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Development of webpage for radiotracers of different organs

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ABSTRACT

Molecular imaging is the most advanced area of medical imaging technology that emphasizes on the imaging molecules of medical importance as opposed to the traditional techniques for getting molecular information from conserved samples of tissue in exchange for the ability to non - invasively monitor of all biochemical activities taking place within an organism in real time. The complete process has been dividing into four major steps like Information collection, Analysis, Comparison between radiotracers and solution generation. Information on different types of radiotracers will be collected along with their unique physical, chemical, and radiological properties. The radiotracers production constraints, expectations of radiologists with an ideal radiotracer will be noted. Once the desired information is collected, will be analysed as per the requirement in image modality. Radiotracers analysed as per their usage, success rate in production, market share, application in different diseases etc. to create a design for creation of ideal radiotracer. In the designing of the webpage which help radiologists in guidance for the selection of appropriate radiotracer for a specific organ After the identification of more stable radiotracers for different parts of the human body. A responsive webpage is design for radiotracer as tool for selection. The webpage is made with the use of bootstrap algorithm. The responsive webpage is design with the use of Sublime test software.

Keywords: Molecular imaging, Radiotracers, Medical Imaging, Non-invasive, Bootstrap, Image quality, Sublime text

1. INTRODUCTION

The use of PET (Positron Emission Tomography) for molecular imaging in the area of oncology has gained popularity during the last decade. PET imaging is a non-invasive method for gathering both quantitative and qualitative data on biological mechanisms. It incorporates CT (computed tomography) and a radioactive tracer. Depending on what the doctor wants to assess, a particular sort of tracer is employed. To successfully deploy

PET imaging in clinical settings, studies and research are required in a number of crucial areas, including radiotracer availability and selection. Radiopharmaceuticals or positron-emitting radioisotopes attached to an organic ligand are known as radiotracers (targeting agent). The selection of an acceptable radionucleotide and vector molecule, their requirements for combination, the location and type of the molecular target, the intended use, and the radiopharmaceutical's short half-life are all factors that are considered. Clinically validated radiopharmaceuticals are produced in accordance with regulatory standards for medications intended for IV (intravenous) administration after toxicological investigations [1]. PET scanning is among the widely used molecular imaging techniques. A kind of medical imaging known as molecular imaging produces a detailed inside picture of body at molecular and cellular levels. Molecular imaging, in contrast to other diagnostic imaging techniques like PET, X-rays, and CT, allow doctors a larger picture of how the body functions and can assess its biological and chemical mechanisms [2].

Due to their special chemical and physical characteristics, radiotracers are crucial in nuclear medicine and have several uses in diagnostic radio imaging. To enable non-invasive and quick evaluation of functioning of organs, pathology, and physiology, perfusion radiotracers and molecular probes are utilized. Progress in radiotracer coordination chemistry in last 2 decades and recent advancements in reconstruction algorithms and detector technology, SPECT's (Single Photon emission computed tomography) spatial resolution is similar to that of spatial resolution of PET [3]. Gallium 68 radiopharmaceuticals have been employed in a variety of therapeutic applications recently. Lutetium 177 and Gallium 68 also function together to offer diagnostic molecular imaging, which is then accompanied by individualised therapy depending on the results of the scans. For instance, the clinical usage of 68Ga-radiopharmaceuticals in diagnostic imaging has expanded as a result of PSMA targeting tracers such PSMA-I&T, PSMA-11, as well as PSMA617. Ga 68 PSMA-11 (Gallium 68 PSMA-11), an initial drug for PET imaging for PSMA positive prostate cancer, was given FDA approval in 2020 [4].

Prostate cancer is the third most frequent malignancy in the US. As a result, it increases the demand of better imaging, diagnostic, and therapeutic methods [5].

Radiotracers are broadly utilised in the field of oncology, particularly in the diagnosis of prostate cancer, neuroendocrine tumours, breast cancers, insulinoma pancreatic islets, endometrial cancers, ovarian cancers, gastrointestinal stromal tumours, renal cell cancer, and the labelling of carcinoembryonic antigen and human epidermal growth factor receptor family [6].

Due to their widespread availability and advantageous radiation characteristics, radiotracers are becoming more and more prevalent in PET molecular imaging. Radiologists face difficulty in choosing the best radiotracers for a particular organ's diagnosis and therapy. Understanding the key radiotracer applications in molecular imaging, utilisation in various organs, modality, and potential for future technological implementation are the main goals of this review. The selection matrix for most stable radiotracers in molecular imaging of diverse organs is being created [7].

A class of radioactive elements known as radiopharmaceuticals are utilised for either medicinal or diagnostic purposes. Generally, radioactive materials releasing gamma or beta rays are employed for medicinal purposes

whereas those emitting alpha particles or auger electrons are utilized for diagnostic purposes. Radiotracers are utilised in very small amounts and ingested systemically by the body. In PET scans, however, there are some regions of hyperintensity that indicate localisation to particular tissues due to their biomolecular characteristics. When opposed to non-radioactive drugs, radiopharmaceuticals actively generate radiation, that makes storage more challenging. Radio-imaging is being utilised to detect diseases, examine tissue physiology, and monitor therapies, including implications in customised drug [8].

2. LITERATURE REVIEW

The radiation that is emitted from radiotherapeutic elements either serve palliative purposes or kill the target cells. However, the spinal cord, brain, bone marrow, and kidneys are severely affected by radiation since it is poisonous to biological tissues. As a result, the radiopharmaceuticals are selected in a way that should cause them to prefer tumor tissue over other types of healthy tissue [9].

Radiopharmaceuticals includes a bound radionuclide that is, a radioactive isotope attached to an organic ligand (targeting agent) and its intent is to lead the radionuclide to a site to be treated or to get the images. Nuclear medicine is a branch of radiology that utilizes radiopharmaceuticals to assess biological processes, organ function, and to choose the best course of treatment, particularly for cancer. Recruiting the metal complexes and radionuclides already used as radiopharmaceuticals is the goal of this work. Technetium (99mTc) compounds such methylene diphosphonate MDP-99mTc and sodium pertechnetate, as well as compounds of thallium (201Tl), indium (111In), iodine (123I and 131I), gallium (67Ga, 68Ga), sulphur (35S), chromium (51Cr), fluorine (as fluorodeoxyglucose, sodium fluorine and 18F-FDG, Na18F), and phosphorus (32P), are the primary metal complexes. These radiotracers are used in the early detection of several disorders, most notably cancer. Technetium compounds are now primarily employed in radiotracers all over the world. The radioactive 18fluorine has the best properties for PET, while 99mTechnetium has the greatest properties to mix with gamma cameras [10].

2.1 Application of radiopharmaceuticals

There are two main applications for radiopharmaceuticals. First imaging modality involves the administration of radiopharmaceuticals by oral, inhalation, or intravenous in order to visualise the essential organs that are impacted, such as the lungs, kidneys, heart functions, and thyroid, as well as the blood flow and bone metabolism. Second, in therapeutic modalities, the affected organ is targeted with specialised radiopharmaceuticals that give a high dosage of radiation [11].

It consists of two components: radionuclide (a radioactive element) that allows for external scanning, linked to a non-radioactive component, a bioactive molecule, drug, or cell (white and red blood cells, for instance, that have been labelled with a radionuclide), that functions as a ligand or carrier, and is in terms of handling the radionuclide to a particular organ [12].

2.2 Radiopharmaceuticals interaction with the target organ

Radiopharmaceuticals are chemical compounds which are absorbed by target organs. Then, these chemicals are radiolabeled so that it is possible to study their blood flow, localised concentration, or the cancer stage in

certain organs. For instance, 177Lutetium (177Lu) is synthesized from 176Ytterbium (176Yb), which is irradiated to produce 177Yb, which then quickly transforms back into 177Lu. Cancer is treated with 90Yttrium (90Y), particularly non-Hodgkin lymphoma. As additional radiation agents, 153Sm (153Sm), 32phosphorus (32P), and 131Iodine (131I) are also employed [13].

Tracers are compounds having particular nuclear, atomic, biological, physical, or chemical characteristics that may be used to recognise, monitor, or track the behaviour of different biological, physical, or chemical mechanisms. Chemical compounds that have had one or more atoms replaced out for radioactive isotopes are known as radioactive tracers. The radiotracer, which is radioactive, aids in the detection and diagnosis of certain biological and chemical processes, are often used to conduct diagnostic tests on industrial reactors, such as evaluating the flow rates of gases, solids, and liquids. In imaging modalities, radiotracer are used for flow visualisation through various techniques, including SPECT, PET and CARPT (Computed Radioactive Particle Tracking). Radiotracers are often employed in industry for process study, optimization, and troubleshooting, like in the transfer of sediments, as well as for the detection of particular reasons of inefficiencies in processes or plant operation. A very important and essential stage in radiotracer study is choosing the right radiotracer. The radiotracer exhibits the same behaviour as the element that has to be monitored. Therefore, a viable radiotracer in industry must meet a few fundamental conditions, including a reasonable radiation energy and half-life, chemical and physical stability, and ease of detection. To prevent inaccurate results in systemic use, it is important to understand the radiotracer's internal behaviour, phase change, decomposition, chemical interaction with the components system before using, or undesired adsorption and absorption [14].

2.3 Application in diagnosis and treatment of diseases

Radiopharmaceuticals have various applications in oncology, neurology, hematology, cardiology, thyroid applications, and others. Further, application in oncology growing day by day and not limited to early cancer diagnosis, treatment effectivity determination, basic cancer physiology determination etc. For example, Fluorine-18 fludeoxyglucose is indicated for assessing abnormal glucose metabolism in tumors. USFDA has approved around 50 radiopharmaceuticals for diagnostic as well as therapeutic use. There are over 30 approved products of Technetium alone for diagnosis purposes; even for the same indication, various radiopharmaceuticals are in market. For instance, Vizamyl, Amyvid, and Neuraceq are approved for Alzheimer’s disease only [15].

The key players are focusing on obtaining approvals or adopting strategies such as mergers and acquisition to drive the market growth and strengthen their position in nuclear medicine market. For example, the acquisition of North American rights of Lymphoseek, a radiopharmaceutical diagnostic imaging agent in 2017 by Cardinal Health, Inc. from Navidea Biopharmaceuticals, Inc. opened the opportunity to earn upto US$ 227 million for Navidea through 2026.Coronavirus pandemic has negatively impacted the development, production, and supply of nuclear medicines and affected growth of the radiopharmaceutical businesses of various companies across the globe, as COVID-19 pandemic has led to lockdown in several countries, globally. This lockdown has resulted in closure of industrial establishments, except manufacturing of essential commodities and disruption in supply chain of the radiopharmaceuticals and kits for diagnostic and therapeutic use. This has led

to shortage of supplies and difficulty in access to therapeutic tracers such as 123I, 123I-MIBG, and 131I-MIBG, cold kits access etc. Other factors which restrain the growth of the radiopharmaceuticals in nuclear medicine market include; closures of nuclear reactors disrupting the supply of isotopes (e.g. shut down of National Research Universal (NRU) in Chalk River, Ontario, Osiris reactor in France), elevated development costs of radiopharmaceuticals comparative to return on invested capital, developing cost of a drug for diagnostic imaging to commercialization is in US$ 100 to US$ 200 million range, heavy dependency on availability of Technetium-99m for diagnostic use [16].

3. METHODOLOGY

Molecular imaging using PET scan is becoming more and more reliant on radiotracers because of their low cost and advantageous radiation characteristics. Radiotracers has a growing influence in molecular imaging by PET, due to its easy availability, good radiation properties. Radiologists faced difficulty in selecting the right radiotracers for specific organ diagnosis and treatment in order to provide the information regarding radiotracer the webpage is developed. The complete process has been dividing into major steps: Information collection, Analysis and solution generation as shown in the figure 1. Firstly, information on different types of radiotracers will be collected along with their unique physical, chemical, and radiological properties. The radiotracers production constraints, expectations of radiologists with an ideal radiotracer will be noted. Once the desired information is collected, will be analyzed as per the requirement in image modality. Radiotracers will be analyzed as per their usage, success rate in production, market share, application in different diseases etc. to create a design for creation of ideal radiotracer**.** A separate focus will be done on the market aspect of the radiotracers, current trends, and its use in hospitals, set up cost evaluation, customer satisfaction, ease of usage, earning vs investment ration, market capture, investment in research and nuclear reactors etc. to get financial implications in radiotracers usage and development of a business model. After this exercise, the final approach will be to rationalize the workflow of suitable radiotracer, develop business model using risk benefit approach, design a selection matrix which will help radiologists in making choice for the appropriate radiotracer for a specific organ and diseases [17].

Figure 1: Workflow of radiotracers selection [17].

3.1 Information collection of basic mechanism of action of radiotracer

Radiotracers work in similar method as antigen- antibody reaction like lock and key. A radiotracer is basically a chemical substance labelled with radioactive isotope. Once injected, it binds to the specific tissue target, like ligand and then is expressed at the tissue level. The radiotracer being radioactive, decays by emitting DNA damaging radiations or energetic beta and gamma particles. Same is imaged using PET. There are various radiotracers available in market which are produced with the use of Gallium, Fluorine and FDG [18].

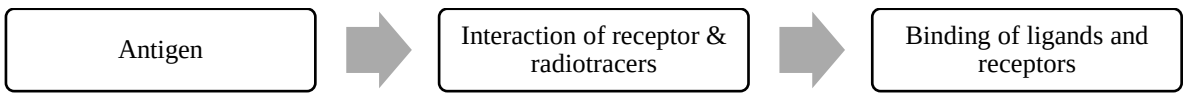

Figure 2: Basic mechanism of radiotracers [18].

3.1.1 Basic mechanism of Gallium-68

Ga is an element with atomic symbol Ga, atomic weight 69.7 and atomic number 31. It is a group 13 of the periodic table and share similar properties like the other metals of the group (aluminum, indium, and thallium). It is a trivalent, rare trace metal with silver texture. It is liquid above room temperature and found in bauxite and zinc ores**.** Generation of Ga-68 in this the parent radionuclide is Germanium 68, from which Gallium 68 is generated vide radio decay as shown in the figure 3. GE- 68 is fixed on the resin type column chromatography, which then decay into Ga 68 continuously. The Ga-68 is removed from the generator by eluting it off using desirable reagent. Principle of elusion in the generator, HCL solution is the eluting agent. Ga 68 being soluble in the HCL solution gets dissolved and elutes off the column as gallium chloride (GaCL3). Ge-68 on the other hand is insoluble in the HCL solution and therefore, remains fixed on the column and continues to decay to provide additional Ga68 in further elution. The GE 68 remains fixed on the column throughout the process and is surrounded by heavy lead shield as shown in the figure 3 [19].

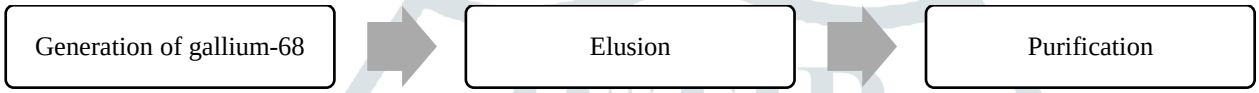

Figure 3: Generation of Ga-68 [19]

Purification of the Ga-68 is eluted in the form of GaCl3 and so needs to be purified to make it usable by patients as shown in the figure 4. The generator is so designed that the HCL elution and Ga-68 elution occurs in two different vials.GA-68 FAPI i.e., Gallium 68 FAPI (Fibroblast activation protein Inhibitor) is the main Gallium radiotracer used in imaging. It works in the same principle as discussed earlier i.e., Antigen Antibody interaction. The fibroblast cells, which are found throughout the body, often express dipeptidyl peptidase 4, but not much or no FAP. However, unlike the similarly related dipeptidyl peptidase 4, that only has exopeptidase action, malignant fibroblasts selectively produce FAP, that also has endopeptidase activities. Fibroblast activation protein (FAP) is highly expressed in the stroma of several tumour entities particularly colon, pancreatic, and breast carcinomas and characteristic biomarker for cancer detection inhibitors (FAPIs) consequently, have been already designed as cancer drugs. The radiotracer example ^{68}Ga-FAPI-2 is designed in similar fashion for PET imaging. The radiotracer due to similarity in structure, binds to the target receptor and being inhibitor does not express the proteins. However, the radioisotope Ga 68 decays and emits beta and gamma particle which is then visualized using PET imaging. Recently, quinoline-based PET tracers which function as a FAP inhibitors (FAPIs) have also been formed. A common diagnostic technique for detecting cancer, including colon, neck and head, pancreatic, breast, and lung cancer, is 68GaFAPI PET/CT [20].

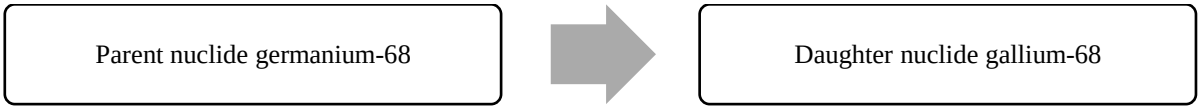

Figure 4: Half-life of gallium 68 [20].

3.1.2 Basic mechanism of Fluorine-18

Fluorine-18 is produced either a cyclotron or linear particle accelerator. The radioactive fluorine 18 could be produced by small cyclotron in two various chemical forms: Electrophilic fluorine and Nucleophilic fluoride as shown in figure 3.7. Enriched [^{18}O] water is bombarded with high energy protons (~18 MeV protons),

leading to formation of Fluorine in the form of a water solution of [^{18}F] fluoride, which is further used to produce various radio pharmaceuticals chemically. In the figure 3.7 the process of breakdown of the Fluorine-18 is shown. The fluorine produced is in the form of a water solution of [^{18}F] fluoride, which is then used in a rapid chemical synthesis of various radio pharmaceuticals. cyclotron-based F-18 production; cyclotron-accelerated particles are bombarded on [^{18}O] water target and ^{20}Ne gas target [21].

3.1.3 Basic mechanism of F-18 (Fluorine 18 Fluoride D oxy Glucose)

A radioactive fluorine-18 radionuclide replaces the hydroxyl group at region C-2 of glucose to produce ^{18}F FDG, a glucose analogue. The US Food and Drug Administration has given ^{18}F FDG approval for clinical use in PET imaging, and it is often used in a variety of purposes, including evaluation of glucose metabolism in the brain, heart, and lungs. ^{18}F FDG is manufactured in the same way as Fluorine18. At the second position of glucose, a hydroxyl group (OH) is replaced and combined with ^{18}F as shown in figure 5. In a cyclotron, one hydrogen atom from regular glucose molecules is swapped out for an atom of radioactive fluorine to form FDG. FDG is administered as a multidose vial or as a single dosage in a syringe and is kept at a regulated room temperature. For body scanning administered by saline IV, the suggested dosage of ^{18}F FDG for an adult (70 kilograms) is between 185 and 370 MBq (5 and 10 mCi). It gets absorbed by body within 60 minutes, and 45 minutes after the absorption, scanning is done to take desired imaged decays by emitting a positron, which further collides with electron of human body x, with release of gamma radiation by annihilation process. The amount of ^{18}F-FDG that accumulates in the tissue over a specific period (Standardized Uptake Value (SUV)) is used to calculate the rate of glucose uptake by that tissue [22].

Figure 5: Cyclotron based production of ^{18}F-FDG [22].

3.2 Analysis of radiotracers

In the comparison of F-18 FAPI and Ga-68 FAPI comparison of performance for improved picture quality. When used in sarcoma patients' PET (positron emission tomography), 68Ga-FAPI46 has shown significant tumour uptake with increased tracer uptake in the majority of primary and metastatic lesions, gallium 68 fibroblast-activation protein inhibitor PET/CT is reported to be superior to fluorine 18 radiotracer (FDG) PET/CT in the identification of metastatic and primary lesions in duodenal, colorectal, and gastric malignancies. Primary lung cancer has a high detection rate on [18F] F-FAPI PET/CT. Using 18F-FAPI PET/CT, the tumour delineation was more distinct. Higher lesions than [18F] F-FDG PET/CT, particularly in the brain, lymph nodes, and pleura. For main staging of LAD, [18F] F- FAPI was superior to [18F] F-FDG. However, compared to [18F] F-FAPI PET/CT, brain MRI may detect more and more small lesions. metastatic lesions in the region of brain, liver, momentum, and mesentery. It also revealed more metastatic lymph nodes in the neck, supraclavicular and paraaortic regions. GA-labelled FAP ligands (68Ga-FAPI) are showing promising alternatives to 18F-FDG in cancer patients [23].

In uptake comparison of 68Ga-FAPI and 18F-FDG in Colorectal, Gastric Cancers and Duodenal. The mediastinal lymph nodes and gastro jejunal anastomotic site exhibit high tracer uptake on 68Ga-FAPI PET/CT.

68Ga-FAPI PET/CT was shown to be more sensitive than 18F-FDG PET/CT in detecting primary tumours. To better detect primary and metastatic lesions in colorectal, duodenal cancer and gastric, fluorine 18 fluorodeoxyglucose CT/PET is outperformed gallium 68 fibroblastactivation protein inhibitor CT/PET, with greater tracer uptake in the majority of primary and metastatic lesions [24].

3.3 Solution generation

After the identification of more stable radiotracers for different parts of the human body. A responsive webpage is design for radiotracer as tool for selection. The webpage is made with the use of bootstrap algorithm.

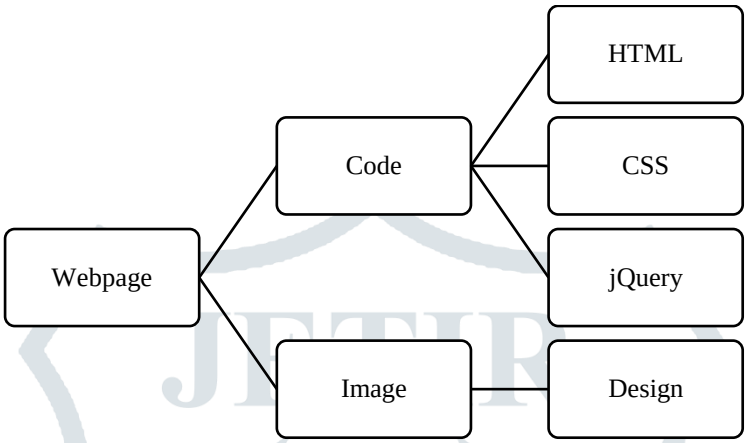

Figure 6: Flowchart of web design

The flowchart shows the separate step of the process of designing of the webpage in the figure 6. The diagram illustrates the workflow required to develop the webpage. In the designing of the webpage jQuery, HTML, CSS used in the designing of the responsive webpage.

4. RESULT

This section discusses the result and analysis of various parts of the responsive webpage. The functionalities discuss include the framework of responsive webpage with the bootstrap algorithm, responsive button, display card.

4.1 Overview of responsive webpage

The most important step in the imaging technique is radiotracers selection. The fundamental property of radiotracer is that it should behave in the same manner as that of material to be traced or diagnosed. The radiologist often confronts with selection of an ideal radiotracers for effective imaging of an organ. This website provides a solution to radiologist. An attempt is made to clarify the radiotracers usage as per organ. According to the research, the relevant and appropriate radiotracers which should be used in a particular case can be identified through this webpage.

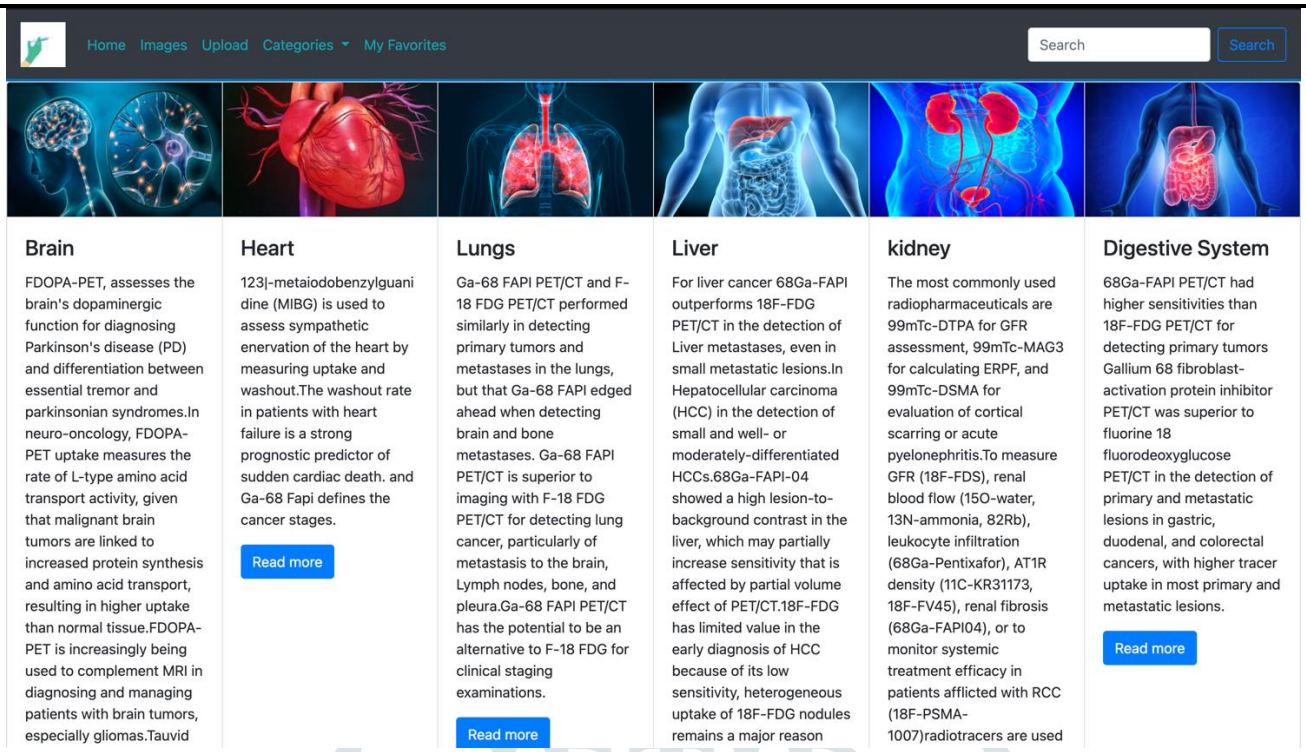

Figure 7: Screenshot of webpage of efficient radiotracers selection.

5. DISCUSSION

This chapter discusses the summary of the work findings and the conclusion of the research. An effort is made to understand the shortcoming of the research and methods to improve are suggested.

6. CONCLUSION

The main objective of this project was to tool which involves the design responsive webpage for the guidance of radiologist for effective radiotracers selection organ-wise. After analyzing the major radiotracer application in molecular imaging, use in different organs, modalities and future technology implementation opportunities and the comparative analysis of radiotracers, clinical aspects. In uptake comparison of 68Ga-FAPI and 18F-FDG in Colorectal, Gastric Cancers and Duodenal. To better detect primary and metastatic lesions in colorectal, duodenal cancer and gastric, fluorine 18 fluorodeoxyglucose CT/PET is outperformed gallium 68 fibroblastactivation protein inhibitor CT/PET, with greater tracer uptake in the majority of primary and metastatic lesions. When staging lung cancer, Ga-68 radiotracer performs better than F-18 FDG. When it came in identifying primary tumors and lung metastases, F-18 FDG PET/CT and Ga-68 FAPI PET/CT performed similarly, but Ga-68 FAPI had a slight advantage when identifying bone and brain metastases. Ga-68 FAPI PET/CT is superior than F-18 FDG PET/CT imaging for detecting lung cancer metastases to brain, lymph nodes, pleura, and bone. For clinical staging exams, [Ga-68 FAPI PET/CT] has the ability to replace F-18 FDG. Ga-68 FAPI PET/CT indicated more probable metastases in the brain. After the research analysis the webpage with the use of bootstrap algorithm is developed which helps the healthcare worker for efficient knowledge about the radiotracers.

7. FUTURE SCOPE OF WORK

A future scope would be to concentrate on the following steps to further improvement of the webpage.

- A portal system can be incorporated where radiologist register themselves with the help of their data like name, age, location, hospital name and designation.
- In this platform radiologist share the issue regarding the PET scan and radiologist.
- This webpage provides a global platform where radiologist across the world can upload the pet images and ask doubt in the platform.

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