of fibre-like cells that connect or link one other.

Tumor: An abnormal swelling, or growth (tumors is Latin for swelling). All tumors (benign and malignant) can show growth or proliferation regardless of adjacent tissue.

Benign: Tumors or growths not spreading or penetrating malignancy; (e.g., adenoma).

Malignant cells are cancerous cells with the ability to spread, infiltrate, and destroy tissue. Because of genetic defects, malignant cells tend to develop quickly and uncontrollably (e.g., hepatoma)

1.2.1 Normal/healthy liver and disease liver

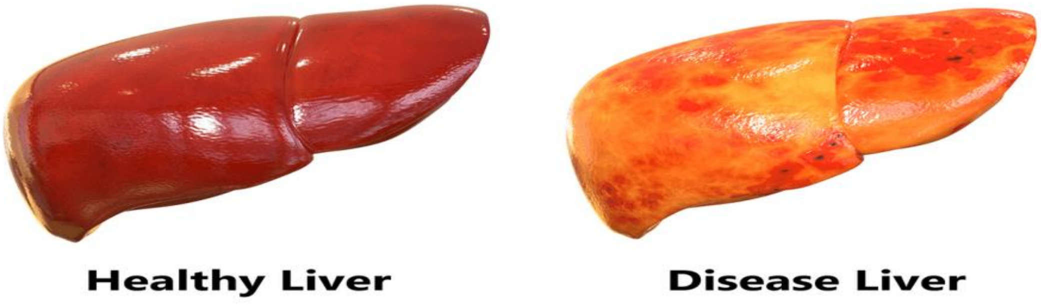


Figure 1.1 anatomy of healthy and disease liver respectively

The liver is nourished with approximately one pint (13%) at a time of the body's blood. There are also two principal lobes, all of which have eight segments with about 1,000 tiny lobes. These lobes are linked to tiny pipes or bigger ducts creating the common conduit. Bile produced by liver cells is transported by the common duct to gallbladder and duodenum through the common bile duct. The liver secrets bile and has important role in regulating most chemical levels within the blood. This aids in removing or eliminating unwanted or toxic substances from the liver (Wang et al., 2015). The liver acts as a conduit for blood leaving the intestines and stomach. The liver processes this blood, breaking down, balancing, and creating nutrients, as well as metabolizing medications to absorbable and harmless forms for the body. (Mitra & Metcalf, 2009). There are more than 400 important liver functions.

- ❖ Bile production that assists in the elimination during digestion of waste and lipid breakup in the gut.
- ❖ Certain plasma proteins are synthesized
- ❖ Conversion of glucose excess to storage glycogen (glycogen can then be transformed into energy glucose) to balance and glucose if necessary
- ❖ The levels of Blood Amino Acid are controlled, which constitute protein building blocks.
- ❖ The processing of haemoglobin to take advantage of iron contents (the liver stores iron)
- ❖ Urea is an outcome of ammonia metabolism and is excreted within the urine.
- ❖ Purifying blood of drugs and other poisonous substances (chemicals)
- ❖ Checking coagulation of the blood
- ❖ The resistance of infection is accomplished through the production of immune components and removing circulatory pathogens.
- ❖ Red blood cells Clearance of bilirubin. The skin and eyes become yellow as the levels of bilirubin grow.

1.3Diagnostics

1.3.1 Biological

Three indicators are most common here and a blood test is done. The three most frequent markers are total alpha fetoprotein (AFP), agglutinin reactive AFP lens (AFP-L3), and vitamin K deficiency protein, or antagonist-ii (PIVKA-II). Total AFP has a sensitivity of approximately 60% and 90% in identifying hepatocellular cancer. (Park et al., 2017; Reis et al., 2015)

1.3.2 Medical imaging

Under the imaging techniques, we would consider nuclear medicine and radiology.

a. *Nuclear medicine*

Nuclear medicine imaging is frequently conducted using a variety of methods. Scintigraphy is one example, in which the collected radiation generates 2D pictures. An additional example is single-photon computed tomography (SPECT) that uses the emitted radiation to produce three-dimensional images, while inside radiation is obtained via gamma cameras. (Madsen, 2007). Positron Emission Tomography (PET) is also an example of medical imaging method that provides 3D rather than 2D pictures. (Muehllehner & Karp, 2006). The major difference between medicine tests diagnostic and other imaging methods lies in the fact that the physiological function of the tissue or organ under examination is demonstrated by nuclear imagery techniques, while the anatomy or structure is demonstrated by the regular imaging systems, like computerized tomography (CT scans), and magnetic resonance imaging.

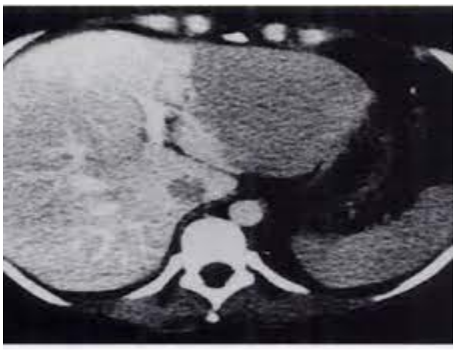


Figure 1.2: Example of Scintigraphy liver lesion

b. *Radiology*

X-ray images (conventional radiology). Although the procedure requires invading the body, some of the rays are absorbed by the tissue contacted. To provide radiological pictures, unabsorbed rays are captured on film (analogue image) or digital media. This is the most commonly used method in the majority of radiological exams, particularly for investigating the skeleton and hence the lungs (Kopp et al., 2018).

Ultrasound. This is a technique for getting physical body images by using sound waves with high frequency. Sound waves high frequency are key in acquiring pictures in real-time. This does not need radiation and is painless (Konopke et al., 2007).

Figure 1.3: An example of Ultrasound liver lesion

MRI is a method that uses the electromagnetic features of the physical body, rather than x-rays when subjected to a strong magnetic flux. The gadget is a very powerful magnet via which RF waves flow (Karaosmanoglu et al., 2016). The integrated energy equipment detects hydrogen atoms in the concerned organs and the computer reproduces pictures of the hydrogen spread throughout the organ. The equipment supplies energy to the system.

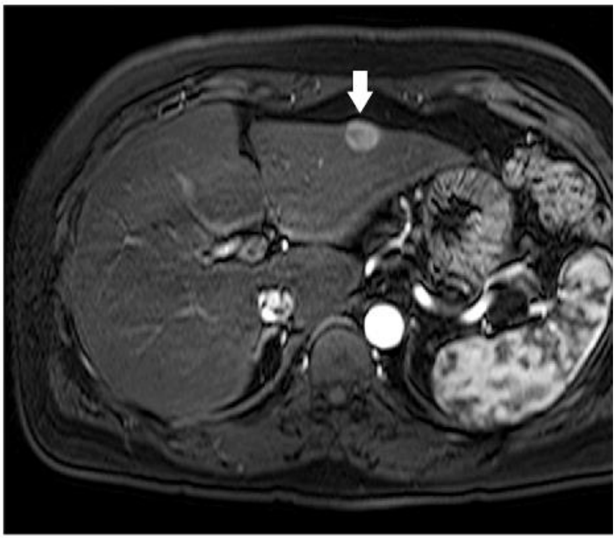


Figure 1.4: Magnetic resonance image of liver lesion

CT Scan. The equipment consists of a table on which the patient is placed and an apparatus with a gap (gantry), in which the table is placed in the test. CT scanning is quite effective for exhibiting various tissue types such as lung, bone and articulation, abdominal viscera and blood vessels. It is particularly excellent in the presentation of many tissue types like lung, bone and joint, abdominal viscera and the blood arteries. (Granata & Magnano, 2013).

Figure 1.5: CT scan of liver lesion

1.4 Nuclear medicine techniques in liver lesions detection

Nuclear medicine is a branch in radiology which examines organ function and structure using extremely tiny quantities of radioactive materials, called radiopharmaceuticals. Medical imaging is a synthesis of several fields. Chemistry, physics, mathematics, technology, and medicine are among them. This field of radiology is typically utilized to aid in the early detection and treatment of anomalies developed in cancer (Teunissen et al., 2011). Nuclear medicine has progressed significantly in cancer detection, therapy planning and thus patient response evaluation since the introduction of new techniques in the 1970s. Due to their high sensitivity, diagnostic applications, such as bone scans, remain the most prevalent in cancer although medicine contributes best in patient care. Stage of new cancer patients and rehabilitation for the planning of therapy. Repetition medicine provides non-invasive therapeutic response information and disease information. Often tests with minimal damage and modest radiation absorption are repeated. Often clinical laboratory findings are closely linked to the outcome (Sundin et al, 2017). Nuclear Medicine procedures include in vitro techniques ready to detect and characterize liver metastases. Among the in vitro applications, circulating tumor markers level determination provides information about the response to therapy and therefore the presence of active disease. While after a successful antineoplastic treatment the serum biological marker level usually falls, a progressive increase represents an alarm signal of residual tumor or metastatic dissemination. However, if this method doesn't identify the location of the lesion, therefore complementary imaging techniques are needed to verify or exclude the diagnostic suspicion. The most advantages of the in vitro methods are the low cost and, consequently, the likelihood of periodically checking of tumor activity. The in vivo medicine techniques are usually performed as a second-level test. They are tasked with detecting and characterizing hepatic metastases when radiological methods are inconclusive or when selected tumor-seeking agents are often used. Moreover, the introduction of PET procedures has provided physicians with a useful tool for the evaluation of tumor behaviors (glucose consumption, protein, synthesis, receptor expression). An extra significant diagnostic improvement is represented by the recent introduction of the multimodality co-registration of images (CT scan, MRI, SPET, and PET). The fusion imaging allows superimposition of the functional and metabolic information to the morphological one (Gharib et al., 2004). Medical imaging, in particular, has been impacted by the AI hype of recent years. Though artificial intelligence (AI) is a hot topic in the news and medical journals, some people are unsure of what it is and how it works. This leads to both optimistic expectations and unwarranted worries about AI. While most individuals use artificial intelligence (AI) on a regular basis - whether it's on a mobile device or in a car - or while surfing the web, many don't even realize they're doing it. It's also possible that AI may require a wide range of easy or repetitive duties in the medical profession, as well. However, instead of the disruption that has been prophesied, a seamless transition is often foreseen, and it appears that this change has already begun in the diagnostic disciplines, notably medical imaging. Radiologists and other medical experts do not regard these developments as a threat, but rather as an opportunity to take a prominent role in the medical sector, helping to influence this transformation process. (Nensa et al., 2019). Early detection and treatment of liver lesion and liver tumor might increase patient’s chances of survival. The most comprehensible data for medical diagnosis of liver tumors is provided by dynamic contrast-enhanced MRI. In spite of this, deep learning may offer an alternative to MRI diagnosis due to the subjective nature of the experience involved. CNNs are utilised to construct a deep learning system (DLS) to identify liver lesions based on enhanced MR images, unenhanced MR images, and clinical information. (Zhen et al., 2020). When compared to analogue PET/CT, digital nuclear medicine technologies such as PET/CT improve the detection of liver lesions in patients with known or suspected liver metastases (Fuentes-Ocampo et al., 2021). Contrast-enhanced computed tomography (CT) of your neck, chest, abdomen, and pelvis, as well as a three-stage liver examination, are required for the initial diagnosis of Neuroendocrine Tumors (NETs). It is difficult to characterize lymph nodes on CT because of the tiny axis diameter, and bone metastases are often overlooked. Comparatively superior to other imaging modalities is contrast-enhanced resonance imaging (MRI), diffusion-weighted imaging in particular. It's possible that an MRI won't detect tiny lung metastases. However, MRI is less reliable than CT in the assessment of vast body regions due to the lengthier examination method. For early liver metastasis diagnosis, ultrasound is commonly used, and the contrast enhanced ultrasound is useful for identifying equivocal liver lesions in CT/MRI.US is a preferred approach to guide the histological diagnosis of NET with a biopsy needle. As NET thoracic lesions are not visible to the US, CT-guided biopsy is used. The most sensitive technique to diagnose pancreatic NETs is endoscopic ultrasonography, which also enables biopsy. Aid for intraoperative ultrasonography in pancreatic and liver lesions. Tumors, preoperative imaging, restaging, and 68Ga-DOTA-somatostatin analogue PET/CT are all recommended in terms of imaging of somatostatin receptors that are significantly higher than somatostatin scintillations and helps diagnose several NET lesions, such as lymph gland, bone metastasis, liver metastases, peritoneal lesions, and somatostatin receptor first

1.5 Artificial Intelligence in nuclear medicine

AI techniques notably, deep learning (machine) approaches are essential components of most up-to-date medical imaging advancements. They are use them to handle a wide range of tasks, including image reconstruction and processing (denoising or segmentation), analysis, and modelling (Visvikis et al., 2019) In recent years, artificial intelligence (AI) has gained a lot of attention for its potential use in medical applications (Zaharchuk & Davidzon, 2021). Artificial intelligence means human intelligence emulation in robots designed to think like men and to imitate their activities. Artificial information (AI) The phrase also applies to all machines that show qualities like learning and problem solving akin to an individual's mind. AI's capacity to streamline and take action, with the simplest probability to achieve a specified objective, is the perfect attribute. (Amisha et al., 2019) AI covers various fields, such as machine learning, deep learning and the processing of neural language, robot technology, expert systems and logic. Python is the finest of the several programming languages we have. We'll use the Python application since it's extremely simple and can quickly be learnt and has a host of additional AI techniques that can easily be implemented using the python library. Therefore, we may call the functions and it is notable because python can support many paradigms such as procedural programming and object-oriented programming. The phrase "Artificial Intelligence" refers to computer systems designed to repeat cognitive human activities such as learning and solving problems. Machine Learning

(ML), an AI industry, first evaluated data to build algorithms that reveal behaviors patterns that usually provide prediction models. A variety of medical research projects have been using ML methods like support vector systems, artificial neural networks (ANNs) and classification and regression trees. (Rene et al, 2020). Throughout the past decade, technological progress has resulted in the development of deep-learning (deep learning), a multi-level ANN model that is very useful in the analysis of the radiological image, for the development of multiple layered neural network algorithms using techniques like neural network (CNN). (Yang & Bang, 2019; Le Berre et al., 2020). HCC has specific radiological characteristics that enable it to be diagnosed even without a histological examination. As a result, the study of imaging tests becomes more essential since their interpretation isn't always simple, and they vary depending on the condition, as do prediction and response to therapy, both of which are affected by a variety of circumstances. All of this leads to a huge amount of knowledge that can be integrated into and analyzed to evaluate AI. Many research has been carried out recently to help make choices and overcome human judgment limits (Le Berre et al., 2020; Briceno, 2020). In addition to a forecasted estimate, artificial intelligence may conduct integrated radiological, clinical and histological analysis, provide information helping to diagnose accuracy, tumor stage, treatment planning utilizing segmentation methods, and assess the existence of microvascular invasion (Pérez & Grande, 2020). With all of the abovementioned advances in the identification of liver lesions and tumors using artificial intelligence in nuclear medicine, it will be appropriate to use this at the nanoscale and micrometre scale, which is in small systems (organs, tissues, cells, organ system, and organism). AI has numerous advantages, one of which is that it takes less time to accomplish a task and can perform multiple tasks at the same time. Because early detection of liver cancer, as well as any other disease, is critical for responding to treatment and saving lives, it is critical to employ not just suitable procedures but also to save time, minimize human mistakes, and conserve resources. With all the aforementioned advancements, detection of liver lesions and liver tumors with artificial intelligence in nuclear medicine, will be fitting to apply this in the nanometer and micrometre scale that is in miniature systems (organs, tissues, cells, organ system, and organism). AI has several advantages but one of them is using the lesser time to perfume a task and do multiple tasks at the same time. Because early diagnostics of liver cancer, as well as any other disease, is indispensable for the response to treatment and in saving lives, it is important to use not only appropriate techniques but also saving time, minimizing human errors and resources.

CHAPTER 2 LIVER LESION AND TUMOR

2.1 Structure of the liver

2.1.1 Embryology of liver

Liver, gallbladder, and biliary system all develop from a ventral proliferation of endoderm that develops into mesoderm from the caudal foregut. This protrusion occurs during the fourth week of embryonic development and is known as the hepatic diverticulum or liver bud. The endoderm of the liver bud develops into hepatocytes, whereas the mesoderm develops into tissue and blood vessels. Throughout the foetal period, the liver performs a hematopoietic function. (Lemaigre, 2009).

2.1.2 Anatomy and physiology of the liver

Each of the liver's four lobes has a different function, such as caudate, quadrate, and right. The quadrate lobe is found on the inferior surface of the proper lobe. Prior to the left and right lobes, you will find the caudate lobe (Abdel-Misih & Bloomston, 2010).

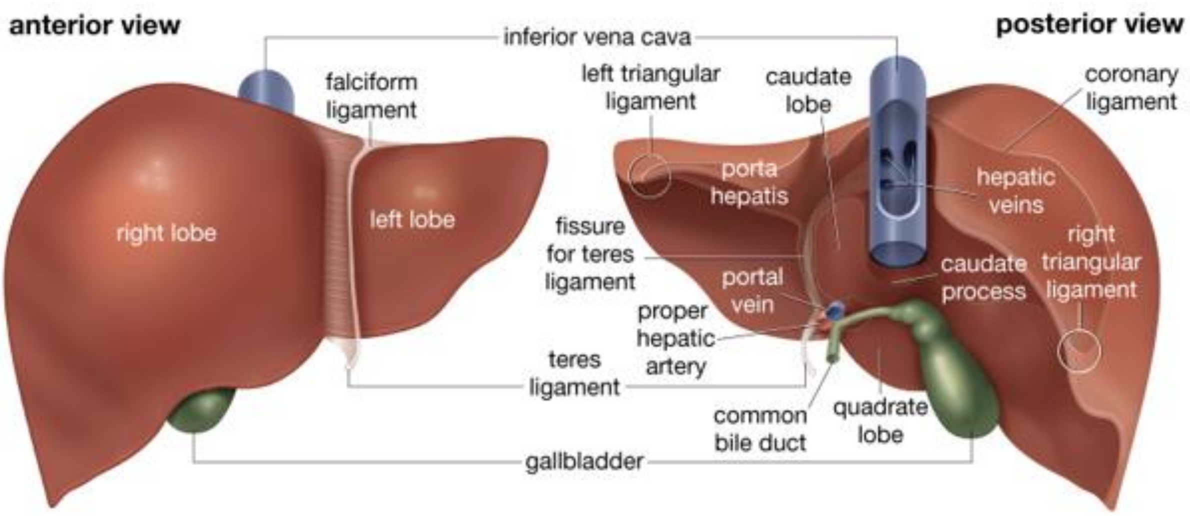


Figure 2.1: Liver anatomy

Liver is the body's biggest gland and is well situated to accept absorbed nutrients as well as cleanse absorbed medications and other toxic chemicals. It functions as both an exocrine and an endocrine organ. The liver's exocrine functioning is most notable in the production and excretion of bile salts into the common duct, as well as the conjugation of bilirubin and excretion into the gut (Esteller, 2008). The liver's endocrine activities include blood sugar regulation via insulin and glucagon (Aronoff et al., 2004). The liver produces vital proteins such as fibrinogen, albumin, prothrombin, and other amino acids, as well as changes proteins to form enzymes and peptide hormones (Knight et al., 2005). The liver is involved in carboxylic acid metabolism as well as the synthesis of lipoproteins, cholesterol, and phospholipids. It is also involved in carbohydrate metabolism, including glycogen storage and gluconeogenesis (Adeva-Andany et al., 2016). It is also involved in carboxylic acid metabolism and transforms ammonia to urea (Mavri-Damelin et al., 2007). Vitamins and minerals such as iron are stored in the liver. In summary, the liver is an essential mediator from the gut to the blood, and it is involved in the metabolism of macronutrients, hormones, plasma components, and exocrine and endocrine chemicals (Vernon H. et al, 2020).

2.2 Disorders or diseases of the liver

The liver is our body's biggest organ. It aids in the digestion of food, the storage of energy, and the removal of toxins from our bodies. There are several liver disorders including;

- Those caused by viruses, such as hepatitis A, hepatitis B, and hepatitis C.
- Cirrhosis and fatty liver disease
- Cancer of the liver
- Hemochromatosis and Wilson disease are examples of inherited illnesses.

2.3 Introduction to liver lesion and tumor

These are erroneous cells or tissues. Liver lesions, often known as liver masses or tumors, are frequently either benign (noncancerous) or malignant (cancerous) (cancerous). Benign liver lesions are extremely frequent and, in most cases, are not the reason for worry. Malignant liver lesions, on the other hand, necessitate intervention and therapy.

2.3.1 Types of liver lesions and tumors

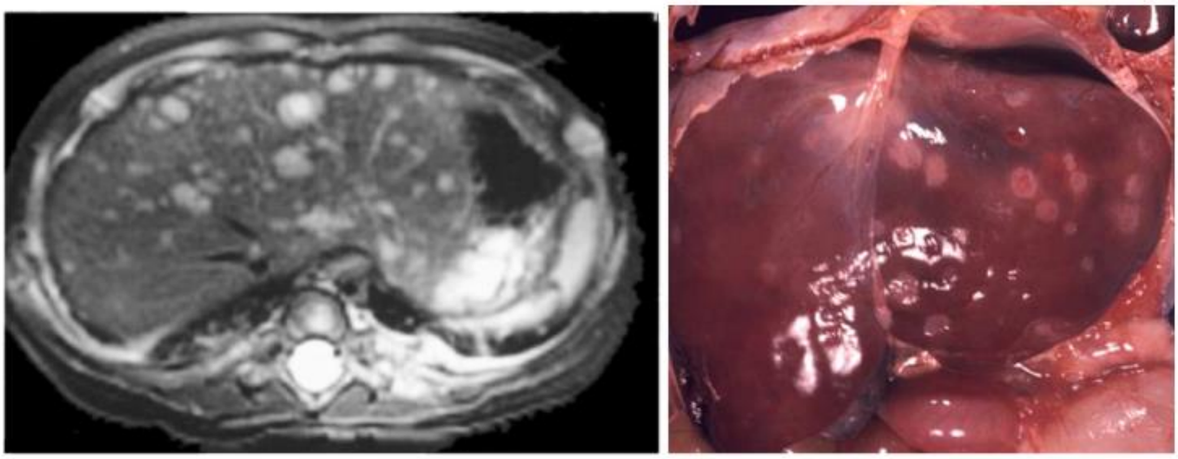
We are going to discuss the two types of liver lesions and tumors which are: benign and malignant.

a. Benign Liver Lesions

Benign liver lesions affect roughly 20% of the general population. They are frequently left untreated. They do not spread to other regions of the body and are usually not dangerous. However, if liver lesions cause discomfort, enlarge, threaten rupture, or cause internal bleeding, they will be surgically removed. Hemangioma liver lesion, hepatic adenomere liver lesion, focal nodular hyperplasia liver lesion, biliary hamartomas, lipomas, and liver cyst are all examples of benign liver lesions and tumors.

i. Hemangioma

A hepatic hemangioma is an abnormal mass of blood vessels that is the most common type of benign liver disease. They are seen in around 5% of individuals, are asymptomatic, and usually go unnoticed. They do not represent a hazard in and of themselves, but they are frequently confused for other malignant tumors in radiographic pictures. To avoid misinterpretation, worrisome images must be evaluated by a specialist radiologist with substantial competence in abdominal imaging. (Christison-Lagay et al., 2007).



A B

Figure 2.2 hepatic hemangioma.

Figure A, Multifocal hepatic hemangioma axial vision, which shows a homogeneous hyperintense signal at MRI. B, Multifocal liver view Infantile hepatic hemangiomas (IHHs).

ii. Hepatic Adenoma

Hepatic adenoma lesions are rare benign liver lesions that occur three to four times per 100,000 women. They're usually discovered in women who use pills daily or in sportsmen who utilize anabolic steroids. Some hepatic adenoma lesions are quickly malignant, causing spontaneous bleeding and rupture. It is critical to distinguish hepatic adenoma from other liver lesions to provide better patient care. A hepatic adenoma is frequently discovered via radiographic imaging, but differentiating it from other tumors is challenging and necessitates the services of a radiologist who specializes in this field. (Tsilimigras et al., 2018).

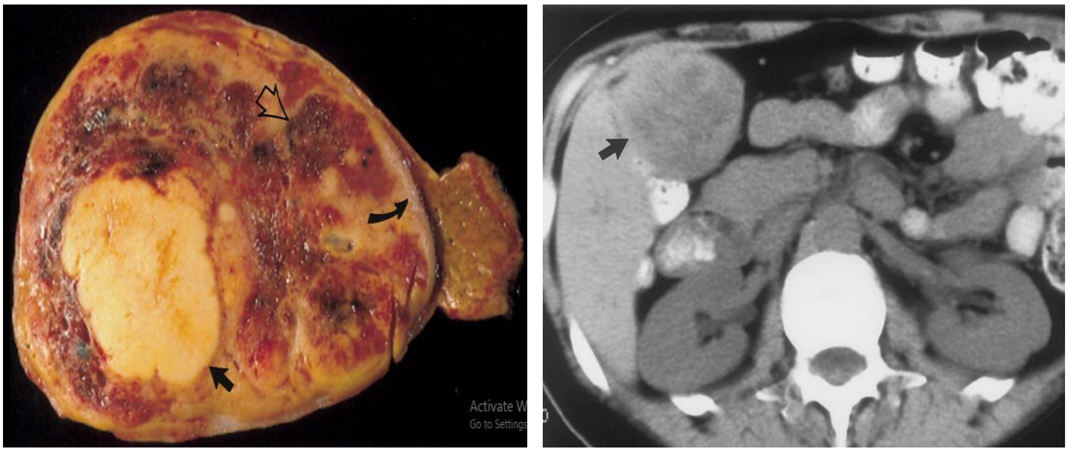


Figure 2.3: Hepatic adenoma.

Unenhanced 5 cm-diameter CT scan is displayed at the place of the arrow in the first image at the lower lobe (right) of the liver, which is exophytic and somehow hypoattenuating tumor. On a CT artery-phase scan, the tumor shows heterogeneous improvement. Keep an eye on the pseudo-capsule enhancing (arrows). A confined mass with considerable bleeding (open fleck), a partial capsule (curved flew), and a focal length of yellow-toned tissue is seen on the removed specimen (straight solid arrow). The cytoplasmic lipid content of these tissue focuses was showed to be much greater by histological investigation. The second figure shows a CT scan with an exophytic, somewhat hypoattenuating tumor of 5 cm diameter. On a CT artery-phase scan, the tumor shows heterogeneous improvement. Keep an eye on the pseudo-capsule enhancing (arrows). A confined mass with considerable bleeding (open fleck), a partial capsule (curved flew), and a focal length of yellow toned tissue is seen on the removed specimen (straight solid arrow). The histological investigation has found that the cytoplasmic lipid content of these tissues is significantly greater (Grazioli et al., 2001).

iii. Focal Nodular Hyperplasia (FNH)

FNH liver lesions are the second most encountered solid benign liver lesion. Liver lesions caused by focal nodular hyperplasia are typically asymptomatic; nevertheless, some individuals may feel stomach pain and minor gastrointestinal discomfort. While focal nodular hyperplasia lesions are not life-threatening, differentiating them from other liver tumors can be challenging. As a result, there is a significant likelihood of misdiagnosis. The imaging characteristics of focal nodular hyperplasia lesions are similar to those of the fibrolamellar form of hepatoma. FNH display similar characteristics as in hepatic adenomas. Proper diagnosis is required to avoid unnecessary biopsy, surgery, or other invasive treatment methods. To make sure of an accurate diagnosis, it's highly advised that patients get several complementary imaging scans, which the pictures be interpreted by an experienced subspecialty radiologist (Mathieu et al., 2000).

iv. Lipomas

Liver lipoma is an uncommon benign mesenchymal tumor that does not progress to malignant degeneration. Lesions can sometimes be asymptomatic, but depending on their size, they might cause stomach discomfort. Typically, liver lipomas are discovered incidentally during radiological exams for other reasons, and there is no evidence of a known genetic cluster or predisposing factors, although it appears to have a strong connection with an imbalanced lipidic profile (Manenti et al., 2017).

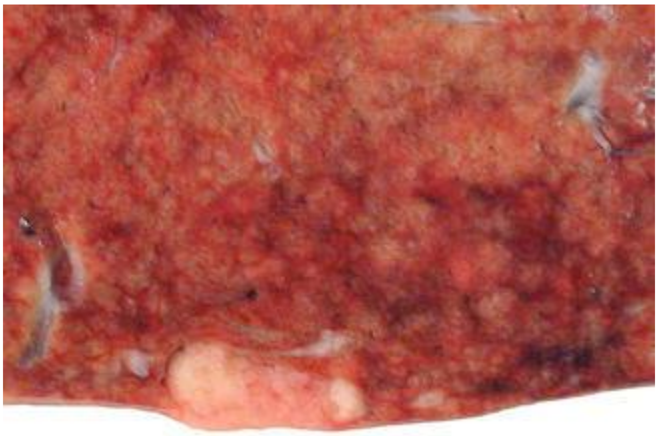


Figure 2.4: Subcapsular lipoma of the liver

Hepatic lipomas frequently appear as a single mass, which is roughly limited in size but not fully encapsulated, measuring tumors of between millimetres and several centimetres.

v. Liver cysts

A hepatic cyst is a fluid-filled sac that develops within the liver. They are benign, which means they are not malignant. These cysts, in most cases, do not require treatment unless symptoms emerge, and they seldom impair liver function. Because a small liver cyst typically does not produce symptoms, it might lie undetected for years. Some patients do not notice pain or another discomfort until the cyst enlarges. Liver cysts are caused by a bile duct abnormality; however, the specific cause of this deformity is unclear. Bile is a fluid produced by the liver that assists in digestion. This fluid is transported from the liver to the gallbladder via ducts or tube-like structures. (de Reuver et al., 2017).

Figure 2.5 Liver cyst

vi. Biliary hamartomas

Biliary hamartomas (BHs) are unusual favored liver tumors that are historically characterized as innate deformed biliary ducts and stroma engulfing. They are also known as von Meyenburg Complexes (VMCs). Originally characterized in 1918 by Meyenburg as BHs. In general, BHs are effects of defects in the bile canal or a gradual rebuilding of tube plates when tiny intrahepatic bile canals are embryologically developed. BHs are generally asymptomatic, sometime detected by coincidence (Huang et al., 2020).

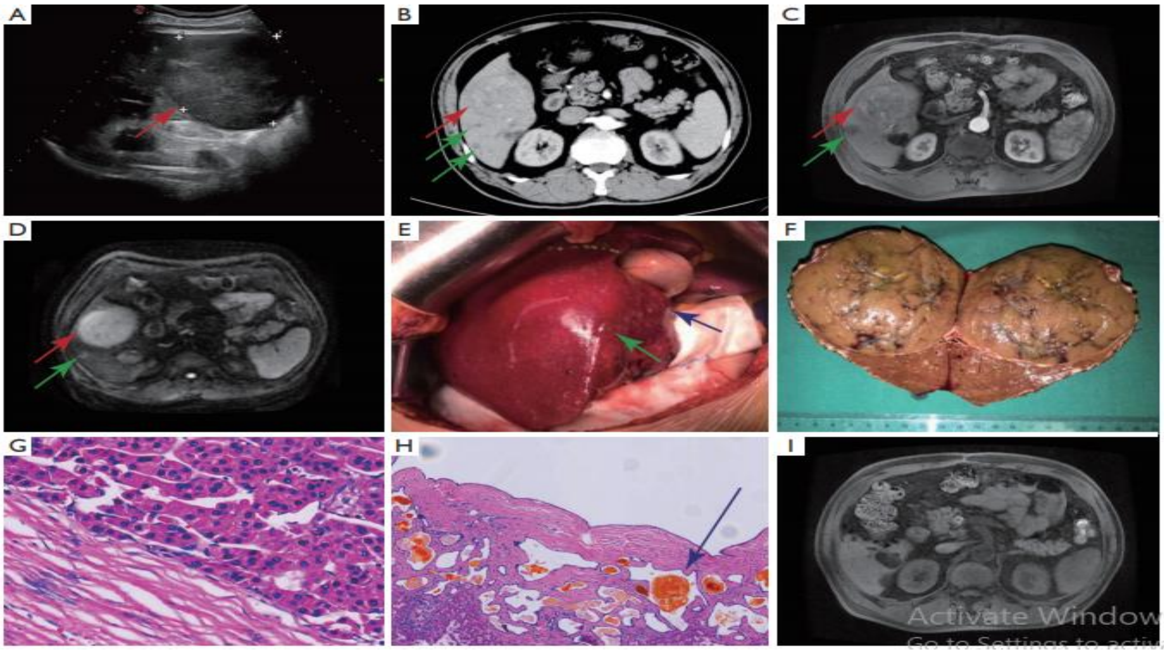


Figure 2.6: Biliary hamartomas

There are a lot of scattered lesions in the liver in the images of large histological specimens (A), B, C, and D, as well as in the MRI images; Gross appearance (E, F) a tumour with a cut face and a liver occupancy (blue arrow); histology (G, H) hematoxyline and eosine staining; It has been discovered that there is a well-defined, hypoechoic mass in the abdomen (red arrow).

b. Malignant liver lesion and liver tumor

These types of liver lesions are divided into two types: primary and secondary. Primary liver lesions, also known as hepatoma, is cancer that begins inside the liver. Secondary liver lesions, also known as liver metastases, is a form of cancer that spreads from another organ to the liver. Secondary liver cancer is dominant in United States than hepatoma. Cancerous liver lesions can be fatal. Following a diagnosis, immediate attention is necessary, as is thorough follow-up (Lyu et al., 2017). Hepatoblastoma, intrahepatic cholangiocarcinoma (bile duct cancer), and angiosarcoma are examples of malignant liver lesions. Nevertheless, we will discuss two examples of primary and secondary liver cancer.

vii. Hepatoma (Hepatocellular Carcinoma Liver Lesions)

Hepatoma is the most prevalent primary malignant liver lesion. Cirrhosis, last phase of liver damage caused by variety of diseases and situations, but is most commonly associated with persistent drinking or hepatitis B or C infection. Early diagnosis is critical for successful treatment of the world's fifth prevalent cancer, and hence the third common cause of cancer related dead. However, diagnosing hepatoma liver lesions can be challenging since they need a variety of imaging presentations and can be readily confused with benign liver lesions. To confirm a diagnosis, a second opinion from a subspecialist radiologist is strongly advised (Buell, 2015).

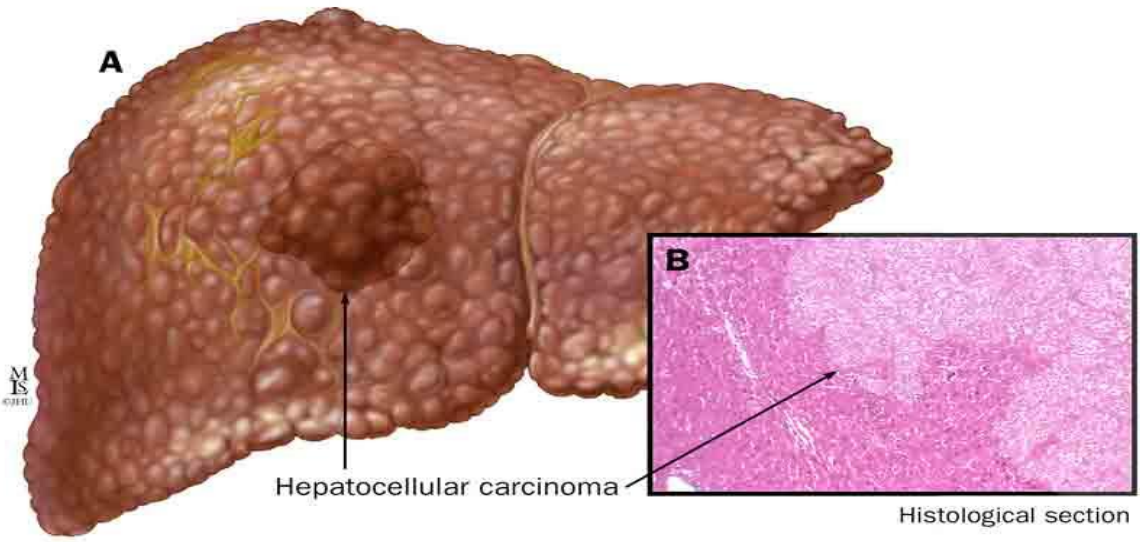


Figure 2.7: Hepatocellular carcinoma

viii. Liver Metastases (Hepatic Metastases)

Liver metastases, also known as secondary cancer of the liver, occur when cancer spreads from another region of the body to the liver. Hepatic metastases and benign liver lesions share several traits. Hemangiomas and FNH are particularly difficult to distinguish from metastatic disease and contribute significantly to image interpretation uncertainty. A thorough grasp of the various manifestations of hepatic metastases is required for appropriate diagnosis. Follow-up imaging is important in patients care especially those receiving therapy for hepatic metastases. Metastasis of the livers is widespread in several malignancies, including CRC, carcinoma, melanoma, carcinoma and carcinoma, with CRC the most prevalent primary illness in the liver. A substantial role is played by tumour cell interactions with its milieu in terms of metastatic burial, survival, and progression. Cells such as hepatic endothelial sins, cups and stellate hepatic cells, parenchymal hepatocytes, dendritic cells, resident natural killer (NK) cells, as well as monocytes, macrophages, and neutrophils, might help improve the quality of hepatic metastases (Tsilimigras et al., 2021).

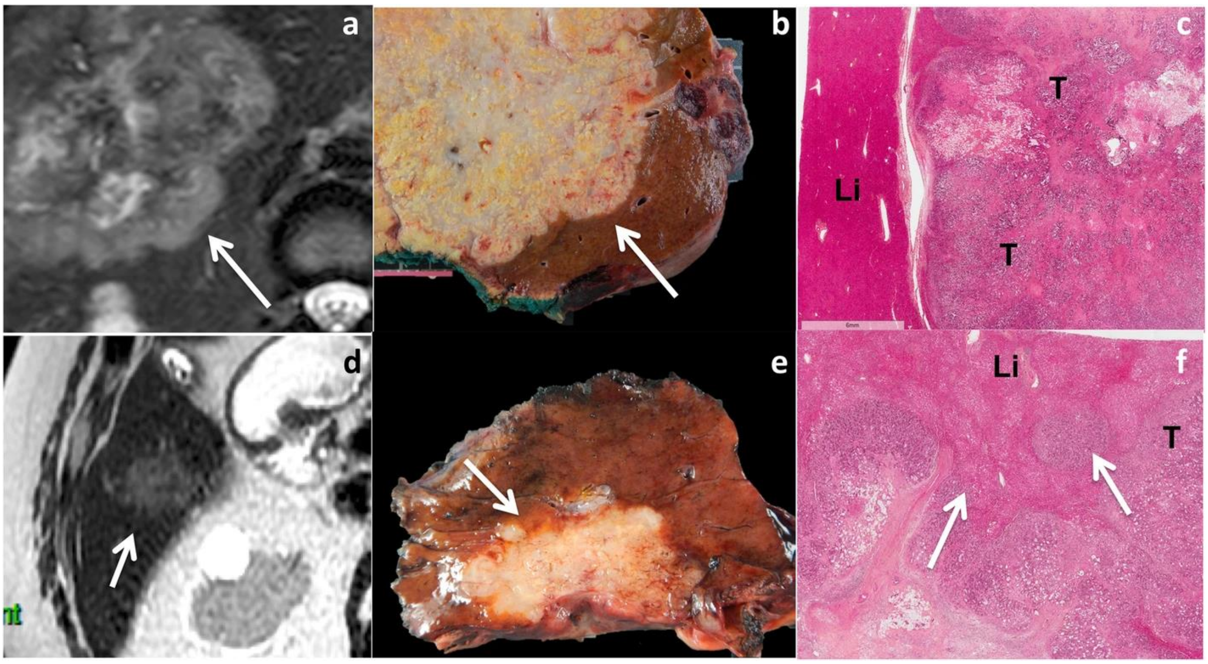


Figure 2.8: Colorectal liver metastases

Examples of gross pathological and histological examinations as displayed in Figure 2.8 are the pushing (a-c) and the infiltrative (d-f) development patterns in nonspecific adenocarcinoma liver metastatic rectal cancer patients, respectively. The pulling pattern is tumor limited by the T2-weighted MR and a major pathological condition (a, b-arrows), but the infiltrative pattern is considerably more poorly defined (d, e- arrows). The distinction between the two patterns is evident on histological examination: The pushing pattern (c) shows that the liver cells (Li) is pressed by the tumor (T) but not inside the hepatic plates. The infiltrative pattern (f) is marked by liver invasion (Li) Tumor cell parenchyma (T-arrows) (Paulatto et al., 2020).

2.4 Signs and Symptoms of liver lesions and tumors

In general, benign liver lesions show no symptoms. Many people only discover a separate health problem when they go to an imaging exam such as an ultrasound. The symptoms differ depending on the type of lesion if it does create issues. (Assy et al., 2009; Grazioli et al., 2017). They could include:

- ❖ Blowing, swelling or pain in the belly
- ❖ feeling full
- ❖ vomiting and nausea
- ❖ feeling weak or weary or feeling weak or feeling tiresome or feeling weak

- in the eyes or the yellow skin.
- fever

Other symptoms can affect the digestion, such as:

- Feeling of being ill
- Pain in the upper right side of your belly or in your right shoulder
- Indigestion symptoms, such as feeling full extremely fast while eating
- A highly bloated tummy that is not linked with

2.5 Diagnostics

When a liver lesion is suspected, a blood test, an imaging test and a biopsy is required to confirm it. In some cases, one test is sufficient and in others more than one test maybe required.

2.5.1 Blood test

This can be used to check for Hepatitis or to ascertain the health condition or functioning of the liver. Blood test might show the level of particular protein for instance AFP. Elevated level symbolizes of cancer of the liver (Cohen et al., 2018; Chang et al., 2009).

2.5.2 Imaging tests

These might indicate the location and size of a lesion on the liver. A resonance imaging (MRI) scan creates precise pictures of the liver using strong magnets and radio waves. A CT scan combining an X-ray series to generate a more complete picture. A scan using positron emission (PET) uses a certain colouring that visibly makes the liver more apparent. (Bonder & Afdhal, 2012; Chiorean, 2015).

2.5.3 Biopsy

To rule out if it is lesion, tumor or not, doctors may extract a little sample or the entire lesion to examine them for damaged cells (Hollerbach et al., 2003).

2.6 Treatment

Treatment for liver lesions and tumors is determined by the degree of the illness (stage), age, general health, and personal preferences.

Surgery

Surgery to remove the tumor. If the tumor is small and the liver still functions properly, the doctor may propose a surgery to remove it and a small amount of good liver tissue that surrounds it (Otte, 2010). Transplantation of the liver. The damaged liver is replaced with a healthy liver from a donor during liver transplant surgery. At this time, liver transplant surgery is only a possibility for a tiny proportion of people**.**

Localized therapies for liver cancer are delivered directly to the cancer cells or environment around the cancer cells. Localized therapy options for liver cancer include:

Cancer cells are heated. Radiofrequency ablation is a technique that employs electricity to heat and kill cancer cells. The doctor inserts one or more thin needles into small incisions in your belly using an imaging test, such as ultrasound, as a guide. When the needles reach the tumor, they are heated by an electrical current, which kills the cancer cells. Cells might be heated using microwaves or lasers (Gervais & McDermott, 2013).

Cancer cells are frozen. Cryoablation is a technique that employs intense cold to kill cancer cells. During the operation, the doctor will insert a nitrogen-containing device (cryoprobe) directly into liver tumors. The cryoprobe is guided by ultrasound pictures, which are utilised to monitor the freezing of the cells (Wang et al., 2020).

Injecting alcohol into the tumor. Pure alcohol is injected into tumors directly, via the skin, or during surgery. Tumor cells are killed by alcohol. Chemotherapy medicines are injected into the liver. Chemoembolization is form of chemotherapy treatment that delivers powerful anti-cancer medicines to the liver. Placing radiation-filled beads into the liver. Small radiation-containing spheres may potentially be implanted directly into the liver, where they would provide radiation to the tumor (Lin et al., 2005).

Radiation therapy

This treatment destroys cancer cells and shrinks tumors by using high-powered radiation from sources such as X-rays and protons. Doctors carefully target the energy to the liver while avoiding healthy tissue in the surrounding area. If alternative treatments aren't possible or haven't worked, radiation therapy could be a possibility. Radiotherapy may help manage symptoms in advanced liver cancer. The patient is laid on a table during external beam radiation treatment, and a machine focuses energy beams at a specific location on the body. Stereotactic body radiotherapy is a type of radiotherapy that involves concentrating many beams of radiation to a particular part of the body at once (Herfarth et al., 2001; Tanguturi et al., 2014).

Targeted drug therapy

Targeted pharmacological therapies focus on particular abnormalities found in cancer cells. By obstructing these Targeted medication therapies destroy cancer cells once anomalies are inhibited. There are several targeted medicines available to treat advanced liver cancer. Some targeted treatments are only available to patients whose cancer cells have specific genetic abnormalities. Tumor cells may potentially be examined in a laboratory to see whether these medicines could help with their therapy (Husseini et al., 2017; Zhang et al., 2019).

Immunotherapy

Immunotherapy harnesses immune system to combat cancer. Because these cells generate proteins that blind the system cells, the body's disease-fighting system may fail to fight the lesions and tumors. Immunotherapy works by interfering with the natural process. Immunotherapy therapies are often reserved for individuals with advanced liver cancer (Matar et al., 2009). Immunotherapy and radiation are sometimes combined (Kreidieh et al., 2019).

Chemotherapy

Chemotherapy is a combination of strong medicines used to destroy cancer cells. It is the most often used therapy for liver lesions that extend to other areas of the body. Chemotherapy use medicines to kill rapidly developing cells. Chemotherapy is frequently given by a vein in your arm, as a tablet, or both. Chemotherapy is most commonly used to treat advanced liver cancer. If there are no symptoms, then the lesion cannot be treated. If it is creating problems but is not malignant, the doctor may prescribe surgery to remove it and relieve symptoms. Trans-arterial chemoembolization (TACE): A form of targeted chemotherapy, which directly supplies the lesion with anti-cancer drugs. It is injected into the blood-transmitting artery with a small tube called a catheter. This also limits some blood flow to the liver to prevent the oxygen that cancer cells require to grow. The side effects of TACE are less than conventional chemotherapy (Johnson, 2000; Litten & Tomlinson, 2008).

Radiofrequency ablation (RFA): Doctor may recommend surgery if the lesion is small. In general, a little sample will be inserted into the liver tumor via minor incidents in the abdomen. The sound will release some acoustic energy that heats cancerous cells and destroys them (Gervais & McDermott, 2013).

2.7 Prevention

Although liver lesions and tumors cannot be fully avoided, they are prevented with regular exercise, watching the body’s weight, and moderate liquid intake (up to 2 drinks each day for men and one for women). Things that cause liver diseases should be avoided. Don't share needles that have already been used.

CHAPTER 3: NUCLEAR MEDICINE IMAGING OF LIVER LESION AND TUMOR

3.1 Background of nuclear medicine

Nuclear medicine has a broad history that includes experts from many areas such as physics, medicine, chemistry, and engineering, all of whom have made significant contributions throughout the years. It took centuries when scientific and international events developed to make Atomic Age one of history's most pivotal development. Democritus, an early Greek thinker, postulated the Atomic Theory, which has become a cornerstone of modern science. He postulated that all the particles in the cosmos be so small that there could be nothing smaller. The early Greek scientist, Democritus, established the Atomic Theory of Matter around 460 BCE - around 370 BCE. In 1808 an English scientist, Dalton, stated that each atom of a particular element, including weight, is similar to any other atom. The fundamental significance of atomic weights and nuclear structure was established in 1871 by the Russian physicist Dmitry Mendeleyev. His work also shows that behavior and properties of matter are structurally important. Pioneering cathode-ray research in 1887, English physician and scientist Sir Crookes. Wilhelm Röentgen, a German scientist, observed some blazing barium platinocyanide across the space from his experiment while investigating cathode rays. This resulted in the development of X-rays in 1895. His work aided in the development of a suitable methods in medicine and significant part in unveiling atom and its nucleus mysteries. Antoine Becquerel, scientist from French, discovered radioactivity in 1896. The nature of the electron was explained in 1897 by English physicist Sir J. Thomson. In 1902, the radioactive elements polonium and radium were discovered by Curie, and her wife, Pierre. They have found that radiation is present. The scientists have been firmly thinking for over two centuries that essential measuring amounts, mass, length and duration, are absolute and unchangeable. In 1905, Einstein proved that they depended heavily upon observer's relative speed and everything he saw. Sir Ernest Rutherford made a significant contribution to contemporary science when he demonstrated what occurs to a component during decay in 1909. It helped in the development of the basic atomic nuclear model, which is still used in modern physics. By 1913, Bohr updated Rutherford atomic model to integrate physics principles. This necessitated the development of a substitute mechanism for the way electrons emit energy. By 1919, Rutherford published a study that proved the possibility of changing from one atom to another as a result of artificially interfering with the activities of the nucleus. Much more importantly, his work proved that an atom's nucleus could be penetrated. Sir James Chadwick, a British scientist, become famous for neutron discovery in 1932. As a result of its lack of charge, the neutron was distinct from all other particles at the time. The Cockroft-Walton accelerator was created by Sir John Douglas Cockroft and Ernest T. S. Walton. Each lithium atom was high enough for two helium molecules to be created in 1932 when the protons increased the speed of their protons. This scenario is the first nuclear transmutation created. To demonstrate this, they calculated in 1938 that an estimated 200 million electron volt of theoretically useful energy could be transformed into a fraction of the weight of one unprocessed uranium nucleus. It was called fission. Ernest O. Lawrecy, at the University of California, Berkeley, produced a series of radioisotopes that might be used for biological and medical study in 1929. In 1937, iron59 (Fe59) was produced using a sophisticated cyclotron by the scientists' John Livingood, Fred Fairbrothers and Glenn T. Seaborg. Iron-59 is helpful in human blood haemoglobin studies. Livingood and Seaborg discovered iodine-131 (I-131) in 1938. Iodine-131 is used to treat thyroid disorders all over the world. Until his death in 1999, Seaborg stayed in the profession. In 1909 the prevalent concept of the structure of the atom was the mushy, semi-permeable balls of atoms with charged particles distributed around them. This theory worked flawlessly for many physical world experiments. On the other hand, physics is not only concerned with the way the world works, but also with the way it operates. A scientist named Rutherford invented an experiment in 1909 to prove the validity of the dominant hypothesis. In it, he showed how physicists could "see" tiny particles for the first time, which microscopes could not observe. A radioactive source discharged an alpha particle flux on a very thin sheet of film in the Rutherford experiment before a screen. When the alpha particles hit the screen, the flashes of sunlight would be small. The alpha particles were meant to pierce the very thin foil and create a tiny cluster on the screen. The initial three letters of the Greek alphabet alpha, beta and gamma, were designated for the three types of radiations. Although radiography, computed tomography and resonance photography remain the methods of carcinoma study, the nature of suspect lung nodules is constrained, mediastina involvement is assessed, the viability of previously treated lesions has been assessed and tumor recurrence is thus diagnosed. (Schmidt et al., 2010; Sommer et al., 2014). There is a broad spectrum of oncological requirements related to cancer: the early and safe detection of malignant lesions; the definition of biological characteristics (proliferative, aggressive, differentiated, etc.), and the need for defining the patient's operability (residual lung and stage function); the nuclear medicine world has focused its efforts on the diagnosis, staging, rehabilitation and monitoring of cancer. One radiopharmaceutical ingredient in this field includes gallium, monoclonal antibodies, somatostatin analogues, lipophilic cations, and positron tracers. (Blower et al., 2019; Wadas et al., 2010). There is much evidence that medical approaches may give additional information concerning anatomical imaging. Niels A. Lassen, David H. Ingvar, and Erik Skinhj had invented methods for the initial xenon-133 inhalation in Southern Scandinavia in the early '60s and measuring local distribution in the brain’s activity for neuropsychiatric disease patients such as schizophrenia was soon developed. To show the two-dimensional image on a colour monitor, later versions would have 254 scintillators installed. This allowed them to produce pictures of the brain's activity and voluntary movement in response to spoken, read, visual, or aural stimuli. For example, sequencing, mental calculations and spatial navigation were studied using the method. Also, the method was employed in the research process. There were medical techniques that allowed people to see most body organs in the 1970s. Both the American Medical Board of Medicine and the American Osteopathic Board of Medicine were formed in 1972 and 1974, respectively. When radiopharmaceuticals were first invented, it was in the 1980s to aid in cardiac diagnostic procedures. When single-photon emission (SPECT) was introduced, the gut was reconstructed in three dimensions and the nuclear cardiology business was born as a direct result. The development of the main positron emission tomography scanner (PET) is one of the most recent advances in medicine (Shukla & Kumar, 2006). Formed by David E. Kuhl and Roy Edwards, single-photon emission computerised tomography evolved from emission and transmission tomography in the late 1950s (SPECT). Their research led to the invention and building of numerous CT devices at the University of Pennsylvania. Tomography imaging techniques were enhanced at the Washington University School of Medicine. A PET/CT prototype by D.W. Townsend, University of Pittsburgh, and SPECT/CT imaging by Bruce Hasegawa, University of California, San Francisco (UCSF) were the results of these discoveries, which were published in 1998. (Townsend & Beyer, 2002). PET and PET/CT imaging evolved more slowly in the early years due to the usefulness of the modality and the resulting need for a local or neighbouring cyclotron, as a result. As a result of the creation of 18 F-labeled standard operations tracers that allow work at facilities that do not have Cyclotrons, medical reimbursement for limited PET and PET/CT applications in cancer has been granted by administrative decision throughout the years. When it comes to cancer, PET/CT images are used to aid in diagnosis and treatment monitoring. Since the beginning of 2011, a fully integrated MRI/PET scanner has been on the market (Boersma et al., 2004; Delbeke & Segall, 2011; Martinez-Möller et al., 2012).

3.2 Nuclear Medicine Diagnostic Techniques and procedures

Nuclear medicine has different techniques and procedures. We will discuss PET, SPECT and hybrid methods like PET (CT/MRI) simultaneously.

3.2.1 Positron emission tomography (PET)

Positron emission tomography scan is an imaging test that permits the visualization of diseases in the body (Sakalihasan et al., 2002). A specific chemical containing radioactive tracers is used in the scan. Depending on the region of the body being studied, these tracers are either ingested, breathed, or injected into a vein in your arm. (Teirstein et al., 2007). The tracer is subsequently absorbed by certain organs and tissues. Tracers, when detected by a positron emission tomography scanner, assist doctors in determining how effectively organs and tissue's function. The tracer will gather in places with higher levels of chemical activity, which is beneficial since specific tissues of the body and illnesses have higher levels of chemical activity. On the PET scan, the afflicted region shows bright patches. (Horsman & Overgaard, 2016). The PET scan may evaluate blood flow, oxygen consumption, sugar metabolism, and much more. A PET scan is often performed as an outpatient treatment. This means that once the exam is over, a person can resume their usual daily activities. In a PET/CT scanner, CT data are often used to correct the PET image without noise to prevent a time-consuming transmission scan.

Figure 3.1: PET scan machine

3.2.2 SPECT

A single-photon emission computed tomography (SPECT) scan allows clinician to examine the interior organs' function. A SPECT scan is a nuclear imaging procedure that produces 3-D images using a radioactive material and a specific camera (Melton et al., 2005). In contrast to X-rays, a SPECT scan produces images that show how your organs are functioning (Mihaljevic et al., 2014). It's possible to see how much blood flows to your heart or if certain regions of your brain are more or less active using a SPECT scan, for example.

Figure3.2: single-photon emission computer tomography scan machine

3.2.3 Hybrid method

PET/MRI: Oncologic imaging is one of the primary potential uses of hybrid PET/MRI technology (Judenhofer et al., 2008). A two-in-one examination in a PET/MRI scan is a combination of photos from a PET scan with an MRI. The new hybrid method combines the characteristics of PET and MRI to give some of the most complete pictures of your body today. (Kwon et al., 2016). MRI provides high soft tissue contrast, which is anatomically important for PET studies. Furthermore, functional MRI methods can augment PET-based tumor characterization. PET scan with a radioactive fludeoxyglucose (FDG) tractor for tumor glucose metabolism may be an established tool for clinical diagnosis and surveillance of different cancers across the body. (Jiménez-Requena et al., 2009). Although they are utilized more and more in tandem, the synergy or potential redundancy of FDG-PET with functionally multiparameter RMI (mpMRI) in cancer is unknown. (Hectors et al., 2018). A two-in-one examination in a PET/MRI scan is a combination of photos from a PET scan with an MRI. The new hybrid method combines the characteristics of PET and MRI to give some of the most complete pictures of the body today. The images obtained are used to diagnose medical problems and arrange therapy for them. (Delso & Ziegler, 2008). For instance, PET/MRI scans of the brain are useful within brain tumors and also liver tumors.

PET/MRI scans function as follows: MRI scans use a strong magnetic flux to produce comprehensive images of the inner elements of the body. They will also provide information on how these structures operate successfully. In PET scans, tracers are utilized to show abnormalities that signify disease. To date, scientists have not been able to employ both PET and MRI to simultaneously scan the image detectors on a positron emission tomography scanner as powerful MRI magnets interact. PET and MRI scans are performed independently, and the resulting pictures are later combined. That merger, on the other hand, necessitates a sophisticated computer procedure. The newly accessible PET/MRI scanner at Stanford can provide the latter at the same time, collecting more information than combined PET and MRI images.

Figure 3.3: PET/MRI scan machine

PET/CT scan: A new efficient and sensitive approach to cancer diagnosis and follow-up is the combination of positron emission tomography (PET) and CT (computed tomography) (PET/CT). When compared PET alone, PET/CT enhances diagnostic performance, its usage has grown significantly in recent years (Lardinois et al., 2003). CT scanning is the usual technique in the broad majority of clinical environments across the world for initial diagnosis and monitoring in cancer patients. If the CT test in the combined PET/CT exam is performed using intravenous (IV) and oral contrast agents as a diagnostic grade CT scan, the standard of a PET/CT joint procedure will be improved and the initial separate CT examination will normally be eliminated from it (Antoch et al., 2004). This leads to a simplified patient diagnosis, economic savings and a reduced patient radiation exposure.

Figure 3.4: PET/CT scan machine

The advantages of hybrid scans (PET/MRI and PET/CT). PET has several advantages:

- ❖ Better diagnostic accuracy and therapy options: brain PET/MRI scans can show aberrant anomalies missing in more than half of tested people.
- ❖ Improved radiation exposure safety: PET/MRI exposes patients to about 50 per cent lesser radiation than PET/CT scans.
- ❖ The combination of two PET/MRI scanners minimizes the need for separate appointments.

3.3 Diagnostic Radionuclides

Radiopharmaceuticals are radioactive mixes containing a bound radionuclide in their construction, intending to direct the radionuclide to a specific location for treatment or imaging. Nuclear medicine is a field of medicine that uses radiopharmaceuticals and has shown to be a wonderfully valuable ally in medicine, aiding in differential diagnosis and treatments, particularly for cancer. As radiopharmaceuticals, radionuclides and metal complexes are often used. MDP-99mTc, Indium (111In) compounds, thallium (201Tl), gallium (67Ga, 68Ga), iodine (123I and 131I), chrome (51 Cr), sulphide (35S), phosphorus, (32P) are the most frequent compounds used as radioactive elements, including technetium (99mTc), sodium pertechnetate and methylene diphosphonates, MDP-99mTc. In the early identification of certain diseases, including cancer, they have had to be important. The bulk of radiopharmaceuticals used in all nations currently comprise technetium compounds. (Boccato Payolla et al., 2019). Most hospitals currently get their radionuclides from one of three sources: nuclear reactors, radionuclide generators, and cyclotron facilities. It should be noted that generators still need the radionuclide parent to be supplied via a reactor or cyclotron source. Some popular methods of producing radionuclides include the use of linear accelerators (Mang'era et al., 2015). The term "classical cyclotron generated radionuclides" refers to radionuclides produced using well-established methods on primarily liquid or gas targets. (Fig. 3.5).

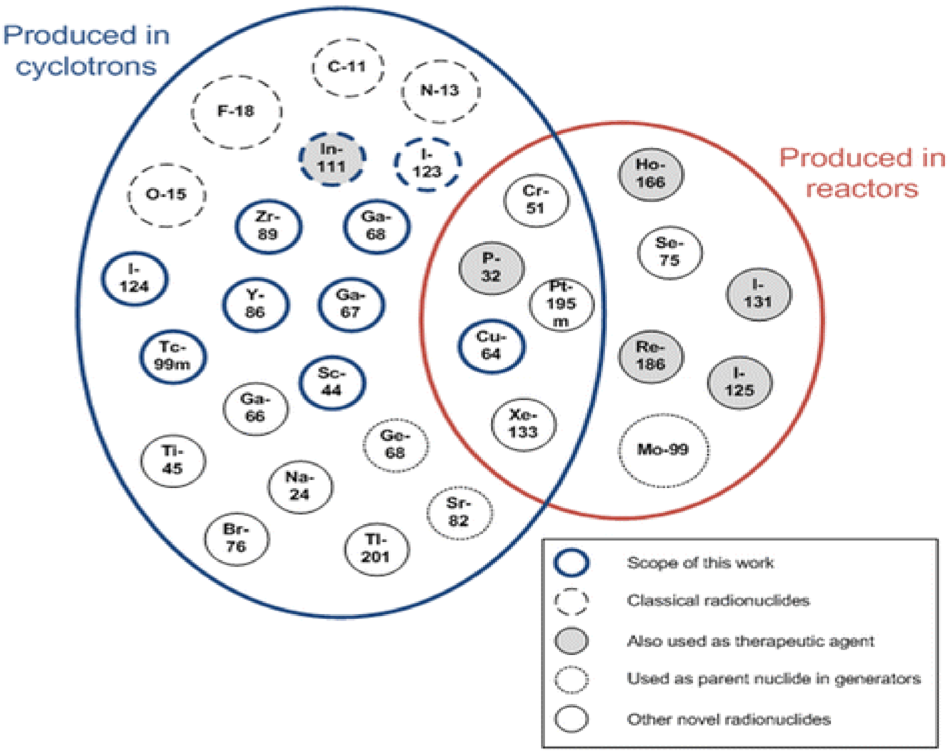


Figure 3.5: Radionuclides used in nuclear medicine diagnostics

3.4 Advantages of Nuclear medicine application in liver lesion and tumor detection.

Nuclear medicine analyses areas or sections of the body that other imaging methods cannot reach, and the information includes the anatomy and function of the organ concerned.

Nuclear medicine provides the most important diagnostic or therapeutic information for a variety of illnesses. A medicine scan is less costly and should provide more exact results than exploratory surgery. Nuclear medicine can diagnose the disease at an early stage, frequently before symptoms or anomalies are identified by traditional diagnostic procedures. PET scans may avoid the need for surgical biopsy or determine the easiest biopsy location by identifying whether lesions are likely benign or malignant. PET scans may give extra information that can be utilized to schedule radiotherapy. (Kadrmas et al., 2009; Blackledge et al., 2011).

3.5 Disadvantages of Nuclear medicine application in liver lesion and tumor detection.

Because nuclear medicine tests employ a little amount of radiotracer, they need a minimal level of radiation exposure. This is generally suitable for diagnostic examinations. As a result, the advantages outweigh the risks. For almost six decades, doctors have used medical diagnostic techniques. As of now, there is no lasting consequence of exposure to the low dosage. The doctor in charge will carefully evaluate the benefits of medication therapy against potential dangers. Before treatment, doctors will go over the various hazards with patients and allow them the opportunity to ask questions. Radiotracer allergies are exceedingly infrequent and generally minor. Always inform the medical staff of any allergies. Describe any issues encountered during prior medical examinations. Mild discomfort and redness from the radiotracer injection, which should go away quickly. Women should inform their doctor and radiological technician if they are pregnant or nursing. (Taillefer, 2005).

3.6 Limitations

Nuclear medicine procedures might take a long period. The radiotracer might build inside the region of interest over several hours to days. Furthermore, imaging might take many hours to complete. Nuclear medicine pictures may not have the same image resolution as CT or MRI images. Nuclear medicine scans, on the other hand, are more sensitive for a range of reasons. The functional information they provide is typically inaccessible using conventional imaging methods (Rahmim & Zaidi, 2008). For these reasons, incorporating artificial intelligence in a field like nuclear medicine would significantly maximize time required and improve accuracy of results.

CHAPTER 4: ARTIFICIAL INTELLIGENCE IN NUCLEAR MEDICINE

4.1 Artificial intelligence

In the middle of the 20th century, a distinct discipline, followed by cycles of optimism and disappointment, was recognized as that of the domain of artificial intelligence (AI) with growing relevance in which diverse AI components affect almost every element of modern technology. In recent decades, a great part of the sector's success has been attributed to developments in computer power, huge digital databases and the emergence, as well as a greater understanding of theoretical components in IT and feasible algorithms. (Roughgarden, 2010). Technical titans like IBM, Google, Microsoft, Apple and Facebook have developed AI with great interest, AI was being developed in earnest by technological leaders such as IBM, Google, Microsoft, Apple, and Facebook by the twenty-first century. Speech might well be used to instruct electrical gadgets to do tasks. In medicine, the software can recognize characteristics in pictures to identify particular disease abnormalities in computed tomography (CT) or other images of the physical body. AI is a wide subject that includes several subfields, each of which tackles the basic problem differently, with the overall objective being to build hardware and software techniques that allow a machine to execute cognitively demanding activities such as making a decision. Machine learning algorithms are educated to do certain jobs using patterns from extensive data sets. Deep learning is a machine learning subset in which man-inspired neural networks and very large amount of data are utilized to resolve highly difficult problems. (Chartrand et al., 2017; Erickson et al., 2017).

4.2 Artificial Intelligence technology

Every year, the digital world becomes more complex. Technological advancements have been developed by scientists and researchers. Artificial Intelligence is a significant advancement in digital technology (AI). Artificial intelligence is a term that encompasses a variety of ideas in information technology, including computers, software development, and data transfer. Nonetheless, the arrival of artificial intelligence comes at a time when cyber-attacks are on the rise. Many corporations and businesses now use Artificial Intelligence to secure their data and information systems. (Mohammad, 2021). The term "artificial intelligence" refers to a branch of research that aims to provide machines with the ability to execute activities such as logic, reasoning, planning, learning, and perception. Despite the use of the word "machines" in the definition, the term "living intelligence" can apply to "any form of living intelligence." similarly, a combined set of skills like creativity, emotions, knowledge and self-awareness may be developed into the concept of intelligence found in primates and other outstanding species. The term AI was firmly related to the 'symbolic AI' study until the end of the 1980s. Sub-symbolic approaches including neural networks, fuzzy systems, evolutionary computation and other computing models began to take a prominent place to overcome the limitations of symbolic AI (Fulcher, 2008). The term artificial intelligence (AI) now refers to the complete concept of the computer, which is both operational and social. In practical terms, Russell and Norvig defined: "Artificial intelligence is to be studied artificially to carry fair logic in its design, to imitate human intellect and behaviors." This notion may be further enhanced by claiming that even people can be more reasonable for certain and clearly defined tasks. Current AI technologies are used for personal assistance in online advertising, driving, aviation, healthcare and photo identification. An example is the vehicles equipped with an automatic steering system, commonly referred to as self-driving cars. Each vehicle features several lieder sensors and cameras to recognize its three-dimensional surroundings and to judge motions under changing circumstances. Another example is Google Deep Mind's Alpha-Go to play the Go board game. (Lee et al., 2016). Current AI technologies, on the other hand, are confined to extremely specialised applications. A drawback of AI is its absence of "common sense," or capacity to assess data other than what it is learned. One instance is Microsoft's AI robot Tay, which was built to engage in social networking chats. (Schlesinger et al., 2018). It had to be unplugged soon after it was launched since it couldn't tell the difference between positive and negative human contact. In terms of emotional intelligence, AI is similarly restricted. AI can only identify fundamental human emotions like anger, joy, sorrow, fear, pain, tension, and neutrality. One of the next borders of personalization is emotional intelligence. (Ringeval et al., 2019). There is yet no real and full artificial intelligence. At this point, AI imitates human awareness to the extent that it can imagine, think, feel and achieve its objectives. Although there is no evidence for this kind of genuine AI to exist by the year 2050, it is crucial to assess the influence not only from technology but also from social, ethical and legal positions of the computer science principles that push AI forward fast.

4.2.1 Expert System

An ES is a subclass of AI that was created to tackle a specific challenge in a specific domain. The developed computer system may replicate the actions of a human expert when solving a problem in a certain subject. An ES is a computer system that mimics the actions of a human expert. The phrase Expert System or Knowledge Base System refers to a computer system that possesses the same knowledge base as a human expert. Expert systems (also known as ES) and knowledge-based systems (also known as KBS) are words that are sometimes used interchangeably. The most frequent form of artificial intelligence application is expert systems. The task domain is characterised in an expert system as the region that human intellectual effort is made to understand (Imanov & Asengi, 2021).

Expert System Architecture

An Expert System's Architecture (ES) Building an Expert System necessitates the integration of several components that result in decision making, such as objectives, facts, rules, and an inference engine; hence, we refer to an expert system as a system rather than a computer programme. Figure 4.1: ES Architecture Source: (Imanov & Asengi, 2021) depicts the knowledge base expert system components.

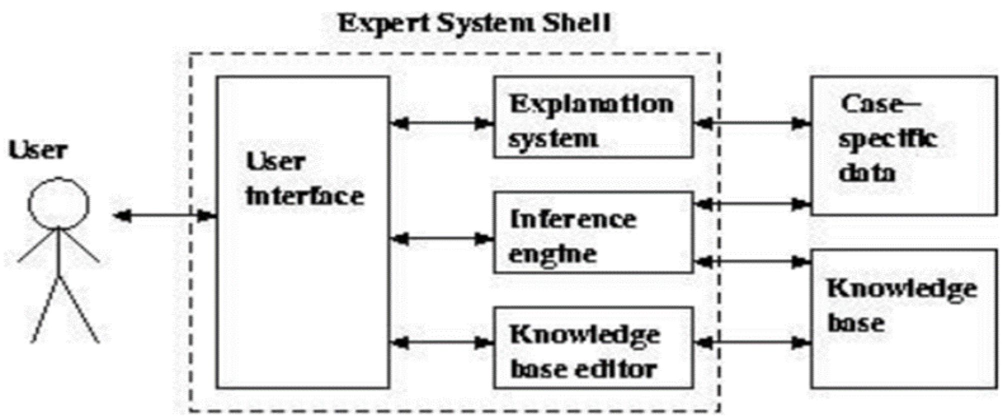


Figure 4.1: Architecture of an Expert System

The Knowledge Base of ES: Expert system's heart. Heuristic knowledge accepted scientific philosophies, and computer methods are used to solve engineering problems. Heuristic knowledge is a rule of thumb that assists in limiting how to continue. An expert system's domain knowledge is kept in its KB, and this module is critical since the system's successful application is dependent on the perfection and dependability of the knowledge contained inside it (Vitkus et al., 2020). The knowledge base is divided into two parts: fixed knowledge (situations, occurrences, and facts about things) and dynamic knowledge (information about the sequence of activity). There are several techniques for representing and organizing knowledge and knowledge bases. To express knowledge, If-Then production rules are employed. Declarative and procedural knowledge are terms used to describe fixed and dynamic knowledge, respectively.

Inference engine representing the domain expert's knowledge in the knowledge base is insufficient; an additional component that directs the execution of the knowledge is required. This expert system component is known as the control structure, rule translator, or inference engine. The type of search utilized to solve the problem is determined by the inference engine. In actuality, the expert system is operated by the inference engine, which determines which rules are helpful, executes the rules, and determines whether an acceptable solution is reached. The nature of the problem field and the method used to represent information inside the knowledge base is the determination of the kind of inference mechanism. (Carreño et al., 2019).

Forward Chaining Someone may opt to start with a preliminary state and then try to attain the goal state while developing an expert system to tackle a specific problem. The process of switching between alternative solutions to go from the preliminary state to the target state is known as search, and the realm of all possible pathways of search is known as the search space (Herawan Hayadi et al., 2018). Forward chaining and backward chaining are the two most used search techniques in rule-based systems. Search in forwarding chaining, as the name indicates, goes in the forward direction. Forward chaining is an information-oriented search method. Forward chaining is a data-driven search method. When the number of target conditions is small in comparison to the beginning state, forward chaining is favourable. The preceding portion is checked first, followed by the subsequent part.

Backward Chaining is a technique that the system supports a desired state or proposal by evaluating known information in the framework. By using inverse operators, the system searches the state space from the target state to the preliminary state. When there are just a few goal states and a lot of preliminary stages, it may be wiser to start with the goal and work your way back to the controller state. Backward chaining is a search with a specific aim in mind.

Chaining in a Hybrid Environment always begins with forwarding chaining, and if a fact is required from the operator, move into the opposite leaf node of the knowledge and have it continued with the forwarding chaining process**.**

Working Memory; the working memory's goal is to collect symbols or trustworthy information that matches the current state of the problem, which consists of data acquired during problem implementation.

Knowledge Acquisition; The methods involved in extracting, constructing and organizing information from the domain expert, so that it can be used in building the system is termed knowledge acquisition. The excellence, comprehensiveness, and accuracy of the material contained in an expert system's knowledge base are crucial to its success. This allows one to learn more about the problem domain from the expert (Wagner, 2003).

The User Interface This is the system component that allows the user to engage with the expert system.

Explanation service; Expert System is unique and unusual in that it can explain to a user how a conclusion was made, which is accomplished through the explanation feature. This is one of the expert system's primary advantages (Imanov & Asengi, 2021)

4.2.2 Machine learning

Neural Networks and Deep Learning are two of the most commonly used words in the media to describe the enthusiasm surrounding current AI. There is a solid explanation why the enormous advances in the performance of AI systems, particularly those of recent research discoveries, have been facilitated for the most part by algorithms that employ Neural Networks. Neural Networks are a type of algorithm that is loosely inspired by biological neurons in the brain (Sheela & Deepa, 2013). Deep Neural Networks (also known as Deep Learning) are simply Neural Networks with several layers of linked neurons in sequence (the term "deep" refers to the number of layers).

4.2.2.1 Machine learning algorithms

This accelerated scientific and technological advancement also opened up new opportunities. Automated machines that are powered by technology incorporate several types of theoretical knowledge, such as statistics and complex algorithms. For future machine-learning development, a simplified analysis of machine-learning algorithms can provide a reference point. This will increase the application of machine-learning algorithms and help facilitate the economic growth of the sector.

a. *Supervised Learning*

Controlled learning is an easy learning method in the process of machine learning. This method of learning relates to the definition of individuals' respective learning goals before learning. It depends on information technology to understand the requirement of learning during the initial training of the machine. To acquire essential knowledge, we shall progressively finish the necessary learning material in a controlled atmosphere. Supervised learning may activate the machine's generalized learning ability in comparison with other learning techniques. It can help folks solve some problems of classification or regression in a pretty systematic way after completing system learning. BN, SVN, KNN and other conventional learning methods are presently in use. Since the complete process of learning has a purpose, the whole learning process is regular and the learning material is consequently more methodical. (Li et al., 2020).

b. *Unsupervised Learning*

Uncontrolled learning is the other way around. Uncontrolled learning means that throughout the learning process the machine does not mark the material in any particular direction, but trusts the machine to complete the knowledge information analysis. In practice, the operating approach is used to enable machine to acquire the essential ideas and content, then to allow machine accomplish series of content learning encompassing concepts and materials nearly as fundamental as tree roots. The fragmented growth of learning has generally extended the spectrum of machinery. Uncontrolled learning includes techniques like autoencoders and deep-belief networks. This is conducive to clustering issues solving and has practical implications for the development of a variety of companies. (Chen et al., 2019).

c. *Reinforcement Learning*

Besides supervised and unsupervised learning, machine learning consolidation apprenticeship approaches also exist. Systematic learning is referred to as strengthening learning in a specific subject. During the specific application procedure, the information acquired throughout the previous period will be utilized. It organizes and analyses feedback data from a particular section to produce a closed processing loop of knowledge. In general, enhancing learning is a kind of learning technique that enhances data collection using statistics and dynamic learning. These techniques are mostly used to address the robot control challenge (Cuocolo et al., 2020). The Q-learning algorithm is two of the most renowned learning algorithms of its kind. The algorithms listed below are classified into one of the three categories listed above;

Support Vector Machine (SVM) Algorithm

The SVM algorithm is a commonly used method in the process of learning machines. This strategy relies significantly on the vector machine approach in the specific application process to complete given data analysis task. Simultaneously, the SVM method uses automatic support from the SVM to examine data to be processed, optimizing data information. A series of sets of research samples should be obtained throughout the real analytical process to compute the sample data on the boundary value to increase the scientific character of the final analysis findings. Suppose, for example, that the data is H (d). The information is initially centrally processed using SVM technology to ensure that it is distributed often. Second, the H (d) plane's border is specified by the plane's greatest length. Finally, the h(d) plane's vector content is evaluated to generate the output vector (Weimin Huang et al., 2013).

Boosting and Bagging Algorithms

The primary benefit of boosting the algorithm as a substitute for a kind of machine algorithm is that the information can be correctly processed and the end processing output may be increased. In practice, with the aid of a boosting algorithm, the function prediction system is created and the system content constantly improved with the assistance of the strengthening learning mode, therefore increasing the processing of knowledge inputs. In the Boosting algorithm, AdaBoost is a basic application. At the same time, the growth of the boosting algorithm is critically guaranteed by AdaBoost. The bagging approach is quite similar in the process of data processing. The discrepancy in practice is due to the random choice of the training set by the bagging algorithm. The Bagging method does not assess the load content during the calculation of the function model and must continuously enhance the information pattern with training so that the results are better accurate. (Huang & Tung, 2017).

Decision Tree Algorithm

The decision tree algorithm is a classic algorithm component among frequently used machine learning algorithms. According to its working principle, the processing of data information begins at the base node of the collection and progresses to its final destination. As a means of simplifying data study, the algorithm will continue to separate branches while also cutting them to improve the material's integrity. There's an examination of the properties of each element, and the node is then extended to support two elements, a process called content analysis. While the tree-like branching technique can help you study more samples, it can also help you discover which content contains samples that are most significant in terms of sample-numbering statistics. The data analysis will select a favorite tree with lots of information, and you will determine the upper bound for the division branch based on this tree (Uribe et al., 2019).

Random Forest Algorithm

The random forest method, like the decision tree algorithm, can be utilised for further processing inside the knowledge calculation process. The random forest algorithm will play an honest role in controlling erroneous data throughout the real usage procedure. As a consequence, the scientific character of the data split findings is effectively improved, as is the accuracy of the information analysis r. Meanwhile different sets of classification trees will be constructed as part of the knowledge analysis process at a time, and the unified approach will be utilised for regression processing (Moazemi et al., 2020; Nensa et al., 2019).

4.2.2.2 Deep Learning Methods

In deep neural networks, which emerged in 2006 as a unique area of engine learning research when used to decrease the size of data in an unattached manner, scientists have since 1979 achieved tremendous strides. It won the ImageNet competition at a wide gap and attracted attention of researchers in 2012, which defeated the latter. To extract image properties automatically from a large quantity of images and subsequently categorise these, profound convolutional neural networks (CNNs) were utilised. Deep learning research has been done in virtually all subject disciplines to tackle complex problems Image recognition, voice recognition, semantic images, language processing and several other tasks have achieved state-of-the-art performance (Yasaka et al., 2018). "Deep learning is a group of approaches in machine learning, which aims to automatically find the essential features of data," Hinton and colleagues said in 2012. Deep neural networks (DNN), like standard neural networks, include artificial neurons organised into input, hidden, and output layers. However, unlike traditional neural networks, deep networks generally include a large number of hidden layers. Deep neural networks' hierarchical structure enables them to discover characteristics at several levels, each of which corresponds to a different degree of abstraction (Tirumala & Narayanan, 2015). Basic characteristics are learned in the first tiers and then presented in the deeper layers to build higher-level ideas. It is frequently used for a variety of data types such as pictures, audio, and text. In order for deep learning to be successful, it is important that hardware multiprocessing capabilities, notably general-purpose graphics processing units (GPUs), vastly improved data availability, and current advances in machine learning algorithms be used. By using non-linear functions successfully, deep learning algorithms may now automatically learn distributed and hierarchical characteristics as well as work with both labelled as well as unlabeled data (Ahmad et al., 2018). It's possible to split the methods into three categories: deep networks for unsupervised or supervised and hybrid techniques. We'll take a quick look at each of these techniques in a moment.

Deep networks for supervised learning: these networks give the ability to recognise and regress patterns. The network tries, based on the labels provided, to distinguish between the data components of various classes, although it is not always successful. In classification and regression tasks, the network learns to link input to the predicted output, allowing it to make better predictions (label). DNN, CNN, and recurrent neural networks (RNN) are examples of common supervised learning architectures. To construct a hierarchy, each layer in a DNN uses a variety of neurons. Next, the output of the previous layer is used as an input for the next. Each successive layer learns more patterns of input files. Lower layers learn low-level information, whereas higher layers learn high-level information (Ahmad et al., 2019).

Because of its multiple layer structure, Deep Neural Network is the most basic of this type. The diagram below depicts the architecture of DNNs.

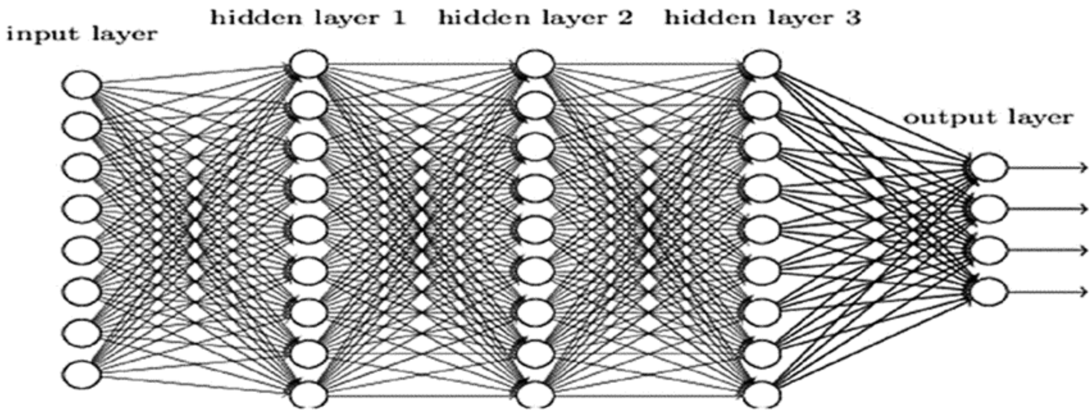


Figure 4.2: A fully connected feed-forward deep neural network

Convolutional Neural Network (CNN), developed in 1979, is another well-known architecture for supervised learning that was designed especially for visual processing such as pictures and movies. They have also proven highly advantageous to nearly every kind of data, including visual, audio and even text. These networks use convolutional, pooling and fully connected layers. While training, the coefficients of the filters/kernels are adjusted to learn significant features that will emerge in the data. Using the input, each filter is individually concentrated to create a function map, where higher activation values represent the situation of the features. The bottom layers of the CNN like DNN learn simple features, while the kernels learn more and more complicated features as we travel further into the network. The pooling layers decrease the complexity of characteristic maps while introducing an invariant translation point inside the network. The extraction procedure for the network features consists of the convolutional and bundled layers that recognise local features in the input. Local functionality is then integrated to offer global functionalities through fully connected layers. Despite being established earlier, it wasn't until thirty-three years later, in 2012, that CNNs gained prominence when they won the renowned ImageNet competition by an outsized margin. AlexNet was a network made up of convolutional layers, pooling layers, and fully connected layers (5, 3, 3) respectively. (Papandrianos et al., 2020; Wang et al., 2019).

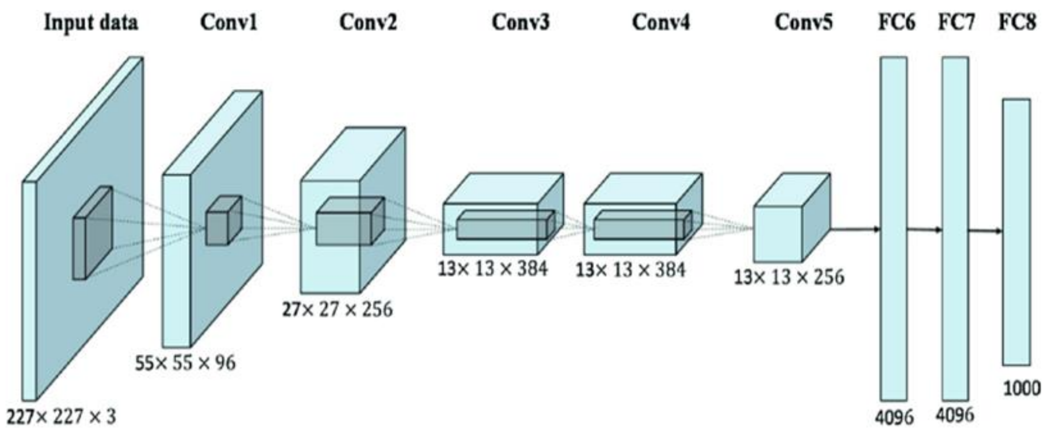


Figure 4.3: Convolutional neural network architecture (AlexNet)

Recurrent Neural Network (RNN) is type of deep network for supervised learning that was created to discover patterns in time series data that could not be done by DNN and CNN, despite their strength. Each unit in the RNN has recurrent connections, allowing the network to store information for a longer length of time. This allows the RNN in sequential data such as speech, film, and text to identify patterns. Long STM (LSTM) networks are a newer and more advanced type of RNN that increases the pattern recognition capacity of RNNs. (Qin et al., 2019)

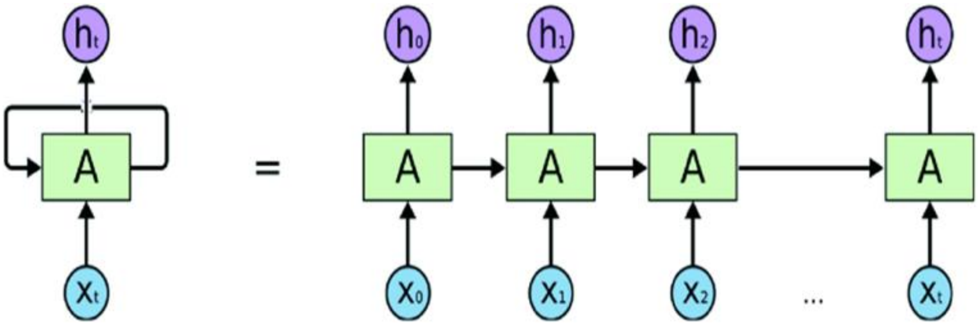


Figure 4.4: Recurrent Neural Network (RNN) architecture with single recurrent unit

Unsupervised learning using deep networks: Unsupervised learning refers to learning methods in which during the whole learning process, task-specified surveillance data is not given. Deep autoencoders and deep Boltzmann machines are two of the most widely used approaches for unsupervised learning (DBM). Both Autoencoders and Deep Bottleneck Networks are made up of two different components. The primary component tries to compress the input file to a small representation of its length. Afterward, the initial input of this brief representation is reconstructed with the second component. During training, the autoencoder aims at producing a compact display to recreate the original data at a minimal loss. This method, it learns extremely significant characteristics from the training data without supervision. The compact presentation of the autoencoder is generally utilised as a high-dimensional input feature vector and may be used for a number of applications, such as clustering, indexation, search and dimension reduction or integration in functionality. (Hinton & Salakhutdinov, 2006).

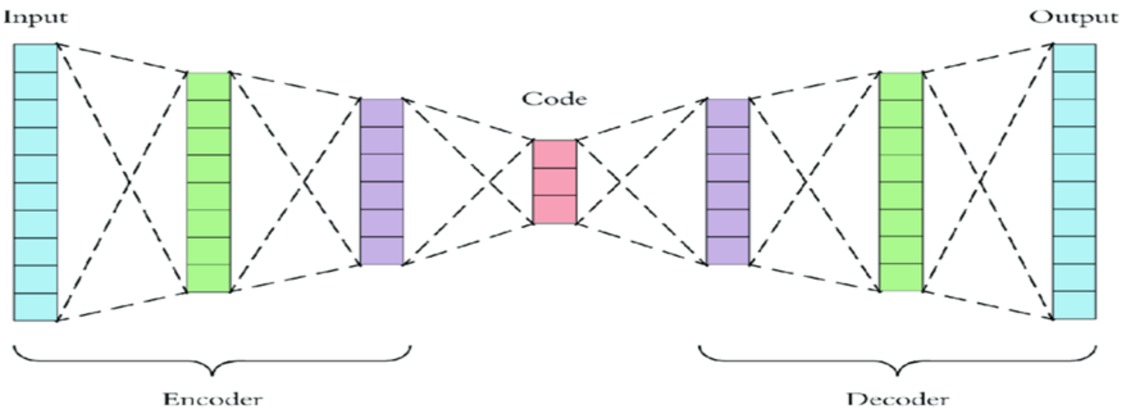


Figure 4.5: Architecture of a simple autoencoder demonstrating the encoder and decoder parts

Probabilistic generative models consisting many or several random layers are the Deep Boltzmann (DBMs). Undirected, symmetrical connections link the top two layers, but top-down, directed connections are connected to the lower levels from the layer over them. (Taherkhani et al., 2018).

The third technique is a hybrid strategy, and the aim might also be discrimination, which can frequently be significantly aided by the results of unsupervised deep networks. In supervised learning, deep networks are typically optimized and regularized. In the unsupervised training technique, for example, a large amount of non-labelling data may be used to determine the starting parameters for the next supervised learning assignment. If there is no discriminatory approach to supervised learning, the technique may be employed to estimate parameters using unattended learning in any of the deep unattended networks.

Deep Learning Applications

In a wide range of applications, profound knowledge has been employed, including computer vision, voice identification, virus detection, x-rays and cars amongst others. The availability of vast amounts of data, combined with extremely competent algorithms, has created enormous potential for academics to develop cutting-edge technologies. The analysis of multimedia content to solve difficult problems is highly competency-rich in deep learning algorithms including CNNs, RNNs, and LSTMs. The CNNs are ideal for classifying images, objects and objects, segmenting, increasing and restored images and video frames. RNNs and LSTMs, on the other hand, are intended for sequential data processing, such as video event recognition, speech recognition, and text image recognition. The two designs can also be used in conjunction to resolve complicated problems. CNNs, for instance, are employed as function extractors while LSTMs are utilized to discover patterns for event/action recognition in video frames (Qin et al., 2019). Both might alternatively be trained independently on the desired task before being combined during the inference phase. Furthermore, there is great improvement of these approaches in past years, and we anticipate further advancements in the future. Below are just a few of the breakthrough; computer vision, information retrieval, Natural Language Processing and multi task learning.

4.2.3 Natural Language Processing (NLP)

This is a branch of Artificial Intelligence and Linguistics that trains computers in human language statements or words. Natural processing of the language was designed to facilitate the life of the user and to satisfy his need to interact in the natural language with the computer. As not all users have a good knowledge of a particular language on their machines, NLP offers those who do not have sufficient time to study or perfect new languages. A language is either a collection of rules or a set of symbols. Symbols are mixed and utilized to transmit or broadcast information; it is also employed in nuclear medicine (oncology) (Kehl et al., 2019). The Rules have a tyrannical hold on symbols. Natural Language Processing is divided into two parts: Natural Language Understanding and Natural Language Generation, both involve the process of understanding and generating text (Figure 4.6).

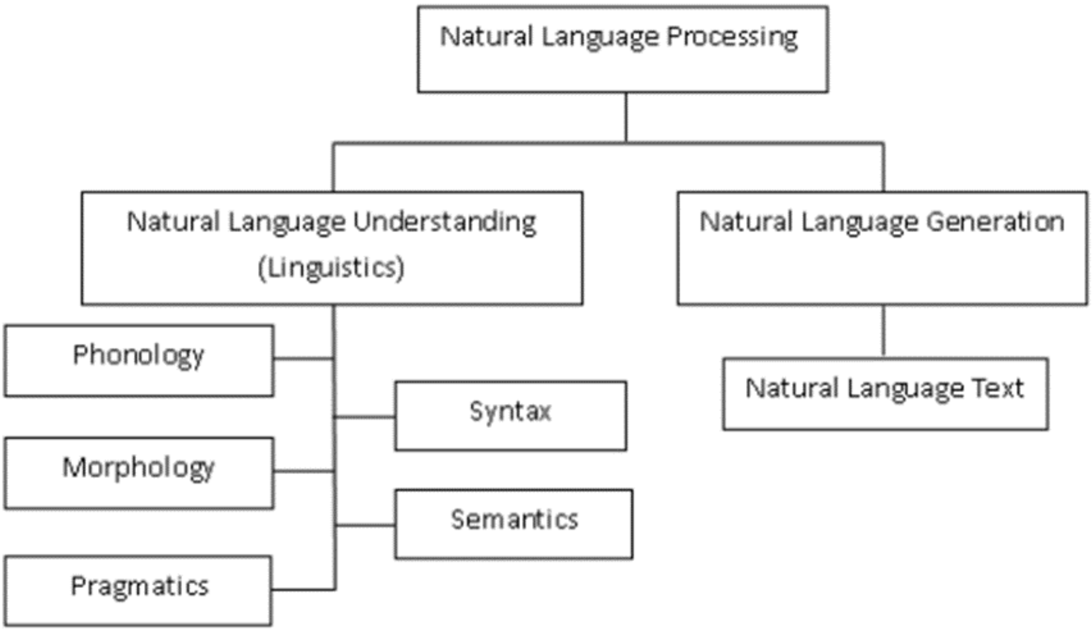


Figure 4.6: Broad classification of Natural language processing

Automatic Speech Recognition

ASR is an automatic machine-based process for decoding and transcript the language spoken. Automatic speech recognition (ASR) The auditory input of a speaker is obtained by a microphone from a standard ASR system and analyzed using a certain pattern, model or an algometric, which often comes in text form (Lai, Karat, & Yankelovich, 2008). It is important to distinguish between speech recognition and voice understanding (or speech identification), which is to recognize rather than transcribe the meaning of a speech. The recognition of speech varies from the recognition of voice, although speech acknowledgement refers to a computer's ability to identify what is said (i.e., spoken words), it combines the ability of a machine to detect speech (i.e., who said what is uttered)

4.2.4 Computer Vision

Computer vision is a branch of artificial intelligence that allows computers systems to extract meaningful information from digital pictures, videos, and other visual inputs — and then act or make suggestions based on that knowledge. If artificial intelligence allows computers to think, computer vision allows them to see, watch, and comprehend. Computer vision functions similarly to human vision, with the exception that humans have a head start. Human vision has the benefit of lifetimes of context to learn how to discern objects apart, how far away they are if they are moving, and if there is something wrong with a picture Computer vision teaches computers to do these activities, but it must do so in a much shorter amount of time, using cameras, data, and algorithms rather than retinas, optic nerves, and a visual brain. Because a system trained to check goods or monitor a production asset may evaluate hundreds of products or processes in a minute, detecting undetectable faults or problems, it has the potential to soon outperform human skills. Computer vision is utilized in a variety of industries, from energy and utilities to manufacturing and automotive - and the industry is expanding. (Li & Zhu, 2020).

Mode of operation of computer vision

A large amount of data is required for computer vision. It performs data analysis repeatedly until it detects distinctions and, eventually, recognize pictures. To teach a computer to detect vehicle tyres, for example, massive amounts of tyres pictures and tire-related objects must be given into it for it to understand the distinctions and recognize a tyre, especially one with no flaws. Machine learning employs algorithmic models to teach a computer about the context of visual data. If enough data is given into the model, the computer will "look" at the data and learn to distinguish between images. Algorithms allow the computer to learn on its own rather than having to be programmed to identify a picture. A CNN aids a machine learning or deep learning model's "look" by breaking down pictures into pixels that are tagged or labelled. It utilises the labels to conduct convolutions (a mathematical process on two functions to generate the third function) and anticipate what it is "seeing." In a series of iterations, the neural network executes convolutions and tests the accuracy of its predictions until the predictions begin to come true. It then recognizes or sees pictures in a manner comparable to humans. A CNN, like a person seeing an image from a distance, first discerns hard edges and basic forms, then fills in information as it executes prediction iterations. A CNN is used to comprehend individual pictures. A recurrent neural network (RNN) is similarly used in video applications to assist computers to comprehend how images in a sequence of frames are connected.

4.3 Artificial Intelligence application in Nuclear Medicine

AI applications in medicine are highly diverse and promising, and they are expected to have a wide range of effects (Hatt et al., 2019). The first phase involves the application of AI at the detector level, including modifications for the many physical processes linked to the detection process (like attenuation, scatter). AI may help procedures other than reconstruction, like denoising, segmentation, and fusion. Finally, AI is frequently used in the development of models based on picture data that may aid in the achievement of expected, tailored image-based therapy. The use of CNN to improve the noise characteristics of PET scanners employing large pixelated crystals and to estimate ToF (time of flight) directly from coincident digitized detector waveform pairs includes recent detector-level studies (Hong et al., 2018; Berg & Cherry, 2018). Integrating a deep neural network into the picture reconstruction process can enhance image quality (Gong et al., 2019). Deep learning approaches for PET/CT and PET/MR mitigation and registration have been proposed and demonstrated to produce highly accurate mitigation maps (Hwang et al., 2019). Deep learning was applied in the same context to improve maximum reorganization of the ToF PET data (MLAA). One of the most widely used image processing programs is denoise, which may be used to recover full-dose PET photographs from low-dose images or to filter directly reconstructed PET images. Deep learning methods are employed. (Gong et al., 2020). Automated lesion identification, counting, and fragmentation can be useful in diagnosis, treatment plan formulation, and response control in all radio (gene)mics applications. For a long time, techniques based on prior shallow frameworks were incapable of achieving the required levels of automation and accuracy to be completely integrated into clinical practise or to handle large numbers of radiochemical analysis patients swiftly. Some recent achievements include the usage of "old" machine learning technologies (Kyriakopoulos et al., 2020), whereas more and more people are depending on deep learning technologies to significantly improve both automation and performance. CNNs are indeed highly efficient in segmenting the medical image (Litjens et al., 2017). This is often explained by the fact that segmentation learning takes place at the voxel level, unlike classification tasks (one label per image) (one label per voxel). The network parameters may be learned effectively because of the vast amount of accessible learning data. For example, the approach with pre-trained CNN obtained the top score despite having very few training samples in the current PET functional volume segmentation MICCAI competition. In multimodal PET/CT segmentation, CNNs were also employed. (Müller & Kramer, 2021). A fully automated solution for this stage in the radiomics process should be developed to identify tumors and segment processes supported by a deep learning framework that removes this major bottleneck. Although the bulk of them are radiological rather than medical, predictive modelling and radio (geno) mics have already put a high emphasis on machine learning techniques. The evaluation of machine and deep learning techniques has shown a more efficient choice of features, stronger model development and harmonization of radiomic PET functions (Visvikis et al., 2019). There have been limited studies investigating the viability of CNNs employing deep networks as an end-to-end technology, with just a few examples of its application in medical imaging, like FDG PET and SPECT (Ding et al., 2019).

CHAPTER 5: METHODOLOGY

Articles on a liver tumor, liver lesion, artificial intelligence and nuclear medicine were extracted for bibliometric analysis studies related to the field of oncology. This study includes liver lesion and AI studies in nuclear medicine, which encompasses the application of AI techniques in PET, SPECT and hybrid methods such as PET/CT, PET/MRI amongst others in the early detection of liver lesions and tumors. The study includes articles from 1st of January 2000 to 30th April 2021 and we compared and analyze data related to the liver lesion, liver tumor and the AI techniques in nuclear medicine as illustrated by the table below;

Table 5.1: Key Words and Results Extracted from Scopus Database

Keyword	Number of results	Document type
Liver lesions OR liver tumor	1363	Articles
Liver lesion OR liver tumor AND detection	2410	Articles
Liver lesion OR liver tumor AND nuclear medicine	730	Articles
Liver lesion OR liver tumor AND artificial intelligence	286	Articles
Liver lesion OR liver tumor AND artificial intelligence OR nuclear medicine	308	Articles

Scopus, BidExcel, VOSviewer, is widely used in bibliometric analysis. Scopus is a collection of abstract and citation databases maintained by independent subject matter experts that is source-neutral. Scopus database includes more than 80 million records, 25 thousand and 700 serial titles, and more than 7000 publishers. Scopus covers fields like physical science (27%), health science (25%), social science (32%) and life science (16%). It equips scholars, librarians, and data analysts with strong discovery and analytics capabilities. Managers of institutional research and funding. Scopus strengthens the connections between individuals, published ideas, and organizations by delivering exact citation search results and automatically updating researcher profiles. Scopus improves institutional research performance, rank, and reputation while preserving the academic record's integrity. Scopus also provides search analysis and discovery features. Scopus provides keyword analysis future with detailed information about access types, year, authors, subject area, document type, source, keywords and others; in effect providing a more precise bibliometric analysis.

In this study, we focus on articles published, not on other documents like reviews, notes, book chapters, conferences just to name a few. It is multidiscipline that is, it includes articles published in various subjects like medicine, computer, engineering, technology amongst others. We included several subject areas to provide a better and clearer view of AI and its applications in the nuclear medicine field, more precisely in liver lesion and tumor detection. The articles from 1st of January 2000 to 30th April 2021 are included in the study for the application of artificial intelligence in nuclear medicine for the detection of liver lesions and tumors. We examine the analysis by three main factors; year of publication, source of publication, and subject areas for NM techniques that support AI algorithms in the detection of liver lesions and tumors.

We use Google scholar, IEEE, science direct, Springer Link, PubMed, and Scopus to extract proper information using liver lesions, liver tumors, AI algorithms/techniques and nuclear medicine techniques as keywords. VOSviewer software is used for visualization purposes. VOSviewer is used to visualize and analyze citations of articles, and in this, we are focus on the visualization for liver lesion and tumor detection with artificial intelligence in nuclear medicine.

CHAPTER 6: RESULTS AND DISCUSSION

We extracted 5251 articles in liver lesion, liver tumor, artificial intelligence and nuclear medicine, 2410 articles liver lesion and liver tumor detection, 286 articles liver lesion/tumor and artificial intelligence, 308 articles in liver lesion/tumor with AI in nuclear medicine, 154 articles on artificial intelligence application in nuclear medicine, 730 articles on the liver lesion and liver tumor in nuclear medicine, 1363 articles on the liver lesion and liver tumor and we selected 50 articles due to their impact factors and open access among these 5251 to do bibliometric analysis.

The figure below illustrates the number of articles per keyword.

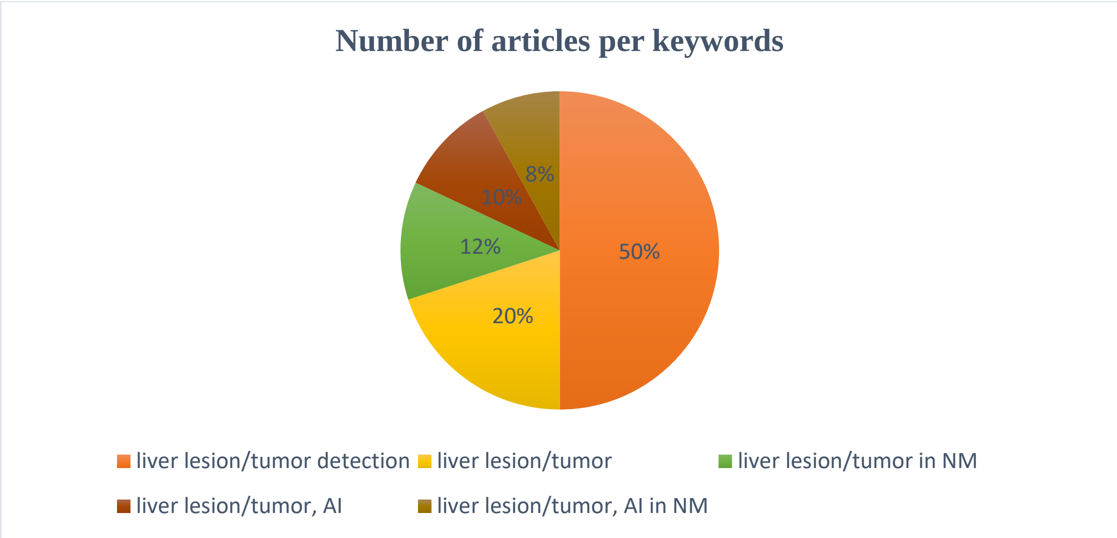


Figure 6.1: Percentage of articles per keyword

Keyword	Percentage of article
Liver lesion/tumor detection	50%
Liver lesion/tumor	20%
Liver lesion/tumor in NM	12%
Liver lesion/tumor, AI in NM	10%
Liver lesion/tumor, AI	8%

Table 6.1: Percentage of articles per keyword

Figure 6.1 and Table 6.1 vividly shows the percentages of the various number of articles per keyword. The highest percentage per number of articles is 50% for the liver lesion/liver tumor detection, followed by 20% for liver lesion and liver tumor articles, next is 12% for liver lesion and liver tumor search in nuclear medicine, also, 10% for the article on liver lesion/tumor, AI in NM and the lowest percentage is 8% for liver lesion and tumor in AI.

This last figure is in a way very significant because it shows the rapid growth and importance of this newly adopted technology in medicine for fast, early and accurate diagnostics of diseases (liver lesion and tumor detection). This affirms that yes artificial intelligence has an important place in the early detection of liver lesion and liver tumors in nuclear medicine.

The figure below shows the number of articles published concerning liver lesion and liver tumor detection with artificial intelligence in nuclear medicine from 2000 to 2021.

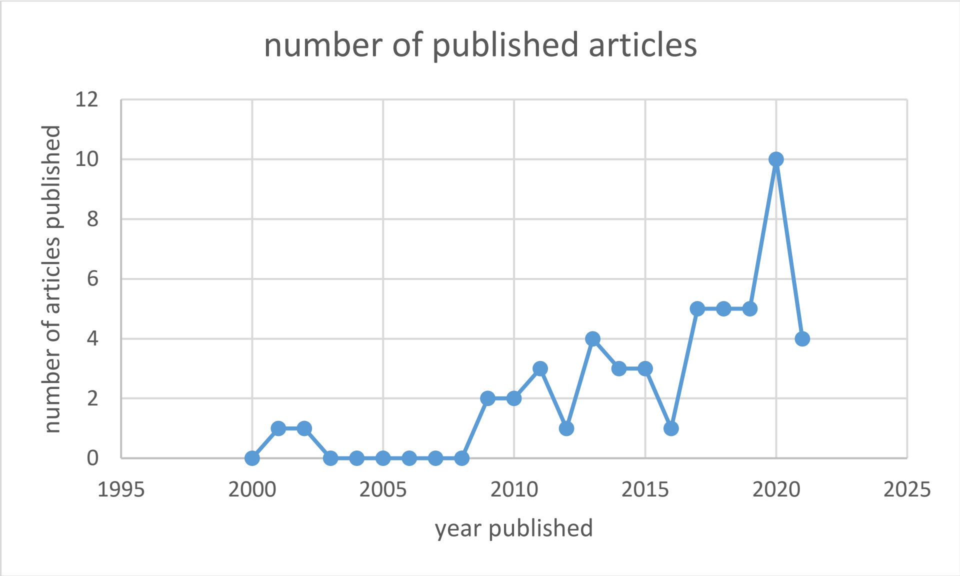


Figure 6.2: Number of published articles within period of study

From the graph, we notice a general increase in the number of articles published every year between 2000 to 2019 and a slight decrease in 2020 because of the interest diverted to covid-19 and a more significant decrease in 2021 because we considered articles from January to April 2021. The shape of the graph indicates that there is a significant increase or improvements for at least two reasons;

- ❖ The implementation of artificial intelligence technology in the field of medicine,
- ❖ Generally, more articles are published in this field with time demonstrating the impact of the liver lesion and liver tumors on human life. Thus, scientists and researchers are working to ensure an adequate solution to remedy the situation

We also considered particular areas and excluded others that are not important to our study. The area included are medicine, pharmacology, biochemistry, engineering, computer science and immunology. The figure below illustrates.

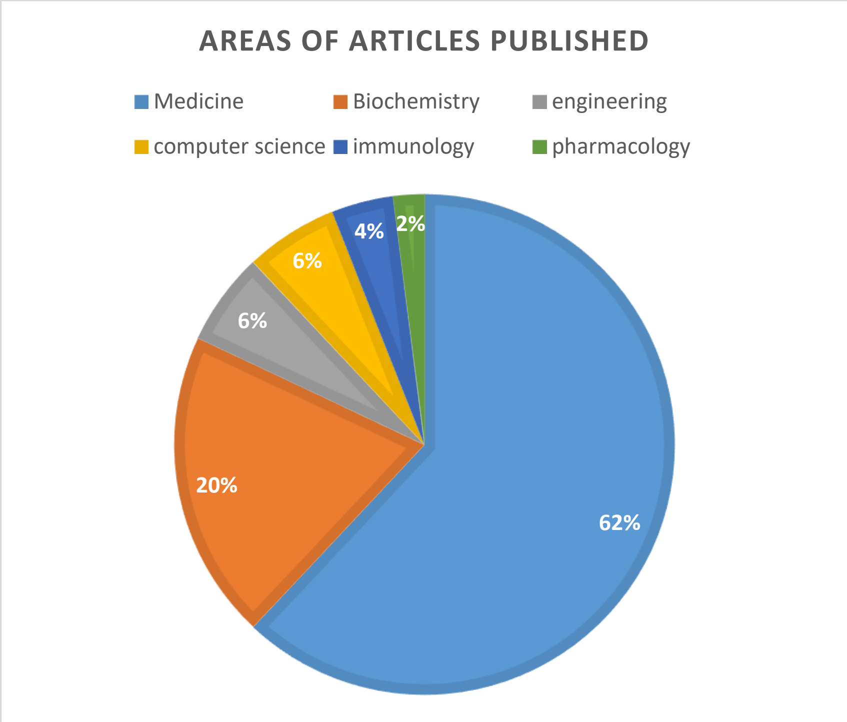


Figure 6.3: Area of interest of published articles

Area of interest	Percentage
Medicine	62%
Biochemistry	20%
Engineering	6%
Computer Science	6%
Immunology	4%
Pharmacology	2%

Table 6.2: Area of interest of published articles

In medicine alone there are more articles than all the other fields put together with 62%, followed by biochemistry 20%, 6% for engineering and computer science, 4% for immunology and 2% for pharmacology.

In this study we noticed that many countries contributed over time and are still doing so as shown in the figure below;

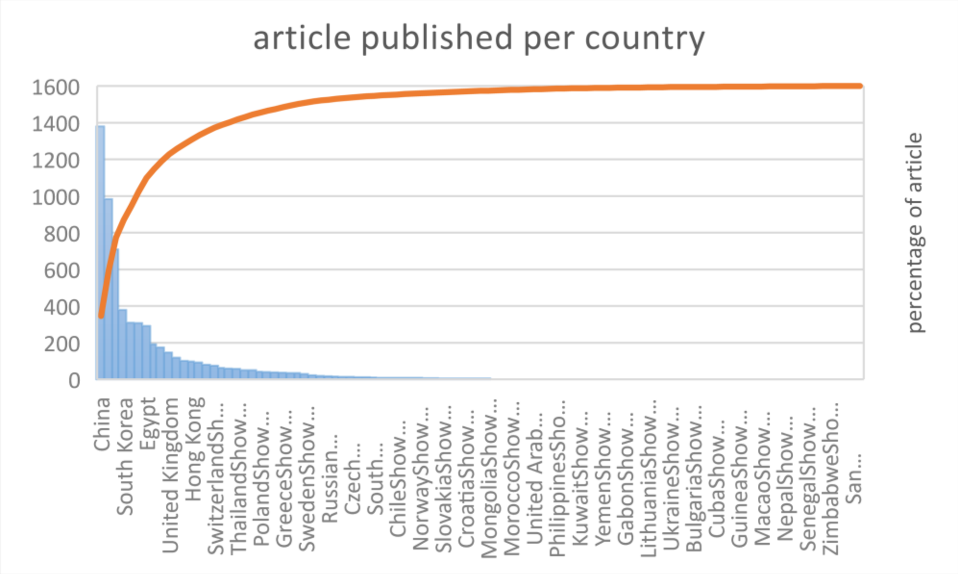


Figure 6.4: Countries and their percentage per article published

There are more than 100 countries that have contributed in one way or another with at least one published article illustrating that artificial intelligence is very important in nuclear medicine for the earl and accurate detection of the liver lesion and liver tumor.

There is been many articles published and a lot of collaboration as well. We use VOSviewer to illustrate as seen in the figure below;

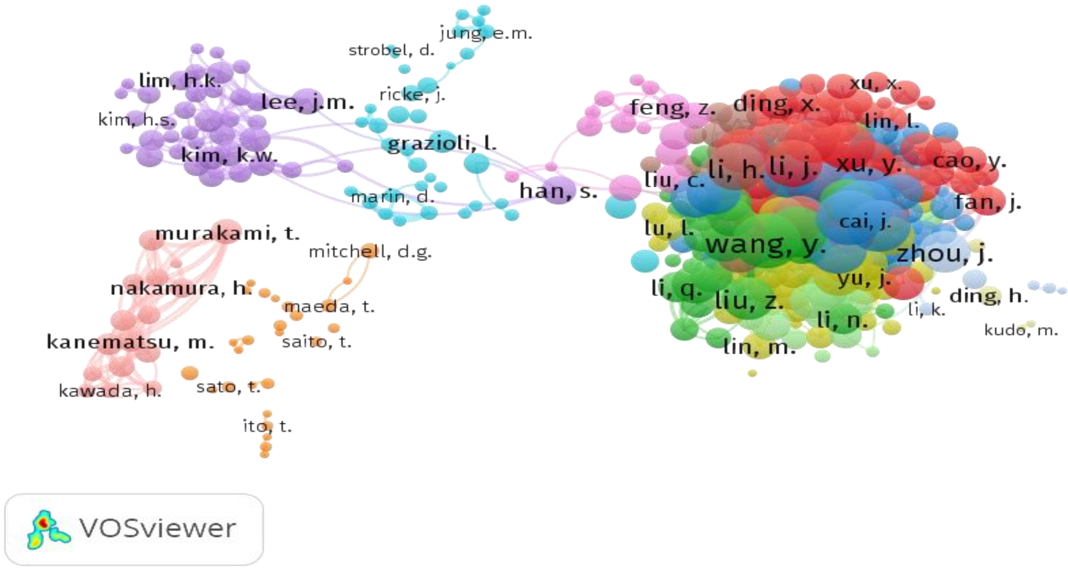


Figure 6.5: VOSviewer co-authorship map on articles in liver lesion and tumor detection

Each cycle represents an author, the size of the cycles shows the activity of authors measured in terms of co-authorship, the links show the collaboration between them, the stronger the link the more the co-authorship. The clusters with the same color show authors in the same field. Sharing ideas or knowledge is vital for intellectual growth and adds more value, likewise collaborating adds more value. From our map in figure 6.5, we can appreciate the collaboration from the links on the map. Having many clusters tangled together illustrates a strong collaboration between authors hence the importance of artificial intelligence in nuclear medicine for the earl and accurate detection of liver lesion and liver tumor.

We also noticed that during the last decade, there has been improvement in algorithms used in Artificial Intelligence, machine learning which is a subset of AI that has algorithms like SVM, amongst others, more development or advancement in technology saw the birth of Deep Learning derived from machine learning, examples of deep learning algorithms are deep convolutional neural network or deep CNN, RNN. In the last decade there is CNN and RNN have emerged with more sophisticated and advanced ways of image recognition. This is also applicable in nuclear medicine. Figure 6.6 illustrates the relationship between AI, ML and Deep Learning.

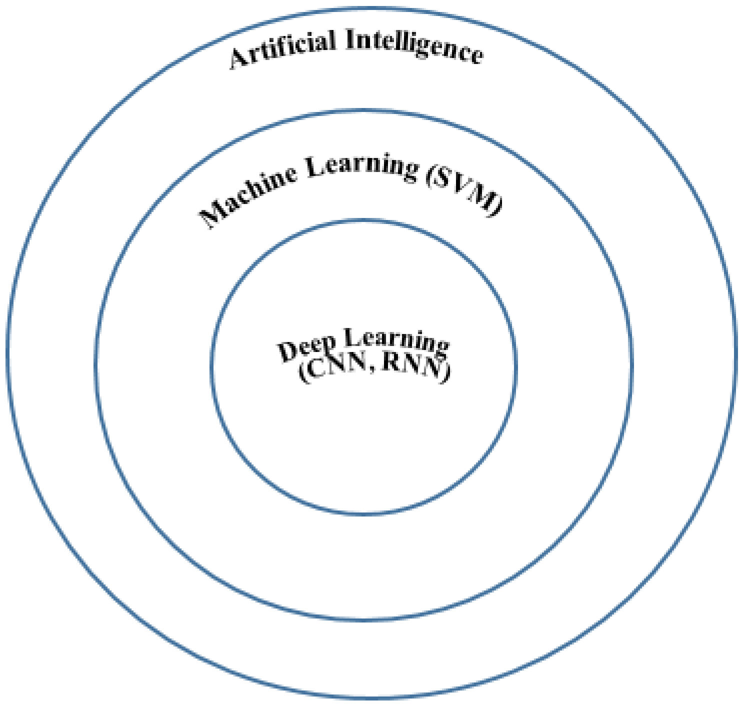


Figure 6.6: Relationship between AI, ML and Deep Learning

Different algorithms have been used throughout this study from 1st January 2000 to 30th April 2021. We obtained the accuracy, sensitivity and specificity by calculating their averages from the 50 articles we selected at random. There is a general increase in the accuracy, sensitivity and specificity. Within this period, machine learning with algorithms such as SVM and Deep learning with algorithms such as deep CNN and DNN, was widely used (Das et al., 2019). There is been improvement in the application of artificial intelligence algorithms.

Scopus was just one of the databases we used as we also used Google scholar and found articles using the same keywords from different sources (search engines) as illustrated on the pie chart below;

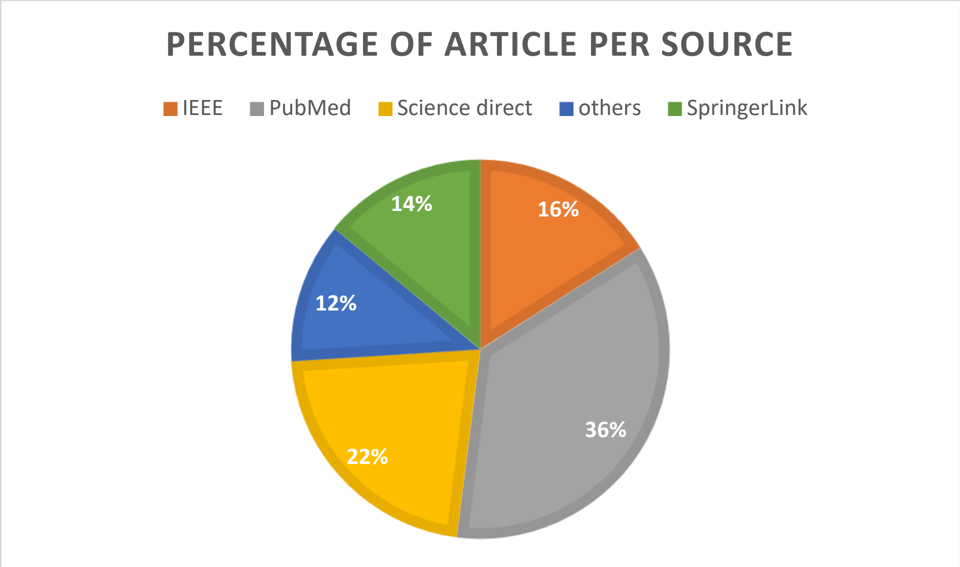


Figure 6.7: Percentages of articles per source on google scholar database

Source	Percentage
PubMed	36%
Science Direct	22%
IEEE	16%
Springer Link	14%
OTHERS	12%

Table 6.3: Percentages of articles per source on Google scholar database

From the pie chart and table 6.3, it is clear that several journals are interested in articles concerning liver lesion and liver tumor detection, artificial intelligence application in nuclear medicine. Thus, showing the importance of artificial intelligence in nuclear medicine in the detection of the liver lesion and liver tumor. PubMed has more articles 36%, followed by Science direct 22%, IEEE 16%, Springer Link 14% and other sources 12% which is the lowest.

The following figure shows articles from the same sources but this time we used the Scopus database and the results obtained are in figure 6.8

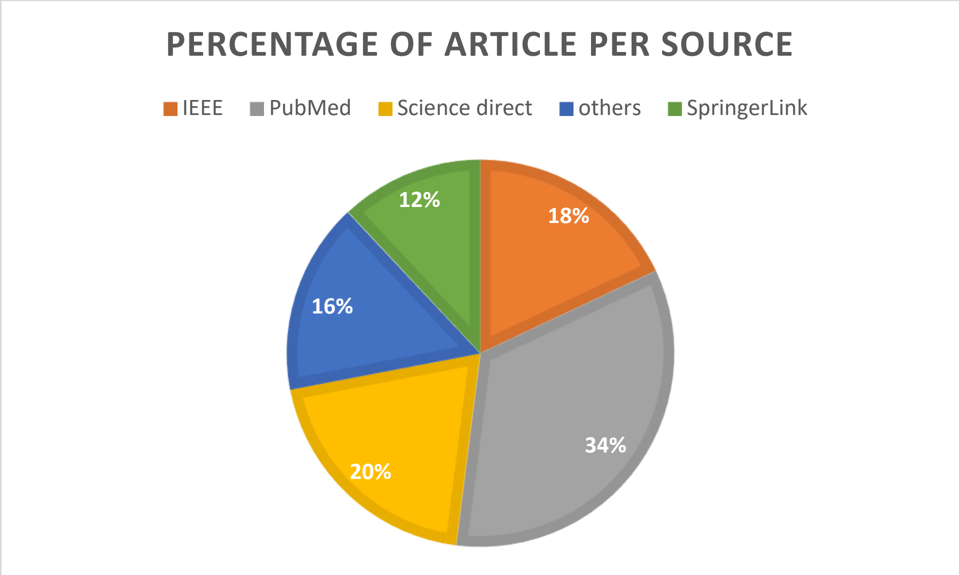


Figure 6.8: Percentages of articles per source on Scopus database

Source	Percentage
PubMed	34%
Science Direct	20%
IEEE	18%
OTHERS	16%
Springer Link	12%

Table 6.4: Percentages of articles per source on Scopus database

Scopus database also had lots of articles from several journals that are interested in articles concerning liver lesion and liver tumor detection, artificial intelligence application in nuclear medicine. Thus, showing the importance of artificial intelligence in nuclear medicine in the detection of the liver lesion and liver tumor. PubMed has more articles 34%, followed by Science direct 20%, IEEE 18%, Springer Link 12% which is the lowest and other sources 16%. Hence the importance of AI in nuclear medicine for early and accurate detection of liver lesion and liver tumor.

In this study we also noticed that there were different nuclear medicine techniques used in the detection of liver lesion and liver tumor. The chart below illustrates the various techniques and their percentages.

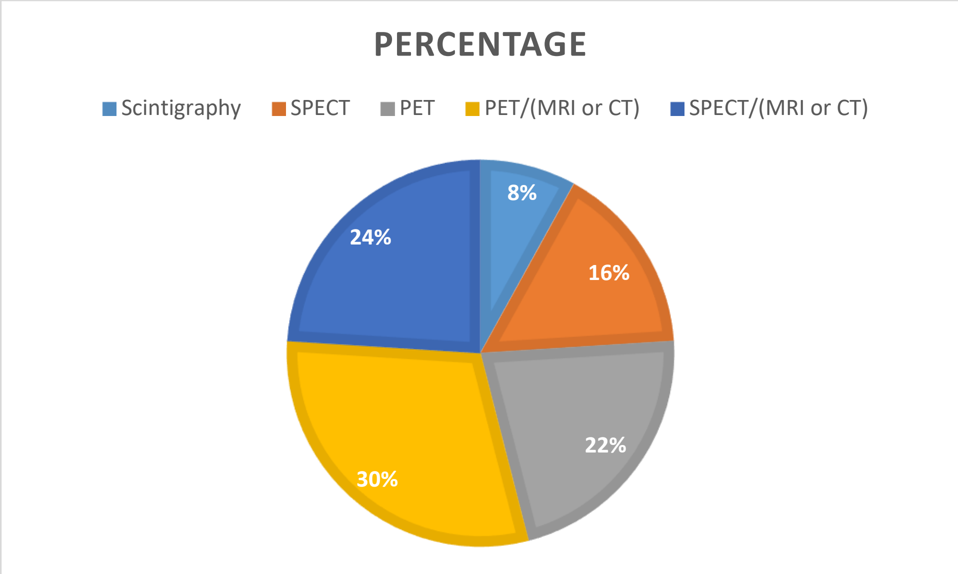


Figure 6.9: Different nuclear medicine techniques and their percentages.

Nuclear medicine technique	Percentage
Scintigraphy	8%
SPECT	16%
PET	22%
PET/ (MRI or CT)	30%
SPECT/ (MRI or CT)	24%

Table 6.5: Different nuclear medicine techniques and their percentages

From the above figure, it is clear that even among the different nuclear medicine techniques, they are some that are preferred to others as per their difference in percentages; from the 50 articles we selected at random, PET 22% is mostly preferred to SPECT 16% due to its spatial resolution, physical nature of nuclear decay of positrons and the scatter radiation can be calculated same as their hybrid methods PET/ (MRI or CT) 30%, SPECT/ (MRI or CT) 24%. These hybrid methods are much more preferred than the individual or single techniques because they not only provide 3D images like PET and SPECT but also provide the quality of whichever technique is combined with them. Scintigraphy 8% is the least because it provides just 2D images.

CONCLUSION

According to this study, Bibliometric analysis of liver lesion and liver tumor detection with artificial intelligence in nuclear medicine. Which was aimed at evaluating the different application of Artificial Intelligence algorithms in detecting liver lesion and liver tumor. After the survey it was noticed that many articles are published, the number of countries involved or interested, the collaboration of authors, the improvement in artificial intelligence algorithms in terms of accuracy, sensitivity and specificity affirms that artificial intelligence has a place in nuclear medicine and it also improves the effectiveness of nuclear medicine output. Thus, the high-quality evidence, robust reporting standards with external validation and comparison to health-care specialists are recommended as first-line for AI application in the medical domain.

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APPENDICES

Appendix 1: Ethical Approval Document

NEAR EAST UNIVERSITY

ETHICAL APPROVAL DOCUMENT

DATE: 01/09/2021

To the Institute of Graduate Studies,

For the thesis project entitled as "BIBLIOMETRIC ANALYSIS OF LIVER LESION AND LIVER TUMOR DETECTION WITH ARTIFICIAL INTELLIGENCE IN NUCLEAR MEDICINE", the researchers declare that they did not collect any data from human/animal or any other subjects. Therefore, this project does not need to go through the ethics committee evaluation.

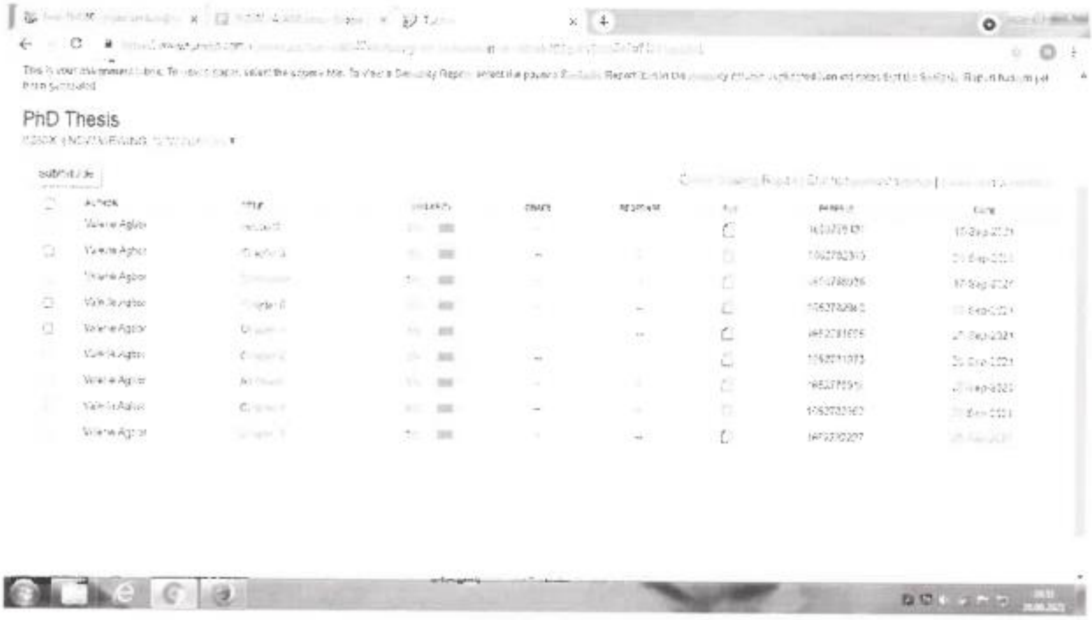
Title: Prof. Dr.

Name Surname: TERIN ADALI

Signature:

Role in the Research Project: Supervisor

Appendix 2: Signed Similarity Report



Prof. Dr. Terin Adali

Appendix 3: References of Articles Used in Analysis

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