Is Preclinical Imaging the Cross Talk between all Branches of Science?

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Editorial

Due to the huge costs and time spent for development of new drugs (around almost $ 1 billion (USD) and 12 Years), investing on the preclinical phase of drug development could be regarded as a great investment for de-risking the clinical phases. Preclinical studies are performed to obtain basic information about the safety, biological efficacy, pharmacokinetics and pharmacodynamics of a drug candidate before commencing clinical trials in human.

It is obvious that completing the preclinical phase requires great amounts of time and money, but with the use of advanced technologies such as preclinical imaging, preclinical studies have seen considerable progress. This happens owing to the ability of seeing in real time and in the same species majority of parameters required for the preclinical phase of drug development. There are several preclinical imaging devices that can be utilized. These devices include Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), Single Photon Emission Computed Tomography (SPECT), optical/fluorescence, Computed Tomography (CT), and ultrasound imaging. These technologies require advanced engineering and scientific skills in order to develop, use and optimize them.

This suggests that in order to have an enhanced preclinical imaging infrastructure, we would require an advanced multidisciplinary collaboration and network between engineering and sciences. In order to accelerate this, we at Tehran University of Medical Sciences (TUMS) Preclinical Core Facility (TPCF) hold international symposium annually on preclinical imaging (all of the modalities) and their applications in various disciplines branded as TPIS (TPCF Preclinical Imaging Symposium). Back in summer 2021, we held our 4th annual symposium and it was on online platform due to Covid-19 pandemic. Numerous presenters from various top centers around the world have joined our platform as speakers, from various disciplines of science and engineering. Centers such as, Weill Cornell Medical College, Duke University, Stanford University, Melbourne University, and ….

We are pleased that Frontiers in Biomedical Technology (FBT) is publishing these abstracts in their journal. We at TPCF are also inviting the readers of FBT to attend our 5th annual TPIS (for more information visit our website on: www.TPCF.ir).

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4th International TPCF Preclinical Imaging Symposium
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FDG Just for Cancer Diagnostic or Cellular Applications too?

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Abstract

Background: Immunotherapy using cells is a promising strategy for tackling various diseases. Various cells such as stem cells, islet cells, immune T cells, NK (Natural Killer) cells or CAR (Chimeric Antigen Receptor) T cells have been studied for various types of cancer, cardiovascular diseases, or autoimmune disorders.

To better assess the safety and efficacy of this treatment strategy, questions about the distribution, location, survival, and number of the therapeutic cells used need to be answered. Using molecular and anatomical imaging which is more efficient than other techniques such as histology, cells can be tracked non-invasively and real-time to answer these questions. In order to track cells, they should be labeled directly or indirectly by different probes or agents to determine their fate with various modalities such as PET (Positron Emission Tomography).

Synthetic radioactive glucose analog, ^{18}F-FDG (^{18}F-fluorodeoxyglucose), has been one of the most commonly used radiopharmaceuticals in nuclear medicine since 1970s. Due to the high metabolism of cancer cells and their need for glucose, this molecule has been used to label cancerous cells in vitro and vivo. This has revolutionized cancer diagnostics.

Due to the low cost, short half-life, and biologically being nontoxic, ^{18}F-FDG, has also been studied for cell imaging. This study aimed to focus on identifying new therapeutic cell types directly labeled with 18F-FDG and imaged with PET for different diseases.

Materials and Methods: Therapeutic cells are directly labeled with ^{18}F-FDG, and non-invasive real-time imaging is performed with the PET imaging to determine the initial distribution, final destination and best route of administration of therapeutic cells.

Results: Various studies have shown that therapeutic cell types can be labeled directly with 18F-FDG for monitoring cardiac stem cells, tracking transplanted islet cells, and finding inflammatory foci.

Conclusion: Specific cell labeling with ^{18}F-FDG and imaging with PET can well determine the safety and efficiency of cell therapy, which plays an important role in the development and translation of preclinical and clinical trials.

Keywords: Molecular Imaging; ^{18}F-FDG; Positron Emission Tomography; Direct Cell Labeling; Cell Therapy.

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Welfare of Laboratory Animals in Preclinical Research Imaging

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Abstract

Background: Animal welfare is one of the main requirements in clinical and preclinical research. So that today, in order to publish the results of clinical work, it is necessary to observe ethical codes, and if these codes are not observed, even with the best results, their publication will be prevented. The practical aspect of these ethical codes is the welfare of animals. Imaging is also a common practice in preclinical research. Therefore, the realization of animal welfare in this area is also essential.

One of the most important steps in imaging laboratory animals is to check the animal's vital signs. These vital signs include heart rate, respiration rate, body temperature, and so on. According to research, standards have been set for each of these cases, which will vary depending on the type of animal. These symptoms can indicate the amount of stress, pain, fear, etc. in the animal. In addition, in imaging process, animals usually have to fast, which can be a factor in disrupting the animal's well-being. Blood sampling of animals is also a common process along with imaging. If all these measures are put together, it will definitely threaten the welfare of the animal. For this reason, it is necessary to take all these measures in principle and in accordance with animal welfare laws.

Materials and Methods: In this article, we will try to introduce the principles of animal welfare in imaging by reviewing the researches. In general, these principles include: laboratory animal anesthesia method, principles of laboratory animal restraint, euthanasia method, monitoring method and evaluation of vital signs of animals during imaging, post-imaging measures, etc.

Results: If all these measures are put together, it will definitely threaten the welfare of the animal. For this reason, it is necessary to take all these measures in principle and in accordance with animal welfare laws.

Conclusion: It can be concluded that the practical aspect of ethical codes in clinical and preclinical research is animal welfare. Observing the welfare of animals not only provides positive effects for the animals tested, but also makes the work of the experimenter easier; Because if welfare is established during work, the animals will be calm and obedient. They will also show fewer behavioral abnormalities. So that, working with these animals is very convenient and the experimenter will also take the least amount of energy to deal with the aggressive behavior of the animals.

Keywords: Animal Welfare; Imaging; Ethical Codes.

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Knife-Edge Slit Collimator Optimization for Small Animal Imaging

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Abstract

Background: Single Photon Emission Computed Tomography (SPECT) collimator design is crucial in small animal imaging for preclinical studies.

In this study, the slit collimator with knife-edge aperture was designed and optimized.

Materials and Methods: Mathematical models were used to optimize the slit collimator. To do so, the sensitivity of the collimator was formulated against source-to-detector distance for a certain amount of the collimator resolution. The first-order derivative of the established formula gives the optimized parameters.

Results: For the fixed resolution of 1.0 mm, the sensitivity for 5.0, 10.0, 15.0 cm was calculated as 7.9×10^{-4}, 1.9×10^{-4} and 8.8×10^{-5}, respectively. In addition, considering 5.0 cm source-tor-collimator distance, for a sub-millimeter resolution (0.5 mm) the sensitivity was calculated 3.9×10^{-4}.

Conclusion: Although the penetration and scattering effect were not considered in this optimization, the results are in good agreement with the reported data in literature. The importance of this method lies both in its speed and relative ease of application in knife-edge slit collimator design and optimization studies.

Keywords: Mathematical Modeling; Collimator Optimization; Preclinical Imaging; Single Photon Emission Computed Tomography.

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Preclinical Dosimetry Model for Evaluation of Kidney Dose and Nephrotoxicity after Peptide Receptor Radionuclide Therapy

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Abstract

Background: Peptide Receptor Radionuclide Therapy (PRRT) is an important class of systemic treatment of patients with unrespectable or metastasized Neuro-Endocrine Tumors (NETs). Radiolabeled somatostatin analogs such as ^{99m}Tc-DTPA-octreotide (DTPA is diethylenetriaminepentaacetic acid), ^{111}In-DTPA-octreotid, ^{177}Lu-DOTA –octreotate (DOTA is 1,4,7,10-tetraazadodecane-N,N_,N_,N_-tetraacetic acid) and ^{90}Y-DOTA-octreotide are most successful in detecting, imaging and therapy of tumors expressing somatostatin receptors. The emphasis of dosimetry for PRRT is aimed at the dose-limiting organs: the kidneys. Radiolabeled peptides, including small antibody fragments, are excreted mainly via the kidneys and are partly reabsorbed in the proximal tubular cells. Renal retention of therapeutic radionuclides causes a relatively high radiation dose to the kidneys, which can lead to kidney failure. This toxicity precludes the use of higher doses, thus limiting the efficacy of therapy. Therefore, it is essential to obtain a thorough understanding of the effect of PRRT on the kidney. For patients without associated risk factors, a 40 Gy Biological Effective Dose (BED) is considered the renal threshold Lethal Dose (LD50). Accurate dosimetry is important in preclinical studies to evaluate the therapeutic efficacy and toxicity and optimize the selection of radionuclide. Preclinical voxel-based dosimetry methods is considered to be an accurate method for dose calculation including nonuniform activity distributions and tissue heterogeneity. The aim of this work was to develop a preclinical dosimetry model based on previously published bio distribution of somatostatin analogs in mice and evaluate the nephrotoxicity effect according to the dose distribution calculated by the model.

Materials and Methods: A non-uniform distribution of radioactivity based on the renal excretion mechanism of peptide molecules, published in previous study, was distributed inside a digital phantom of mice (Moby phantom). Maximum and average absorbed dose in voxels of kidney were calculated by GATE Monte Carlo (MC) simulation for three radionuclides (Lu^{177}, In^{111} and Y^{90}) with a detailed decay schema. Dose values were compared to threshold lethal dose (LD50) for kidney. Also dose-volume histogram was calculated in the kidney for each radionuclide.

Results: Betta particles emitted from Y^{90} and Lu^{177} have the most contribution to the kidney absorbed dose and lead to higher absorbed dose than LD-50. The absorbed dose from these radionuclide are upper than LD50 in voxels with a cumulated activity greater than 0.18 GBq. Although the average energy of internal conversion electrons emitted from In^{111} are in the same range of Lu^{177} betta particles but because of the lower yield of In^{111} internal conversion electrons, the In^{111} absorbed dose is low. The uniformity of the absorbed dose delivered throughout the nephron increased for radionuclides releasing more energy per decay. Y^{90} has the most uniform dose distribution.

Conclusion: Not only the physical properties of radionuclide such as the type and energy of emitted particles are important in nephrotoxicity evaluation in PRRT, but also the activity distribution of somatostatin analog in the kidney must be considered.

Keywords: Nephrotoxicity; Voxelized Phantom; Dosimetry; Monte Carlo.

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Photoacoustic Imaging of Cancer Cells Using Gold Nanoparticles

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Abstract

Background: Photoacoustic Imaging (PAI) is a hybrid modality of optical and ultrasound imaging that provides structural and functional images based on the endogenous or exogenous chromophores with different absorption optical energy densities. Oxyhemoglobin has a high optical absorption and makes PAI of blood vessels and consequently angiogenesis in tumors possible. Gold nanoparticles have desirable optical characteristics for PAI which facilitate the visualization of more depth of tissues with enhanced contrast.

This study sought to review the design, properties and applications of gold nanoparticles as well as their combination with other materials as PAI contrast agents due to the tracing cancer cells.

Materials and Methods: PubMed, Scopus, Cochrane Library and Web of Science databases were comprehensively searched from inception to March 2021. Articles were screened based on the inclusion and exclusion criteria.

Results: 68 studies met the inclusion criteria and their reported techniques, processes and applications of gold nanoparticles in PAI of various cancer cells were categorized and summarized. According to the literature, different methods are evaluated to utilize gold nanoparticles in PAI.

Conclusion: Gold nanoparticles are introduced to the cancer cells in the form of nanoshells, nanorods, nanocages and more complicated shapes for PAI. All of these nanoparticles have their specific properties, manufacturing technique and applications. Selection of the optimal shape of gold nanoparticles for PAI is dictated by the intended application. Gold nanoparticles are joined to various tumor-targeting molecules to detect specific cancer cells and serve as both contrast agent and therapeutic material. Cancer cells present increased permeability and retention effects and consequently concentrate higher contents of gold nanoparticles in any shape in compare to surrounding cells which leads to easier detection of such cells and enhanced contrast as well. The approval of safety of these nanoparticles in humans needs more studies.

Keywords: Photoacoustic Imaging; Cancer Cells; Gold Nanoparticles.

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Application of Artificial Intelligence in Dentomaxillofacial Imaging: A Science Mapping Approach

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Abstract

Background: Artificial intelligence has recently been applied to radiographic images in the field of dentistry, especially Oral and Maxillofacial (OMF) radiology. Radiological imaging diagnosis plays important roles in clinical patient management. Artificial intelligence is recently gaining wide attention for its high performance in recognizing images. Recent researches on artificial intelligence in OMF radiology have mainly used convolutional neural networks, which can perform image classification, detection, segmentation, registration, generation, and refinement. The aim of this study is a brief report on the use of artificial intelligence in recent research in various fields of oral and maxillofacial imaging.

Materials and Methods: Scopus database was searched in Jun 10, 2021 with the following query TITLE-ABS-KEY ((“machine learning” OR “deep learning”) AND image) AND SUBJAREA(DENT). Bibliometric data of 91 results analyzed via VOSviewer software using author keyword co-occurrence, co-citation and co-authorship network analysis.

Results: convolutional neural network, digital imaging/radiology and panoramic radiography were the hottest topics. dentomaxillofac radiol, sci rep and angle orthod had the most influence on the network. Among authors ariji e., ariji y. and fukuda m. had the most influence on the network.

Conclusion: Due to the high performance of deep learning in image recognition tasks, the application of this technology to radiological imaging is increasing. With the development of artificial intelligence, it can be predictable to change clinical practice by helping radiologists practice with better performance, greater reliability, and enhanced workflow for more appropriate recommendations. Development of automatic diagnosis systems, the establishment of treatment plans, and the fabrication of treatment tools could be the other outcomes for this technology. OMF radiologists will play a key role in the development of artificial intelligence applications in this field.

Therefore, we suggest interdisciplinary research in related sciences in the country to be supported by research centers and research institutes. And thus we can benefit from new technologies and researchers in engineering sciences in the clinical and preclinical fields.

Keywords: Artificial Intelligence; Imaging; Mapping Approach.

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Tracking Natural Killer Cells for Cancer Immunotherapy

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Abstract

Background: Natural Killer (NK) cells are part of the innate immune system and represent the first-line defense of the immune system in the control of tumor growth and metastasis diffusion. The ability to kill tumor cells without prior sensitization makes NK cells different from other major lymphocyte subsets. Recent studies have shown a promising role of NK cell-based therapies in the treatment of hematological malignancies, but data have shown that this type of adoptive cell transfer is insufficient in a large variety of solid tumors. This insufficiency is related to physical and chemical barriers in the Tumor Microenvironment (TME) of solid tumors. Several immunosuppressive factors are responsible for NK cell exhaustion and their inability to eliminate cancerous cells. Physical barriers which are caused by dense microenvironment and also a large number of cancer-associated fibroblasts together with abnormal blood and lymphatic vessels will decrease the infiltration rate of immune cells to the TME. To overcome these problems, several groups tried different strategies to develop NK cell-based therapies. Improving the cell motility and constant sensitivity to tumor cells are only a few goals which these groups are trying to achieve.

Materials and Methods: Measuring the therapeutic efficacy of NK cells needs more knowledge of their cellular characteristics, therefore, tracking the NK cell infiltration and migration into the TME is required. Optical imaging, magnetic resonance imaging, and nuclear imaging are the main strategies to monitor NK cells in animal models. Each of these strategies has its own pros and cons. Optical imaging is well-suited for preclinical studies due to its high sensitivity and being non-invasive. Through this imaging technique, scientists can track cells in real-time without any need for animal sacrifice. But this technique is not suitable for clinical studies and also their limited penetration depth is an important disadvantage.

Results: Nuclear imaging is an excellent method to overcome the limited penetration depth. Also, this technique has excellent sensitivity. But this strategy has its own disadvantages. For example, this technique needs a long time to scan, and ionizing radiation exposure is dangerous.

Conclusion: Considering that each strategy has its own limitations, multimodal imaging techniques would help to overcome several limitations. Combining these hybrid techniques can make it easier to track NK cells not only in preclinical studies but also in humans. This ability will improve our knowledge of NK cell manner in TME and the efficacy of different strategies to design more effective adoptive cell-based therapies.

Keywords: Adoptive Cell Therapy; Natural Killer Cells; Cell Tracking; Solid Tumor; Immunotherapy.

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Patient-Derived Xenograft (PDX) Models: A Step Forward in Personalized Medicine

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Abstract

Background: Patient-Derived Xenografts (PDX) is a term that has been used to refer to the procedure of developing and maintaining tumors obtained from a patient diagnosed with cancer, which has been manipulated and engrafted into a second host. Fresh Tumor Specimen obtained from biopsy or surgery is implanted into immunodeficient mice. Afterward, the tumor undergoes serial in vivo passages. Recipient mice commonly used are nude mice, SCID, RAG2(KO), and NOD.SCID mice all have different levels of immunodeficiency. Engraftment rates vary depending on the type of cancer and animal model, ranging from 25% to 100%. The Process of implantation differs from cancer types and/or sub-types. The site of implantation can be categorized into orthotopic and heterotopic. While heterotopic implantation procedure is technically more accessible, the orthotopic method represents a more realistic prospect of tumors behavior, perhaps due to the effects of the microenvironment. The success rate of a PDX system depends on factors discussed above, in addition to tumor type and precision of implantation.

Materials and Methods: PDX models are essential tools for cancer research. They provide a great platform to investigate tumor biology, genotype, morphology, architecture, and molecular features affecting tumor growth. As for drug screening, they also offer opportunities to identify biomarkers of drug response. These models are the best for preclinical efficacy studies, whereas they are often costly and labor intensive.

What can be seen is the continual growth of PDX models' success rates and efficiency in various cancer types. They are also revealing the pathways that may lead to tumors resistance to an anti-cancer drug. Various Cancer types have been studied. Some of the notable examples are Colorectal cancers, pancreatic cancers, Lung cancers (which are one of the most prevalent types of cancer), Melanoma, Breast cancers, Head and Neck cancers, Prostate cancers. Each of these cancers has been studied individually, from the genomic aspect, growth pathway, drug resistance.

Results: A major drawback with utilizing PDX models is that cancer stages may differ in behavior and progression pathways. Early-stage tumor drug test results may contradict end-stage tumors due to their metastasis potential and growth properties. These findings cannot be extrapolated to all patients.

Conclusion: Personalized cancer care is the aim of PDX models. These models also provide the initial data to set up clinical trials and identification, validation, and drug screening—biomarkers that are helpful tools for predicting drug sensitivity or resistance.

Keywords: Patient-Derived Xenografts; Personalized Medicine; Cancer; Cancer Therapy.

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Micro-CT; An Advanced Technology for Restorative Dental Research Studies

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Abstract

Background: Microcomputed tomography (micro-CT) is increasingly being used in biomedical research. Thirteen years after the development of micro-CT technology, it was proposed for endodontic research in the field of dentistry. Since then, different research and reviews have been done on other fields of dentistry. There was not a comprehensive, detailed review of micro-CT applications in the area of restorative dentistry which this article addresses this issue.

The goal of this study was to explore the scientific literature on the applications of micro-CT in preventive and restorative dental research.

Materials and Methods: An electronic search of publications was conducted until 2021 which included only articles written in English. Research studies addressing recent advancements and applications of micro-CT in preventive and restorative dentistry were chosen.

Results: Micro-CT is a powerful technology for experimental and preclinical research that allows for high-resolution 2D or 3D imaging on a small scale. There is no requirement for sample preparation or sectioning with this procedure. So, the specimens can be examined without having to destroy them. As a result, the possibility of examining the internal structure of tissue, mineral density of tooth structure, polymerization shrinkage, adaptation of dental materials, and determining the validity of conventional methods can only be a few examples of the application of this technology. However, the method's high cost, the time required for scanning and reconstruction, the need for computer skill, and the huge amount of data are its drawbacks.

Conclusion: The potential of micro-CT as an emerging, precise, reproducible, and non-destructive tool is obvious which allows qualitative and quantitative evaluation of tooth structure, dental materials, and tooth-restoration interfaces using dedicated software.

Keywords: X Ray; Microcomputed Tomography; Restorative Dentistry; Application.

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Tracking of Transplanted Cells Using Imaging Techniques

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Abstract

Background: Cell therapy is one of the efficient approaches for the treatment of a wide range of diseases such as cardiovascular, ischemia, type 1 diabetes and cancer. In addition to evaluating the therapeutic efficacy of transplanted cells, tracing these cells makes it possible to determine the location of transplanted cells, proliferation, migration, and the duration of their presence in the body. Molecular imaging technology is a non-invasive method suitable for use in this application.

The application of molecular imaging technologies is an important part of cell therapy research.

Materials and Methods: Molecular imaging technology is divided into three main classes, which are: Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT).

Results: Depending on which imaging technique is used, various materials have been proposed to this aim. Magnetic nanoparticles such as superparamagnetic iron oxide, ulterasmall superparamagnetic iron oxide and Gadolinium Hexanedione (GdH), and materials such as 19F-perfluorocarbons, Si-Gold NPs and Metalloproteins are suitable for MRI imaging. In the PET technique, radionuclides (^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{124}I, ^{64}Cu) are used to label cells for imaging. But in SPECT technique, materials such as 99mTc-HMPA, In-111 and Sodium Iodide Symporter (NIS) are introduced for cell labeling.

Conclusion: The minimum number of cells required to be labeled in all imaging techniques are about 10,000 cells. All of these techniques are applicable in preclinical and clinical study.

Tracing cells with biomarkers allows imaging of cells in vivo and molecular imaging of pathophysiological processes, which plays an important role in the early diagnosis of the disease and the beginning of the treatment process. This technique of cellular labeling has advantages over technique such as the reporter gene, which requires the transfer of the target cell or tissue to a reporter -gene bearing (viral) vector, which may present problems in translation to the clinical investigations.

Keywords: Cell Tracking; Magnetic Resonance Imaging; Positron Emission Tomography; Single Photon Emission Computed Tomography.

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Bioluminescence Imaging and Testis: A Literature Review

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Abstract

Background: Bioluminescence Imaging (BLI) is an optical imaging technique, used for the visual recording of the cellular and molecular processes like sensitive cells functionality in vivo. Practically, BLI relies on an enzymatic reaction between luciferase and its common substrate, luciferin. BLI is a high sensitivity, simple operation and high accuracy tool to collect valuable information about the immunology, endocrinology, virology, neuroscience and many other sciences. To use BLI in vivo is still very limited, and also it has not been considerably used in determining real endocrine system activity, especially gonadal function. In the present study we tried to collect various documents to evaluate the benefits of BLI use in determining tissue engineering, cell function and pathophysiology of testicular tissue.

Materials and Methods: A wide spread search was conducted on the online databases including ISI, PubMed, and Scopus via relevant keywords such as "Male Fertility", "Bioluminescence", and "Testis" from my 2021 to July 20, 2021. List of references of included studies were assessed for prevention of miss data. Considering the inclusion and exclusion criteria, finally,15 articles were extracted.

Results: The results of fifteen previous study are included in the present review. Bioluminescence was applied as primary and/or secondary imaging method in pioneering evaluation of processes such as: 1) germinal cell transplantation, 2) Testis gene expression, 3) Testis gene transformations (viral vector or electroporation), 4) Perfect evaluation of mammalian gametes, 5) Oxidative stress and evaluation of organelles function, 6) Testis magnocellular activities, 7) Receptor and ligand imagination, 8) Cytokine signaling in testis, 9) Identification of genotoxic damages, 10) Dynamics of molecular interactions (proteins), and 11) Testicular pathology, especially viral infections. Some of the revealed advantages of bioluminescence are as follows: 1) Noninvasive, 2) NO cellular damage, 3) To decrease killing laboratory animals, 4) To decrease the effects of biodiversity, 5) Exact investigation of cell processes such as spermatogenesis, 6) To determine high accurate gene expression time, 7) Evaluation of gene expression regulating factors, 8) Separation of organs based on the virus load, 9) Ability to exact assess of fertility at the cellular level (gamete and oocyte fusion), 10)investigation of cells movement (gamete), and 11) Adequate resolution at the molecular level.

Conclusion: Bioluminescence is a low-cost, easy-to-implement technique which can consider as an appropriate tool to assay tissue engineering and pathophysiological processes in the testes. BLI is able to assess transplants (cells and genes) success, fast and reliable evaluation of molecular screening, and is also helpful to develop immunotherapy and its components such as vaccines, antibodies, and antiviral drugs. Furthermore, this technique decreases researchers' ethical concerns, especially in animal studies. Considering various benefits of BLI, it can use as a diagnostic method to find causatives of infertility, especially in males, and also in pre-clinical researches to identify unknown aspects of infertility.

Keywords: Luciferases; Bioluminescence; Testis; Male Fertility.

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Anatomy of the Frontal Sinus in the Iranian Native Sheep (Afshari) Using Computed Tomography and Cross Sectioning

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Abstract

Background: Computed Tomography (CT) is an imaging technique which gives us an opportunity to review cross sections of the body in live animals. It makes precise anatomic data which can be used as a reference for comparing with the images of the abnormal cases. The paired frontal bones are situated between the cranium and the face and are united in the interfrontal suture (sutura interfrontalis). The roof of the skull, the calvaria, consists of an external and an internal lamina, which encloses the frontal sinus in its rostral two thirds. Each frontal bone encloses, depending on the species, one or more air-filled cavities, the frontal sinuses (sinus frontales). The present work aimed to describe the normal computed tomography and cross-sectional anatomy of the nasal cavity in Iranian native sheep (Afshari).

Materials and Methods: The samples were collected from slaughtered sheep in any of Tehran slaughterhouse. The skulls were dissected in dissection room of veterinary medicine after imaging in Tehran veterinary medicine hospital. The measurements were made by RADIANT application.

Results: In the dog the frontal sinus is divided into a rostral, lateral and medial compartment. They communicate with the nasal cavity via the space between the second and third ectoturbinate. The cat possesses an undivided frontal sinus and a palatine sinus on each side. The frontal sinus in the equine skull is combined with dorsal conchal sinus and it names is conchofrontal sinus. There is no direct communication between this sinus and the nasal cavity, but they communicate indirectly via the caudal maxillary sinus. In the ox the frontal sinus is divided into several compartments and extends to the nuchal region caudally. In ruminants it extends into the cornual process of the frontal bone, which accounts for the high incidence of inflammation of the frontal sinus after surgical dehorning. From the sixth month postpartum onwards the cornual process starts to pneumatise by invasion of the mucosal lining of the frontal sinus into the cornual process. In the small ruminants the frontal sinus is the largest sinus and its volume is 45/3 cm^3. It extending from the level of the third molar tooth to end of the orbital cavity. The frontal sinus in the small ruminants divided into rostral and caudal parts. The rostral part is contains of middle, intermediate and lateral compartment of frontal sinus. The lateral compartment of frontal sinus is next to the lacrimal sinus (0.256 cm^3 in this case). The caudal part of frontal sinus is contains of nuchal, post orbital and cornual diverticulum of the caudal group of compartment of frontal sinus. The supraorbital canal contains frontal nerve, vein and artry. This canal passes through the post orbital diverticulum. Infraorbital foramen was seen at level of third molar tooth. The cornual diverticulum was not observed in this breed.

Conclusion: The current study provided an acceptable anatomical explanation of nasal cavity. CT and cross-sectional anatomy could be used as helpful database for diagnosis and clinical interference of the nasal and paranasal sinuses in sheep.

Keywords: Computed Tomography Scan; Sheep; Frontal Sinus; Cross Sectional Anatomy.

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Angiogenesis Imaging in Preclinical Studies

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Abstract

Background: In preclinical models and human illness, advances in imaging are changing our understanding of angiogenesis and the evaluation of medicines that promote or inhibit angiogenesis. Vascular imaging allows doctors to count the number of blood vessels and their spacing, evaluate blood flow and vascular permeability, and look for cellular and molecular abnormalities in blood vessel walls. For revealing structural and functional defects of angiogenic blood arteries, microscopic techniques ranging from fluorescence, confocal, and multiphoton microscopy to electron microscopic imaging are particularly effective. Noninvasive, functionally relevant pictures of angiogenesis in animals and people can be obtained using Magnetic Resonance Imaging (MRI), Computed Tomography (CT), Positron Emission Tomography (PET), ultrasonography, and optical imaging.

Materials and Methods: Inflammation (e.g., coronary atherosclerotic plaque), tumor growth, diabetic retinopathy, peripheral vascular disease, and ischemic heart disease have all been linked to vascular development, both physiological and pathological. Given the above, angiogenesis imaging is very important.

Results: This comprehensive knowledge is resulting in the development of a variety of novel and intriguing treatments for cancer and other disorders. However, due to a number of unsolved concerns, care is advised. Given the above, angiogenesis imaging is very important.

Conclusion: For evaluating tissue vasculature on a structural, functional, and molecular level, a variety of imaging methods are available. In the future, multimodality, multiplexing imaging will allow for complete examination of the angiogenic cascade in all of its complexity.

Keywords: Angiogenesis; Imaging; Preclinical Studies.

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Survey Anticancer Effect of Cold Atmospheric Plasma by Positron Emission Tomography

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Abstract

Background: Cold Atmospheric Plasma (CAP) has a wide application in medicine. Some amount of ionized gas is produced by CAP at room temperature. The ionized gas contains positively charged ions, electrons, and neutral particles. Reactive Oxygen Species (ROS) and complex chemical components of the CAP exert many biological effects on bacterial, fungal, yeast, and mammalian cells as well as cancerous cells. This in-vivo anti-tumor effect is one of the important clinical applications of CAP sources.

Materials and Methods: At the first phase of this study, an Atmospheric Pressure Jet Plasma (APJP) system was designed and fabricated. After that, at the second phase, the therapeutic effects of APJP system were investigated. For this purpose, the direct and indirect methods have been implemented using helium gas on Glioblastoma Multiform (GBM) cancer cells in the anterior part of the rat brain. To produce plasma, an AC power supply with a frequency of 20 kHz and a sinusoidal waveform has been used. The variable amplitude of this voltage can be set up from zero to 10 kV. The flow of helium gas with a purity of 99% was tuned by a mass controller flow meter during the experiments. In the direct treatment method of treatment, fourteen days after GBM tumor implantation in rats, plasma radiation was directly exposed to the tumor region through the direct canalization. This is performed in two sequential days for a period of 70.7 seconds.

In the indirect method, Dulbecco's Modified Eagle Medium (DMEM) was used as an interface environment. DMEM was irradiated with plasma for 137.7 seconds. Then DMEM was injected into the vein of the brain. The time of irradiation to plasma or IC50 value has already been obtained by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) method. The IC50 value is the concentration of a drug that reduces the activity (or binding) of another drug to an enzyme by 50%. The MTT assay is a colorimetric assay for assessing cell metabolic activity. The rats were sent to for PET (Positron Emission Tomography) imaging after one-day and three-day treatments.

Results: An FDG PET with 2-[^{18}F]-fluorodeoxyglucose has been used for the evaluation of the direct and indirect APJP treatments. The small animal PET images were obtained with a micro-PET scanner (X-trim PET). Every rats was injected via the tail vein with about 1mci of the 18FDG under general anesthesia. For each small animal PET scan, 3-dimensional Regions of Interest (ROIs) were manually drawn over the brain area transversal images. The ROIs was converted to the Brain to Background Ratio (BBR) using following equation:

BBR= (ROI counts per voxel)/(background counts per voxel).

Conclusion: The results show that the calculated BBR factor for the treated rats is twice less than the untreated rat. Reduction of cancer cells after treatment can also be observed in both cross-sectional and also three-dimensional PET images of the treated GBM tumors by cold helium plasma jet.

Keywords: Anticancer Effect; Cold Atmospheric Plasma; Glioblastoma Multiform; Helium; Positron Emission Tomography.

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Quick Glance at the CLARITY and Novel Tissue Imaging Which is Popular in Neuroscience, Its Future and other Uses in other Organs

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Abstract

Background: Clarity (cleared lipidextracted acryl- hybridized rigid immunostaining/in situ hybridization- compatible tissue hydrogel) is a novel tissue clearing technique which is useful in the field of tissue imaging and lately has been a popular technique between scientist especially whom works in neuroscience field. CLARITY bring a lot of stunning features although it's a difficult procedure to run, for example CLARITY could give you a three dimensional image from your sample.

Materials and Methods: In the first step you need to clear your tissue, which transform your intact tissue to a nanoporous hydrogel-tissue hybrid while the anatomical structure remains intact. It's important to know the "clearing" refers to the lipids and other materials but proteins and nucleic acids remain. In addition, the combination of CLARITY with genetic methods for identification of synapses or for labeling specific circuits is also of interest.

One great benefit of using CLARITY is the structure doesn't change after tissue clearing, it's an amazing benefit for neuroscientist to investigate the disease which has been created by structural problem. Although tissue clearing isn't an only step and beside that you need microscope and computer to do the image processing but after all it worth to do it! Some of great reason to use it in neuro research has been written below:

1. Investigate neuronal circuits without reconstruction
2. Perform molecular phenotyping without destroying subcellular structures
3. Understanding the brain with molecular resolution and global scope has always been challenging

Researcher In other field also started to use this method and find its benefit individually in their fields, for example there is a paper about doing CLARITY on the biopsy from breast cancer and view the 3d sample tissue.

Results: It's been done in embryos to find out the development steps, human sigmoid colon to investigate 3D architecture of intrinsic cholinergic innervation in the human sigmoid colon and the relationship with nitrergic neurons in the enteric plexus, human skeleton, and even the plant tissue. In an amazing case researchers did the clearing to the whole animal model(zebra) to check the infection.

Conclusion: CLARITY is a new method of tissue clearing used for after that tissue imaging and analysis of protein location. Although it has a few drawbacks, it also has multiple benefits over traditional imaging techniques, reducing error and maximizing data that can be obtained from a single sample. In the field of neuroscience, it's been a popular method but still there is a lot of unnoticed usage in other fields of research, even in the diagnostic and prognostic program.

Keywords: CLARITY; 3D Imaging; Brain Mapping.

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Evaluation of Normal Renal Size and its Influencing Factors: A Cross-Sectional Study on the Adult Population of Mashhad

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Abstract

Background: Normal range of kidney size is a controversial issue among different populations given to its impressibility by multiple factors, therefore, this study aimed to provide valid reference ranges for kidney dimensions in the adult population of Mashhad. Also, we assessed the association of kidney size characteristics with some personal predisposing factors.

Materials and Methods: This cross-sectional study was conducted on 938 healthy individuals. Ultrasound measurement, physical examination, and laboratory analysis were performed. Demographic, dietary, and anthropometric data were obtained. The variables were categorized into 5 groups each, and data analysis was performed using the following statistical tests: Pearson correlation test, Variance analysis, T-test, and Chi-square test. A value of $P<0.05$ was considered statistically significant.

Results: Weight had the most association with kidney size followed to a lesser extent by height and age. Even after adjustment for other confounding variables, weight remained as an independent factor, while this effect was resolved for height and age. Also, all values for renal function, body bio-impedance, Blood pressure components, and water intake were notably correlated with kidney size.

Conclusion: This study determined the normal kidney size in healthy adults. We also declared the normal range of kidney size is a dynamic concept and should be assessed for each individual separately according to their personal determinative factors.

Keywords: Kidney Size; Ultrasound; Anthropometric Characteristics; Renal Function.

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Novel Trimodal Imaging Agent Based on Copper Nanoclusters

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Abstract

Background: Providing comprehensive information on anatomy, as well as physiological and pathophysiological processes in living organisms is important for clinical diagnosis. Multimodal imaging approach presents a promising future for biomedical application and undoubtedly provides better visualization in early cancer detection.

Multimodal imaging agent in a special nanoplatform has the potential to combine the advantages and overcome the shortage of various imaging tools for highly sensitive diagnosis. Therefore, design and synthesis of novel, safe, and cost-effective of these nanoprobes has gained considerable attention worldwide.

Materials and Methods: In this study, we prepared amino-modified silica-coated Gd-Copper Nanoclusters, conjugated with AS1411 (Apt-ASGCuNCs) and radiolabeled with technetium-99m (^{99m}Tc) for in vivo SPECT, fluorescence and magnetic resonance (MR) imaging. The synthesized nanoconjugate was fully characterized by TEM, DLS, Element mapping, fluorescence and FT-IR spectroscopy. Moreover, XTT assay and apoptosis and necrosis methods were applied to study toxicity.

Results: The prepared nanoconjugate demonstrated remarkable superiorities over traditional multimodal imaging agents such as rapid diffusion into tumor, biocompatibility, high-yield radiolabeling, stability, rapid renal excretion and mainly renal clearance. Also, results from the imaging techniques indicated potential ability of nanoconjugates to detect tumor tissue.

Conclusion: The suitable features of 99mTc-Apt-ASGCuNCs such as water solubility, no cytotoxicity, biocompatibility, good cellular uptake, high in vitro stability and availability of 99mTc indicate that it is a promising contrast agent for multimodal imaging of cancer tissues.

Keywords: Copper Nanoclusters; AS1411; Multi-Modality Imaging; Chelator Free; Radiolabeling.

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Ethical Dilemmas in the Use of Animal Models in Preclinical Research

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Abstract

Background: The introduction and synthesis of new pharmaceuticals and surgical intervention procedures have an undeniable part in the evolution of medicine. To this end, it is a common practice in medical research to use animal models for vivo experimentation due to the wide-ranging physiological similarities. The rising trend in research to implement this practice has resulted in formulating ethical codes and ethical comminutes dedicated to devising and planning ethical guidelines for research laboratories working on animal models in their preclinical investigations, stressing ethical considerations in all research practices concerning animal models. Animals can be subjected to tension, shock, trauma, and even death. Hence, based on the Russell and Burch 3R's principles, replacement, reduction, and refinement, all research attempts involving animals must take all necessary measures to bring the anguish and pain in them to a minimum following the given instructions. The paper provides an analysis of the determining ethical quandaries associated with animals in preclinical and in vivo research, with respect to the existing regulations and the historical perspective of achieving such studies.

Materials and Methods: An inclusive survey was conducted on fifty relevant publications, including papers, documents, and books, to establish an extensive scientific discourse on the ethical regulations and dilemmas of using animals in preclinical research.

Results: Despite the indispensable necessity of applying animal models in medical-pharmaceutical research, preclinical research faces limitations in this respect, including physiological differences, instability of animal physiology in laboratory conditions, variation in the pharmacokinetic parameters, and random efficacy of medications depending on species. Thus, acquiring the necessary skills in animal modeling, test design, and effect identification is critical to ensure significant research quality and take the highest advantage of animal models in the medical-pharmaceutical context for treating humans in cases where using such models is inevitable. Furthermore, using animals in the research context is supposed to fully abide by organized ethical frameworks and regulations to ensure the anguish and other unpleasant impacts of animals are minimized, the animal is absolved of needless affliction, and most importantly, bring the animal sacrifice in the research context to a substantially low level. It is necessary to provide the ground for formulating laws and guidelines to regulate animal modeling in research and foster better communication between researchers for exchanging experimental data to avoid repetitious practices and thus minimize the use of animal modeling in research. It would be ideal to have the bioethics principles, founded on the so-called "primum non nocere," reflected in animal modeling practice for medical purposes, encouraging the idea that animals are not supposed to take harm than necessary. Thus, bioethical standards should be carefully applied to this vital practice.

Conclusion: Concisely, note that preclinical research is entirely in line with Good Laboratory Practices (GLP), violating which jeopardizes research entirety, accuracy, validity, and reliability due to the potential effects of unfair practices (inadequate animal mismanagement), uncontrolled parameters, and several external factors.

Keywords: Ethical Dilemmas; Animal Models; Preclinical Trials.

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The Correlation of CURB-65 Criteria and Chest Computed Tomography Scan in the Prognosis of Severe Pneumonia in COVID-19 Patients

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Abstract

Background: Confusion, Urea, Respiratory Rate, Blood Pressure, age> 65 years (CURB-65) is a five-parameter score system used to treat the acquired pneumonia in COVID-19 patients. These five parameters include confusion, blood urea nitrogen, respiratory rate, blood pressure, and age. We reviewed the predictive value of CURB-65 at admission in patients with COVID-19 and identify the CURB-65 cut-off value for in-hospital death patients with CURB-65 scores of 0–1 is at low risk of death and can be managed as out-patients. Computed Tomography is a gold-standard modality in diagnosing lung involvement in COVID-19 patients. Here, we aim to assess the usefulness of CURB-65 in predicting 30-day mortality and its correlation with chest Computed Tomography (CT) scan involvement.

Materials and Methods: A comprehensive search was conducted through Medline, Scopus, Pubmed, and Web of Science using the following keywords, and 21 papers were enrolled in our study. The inclusion criteria were utilizing CURB-65 criteria, chest CT scan, and definite diagnosis of COVID-19. Studies using PSI or SOAR criteria and the ones with no chest CT were removed due to the exclusion criteria.

Results: 1034 patients were included overall in the study (192 died, 842 survived). In terms of CURB-65, 486 patients that account for 74% of cases were below 1, considered low-risk patients. Twenty percent of the cases CURB-65 were between 1 and 2. The rest of the population have CURB-65 higher than 2. The prominent features of survivors compared to non-survivors were higher respiratory rate, LDH, and D-dimer, whiles having a lower SpO2 and liver failure. CURB-65 reveals reliability in-hospital mortality. CURB-65≥2 might be considered as a cut-off value in the prognosis of in-hospital death in COVID-19 patients. Patients with CURB-65≥ 2 had more mortality rate, lymphocytes < 800, confusion, and NTproBNP > 500 pg/mL. In predicting mortality, the CURB-65 score had the most reliable outcomes. Chest CT scan were performed in COVID-19 patients, and a range of symptoms from Ground Glass Opacity and Consolidation to Crazy Paving patterns were seen in all of them. The higher the CURB-65 criteria, the more lung lobes involvement patients would have. Patients with CURB≥ 2 had more severe chest CT signs and more admission to ICU.

Conclusion: In one study of CURB-65 in assessing pneumonia, many patients with low CURB-65 scores are not suitable for out-patient treatment because many factors are not incorporated in the score. However, another study shows that CURB-65 is a beneficial prognostic factor in COVID-19 patients, which could be used to quickly triage severe patients in primary care or general practice settings. In addition, the expanded CURB-65 score can be a better predictor of increased oxygen requirement in patients with SARS-CoV-2 pneumonia. Overall, there was a correlation between the severity of pneumonia and chest CT involvement in COVID-19 patients.

Keywords: COVID-19; Computed Tomography Scan; Confusion Urea Respiratory Rate Blood Pressure age > 65.

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The Effects of Low-Dose Radiation Therapy (LDRT) on the Treatment of COVID-19 Patients

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Abstract

Background: Low-Dose Radiation Therapy (LDRT) was successfully used to treat patients with infectious diseases, including pneumonia, with doses ranging from approximately 50 to 550 R (~44-48 cGy). The literature suggests that doses between 0.3 and 1 Gy incite anti-inflammatory properties. To improve the clinical outcomes for COVID-19 patients, we can perform clinical trials for whole-lung low-dose radiation therapy with 0.3-1.5 Gy in one round. This amount of radiation is lower than radiation therapy's doses, but it exceeds the 50 mSv annual occupational exposure limit and the public exposure of 1 mSv/year.

We aim to assess the usefulness of CURB-65 in predicting 30-day mortality and its correlation with chest Computed Tomography (CT) scan involvement.

Materials and Methods: A comprehensive search through W.O.S, PubMed, Scopus was conducted using the keywords, which results in enrolling 25 articles in the study due to inclusion criteria. Twelve studies were removed due to the exclusion criteria.

Results: In one study, a 64-year-old patient was hospitalized with COVID-19 pneumonia and steady progression of the respiratory system's function. Treatment with a single 1-Gy dose to the bilateral whole-lung volume was administered, resulting in the gradual daily remission of ventilatory function and decreased serum inflammatory markers and oxygen support needs. L.E.T. radiation in low doses (<100 cGy) can be a possible therapy for treating viral pneumonia for COVID-19 patients in recent years. A review showed that low doses of X- rays reduced pneumonia mortality from roughly 30 percent to 10 percent on average. we stated that based on its set of mechanism; this may represent a viable treatment option to reduce the cytokine storm-induced ubiquitous inflammatory effects that occurs in the majority of critically ill COVID-19 patients.

Conclusion: The status of the COVID-19 pandemic, effective management of these seriously ill patients is crucial. From this perspective and due to the lack of adequate and validated clinical concepts, low-dose radiation should be surveyed in clinical matters, and it's safe to say that radiotherapy Can be considered a reliable choice for COVID-19 pneumonia management.

Keywords: COVID-19; Low Dose Radiation Therapy; Ventilation Disfunction.

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Early Detection and Classification of Parkinson's Disease Using Machine Learning Aalgorithms

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Abstract

Background: Diffusion Tensor Imaging (DTI) allows measuring Fractional Anisotropy (FA) and similar microstructural indices of the brain white matter. Previous DTI studies in Parkinson's Disease (PD) have demonstrated abnormal fractional anisotropy in multiple white matter regions, particularly in the dopaminergic nuclei and dopaminergic pathways.

To compare DTI data of PD and Healthy Candidates (HC) using FMRIB Software Library (FSL) software and Support Vector Machine (SVM) algorithm.

Materials and Methods: DTI images of 21 Healthy Candidates (HC) and 32 PD of stage 1 and 2 from the Parkinson's Progression Markers Initiative (PPMI) database were assessed using FSL software. Images were initially pre-processed to remove the effects of eddy current distortions, and to remove non-brain tissues in images. Then, FA and Mean Diffusivity (MD) were obtained from bilateral caudate, putamen, globus pallidus, sub thalamic, and substantia nigra. The mean values of FA and MD were then imported into MATLAB for classification. SVM with a Radial Basis Function (RBF) kernel was used for FA and MD data. We also used K-fold cross-validation to evaluate our model.

Results: The results showed that PD patients had reduced FA and increased MD within the basal ganglia compared to HC. The classification accuracy was obtained 65% across the 3 repetitions of the 3-fold cross validation, and the test accuracy and specificity resulted in 81% and 77%, respectively.

Conclusion: Our results showed that the mean FA and MD values of basal ganglia can be a good potential biomarker for diagnosing PD. An automated classification of the scan is also possible and expected to reduce the number of misdiagnoses by assisting the neurologists in making a decision.

Keywords: Parkinson Disease; Diffusion Tensor Imaging; Functional Magnetic Resonance Imaging Brain Software Library Software; Support Vector Machine Algorithm.

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Introduction to Micro-CT and Its Application in Dentistry

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Abstract

Background: Innovation of Micro Computed Tomography (μ-CT) came due to bulk size of ordinary Computed Tomography machine that was not easy to use in dental clinical practice and even in research area. In 1954, first report of investigation using μ-CT was published however particularly in dentistry, first research was published in end of 1980. Micro-CT generates high-resolution cross-sectional images by using x-rays through the object and by reconstructing of these images. Three-dimensional structure can be produced. Although there still remains a long way to incorporate micro and nano CT in clinical dentistry, they have both stablished themselves as great tools to be used in in-vitro studies. A wide range of specimens may be examined directly using Micro-CT including mineralized tissues such as teeth, bone, and materials such as ceramics, polymers, biomaterial scaffolds etc. several studies have also used Micro-CT to properly gage the marginal and internal adaptation of different dental restorations made up of different materials. The great spatial resolution of coproducing voxels in the range of 5–50 μm allows the researchers to directly identify gaps that has never before been possible to find with other imaging techniques without destroying the specimen. The combination of Micro-CT and CAD-CAM systems significantly increases the adaptation of dental restorations to tooth structure. Micro-CT imaging could also be extended to soft tissues and in recent years the development of Micro-CT systems allows in vivo imaging of small live animals.

In present dentistry, radiography has been increasing its potential hence importance and popularity of μ-CT rising day by day. We have gathered information from relevant studies to properly introduce all aspects of this technology and its specific applications in dental research. To introduce Micro-CT and its application in dentistry (especially in the research area.

Materials and Methods: A hand search was performed on articles published until august 2021 in Google Scholar, PubMed, and Scopus. studies using Micro-CT as the imaging and measuring tool were included.

Results: Among all studies, 11 studies satisfied the inclusion criteria and were thus used to write this review.

Conclusion: This review highlights Micro-CT's importance as an imaging and measuring tool with great sensitivity and its benefits over other measuring techniques. It is a testament to Micro-CT's importance in the dental research area.

Keywords: Micro-Computed Tomography; Dentistry.

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