5th International TPCF Preclinical Imaging Symposium

Importance of Preclinical Imaging for Science & Technology

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Editorial

Preclinical imaging is the visualization of living animals for research purposes, such as drug development. Imaging modalities have long been crucial to the researcher in observing changes, either at the organ, tissue, cell, or molecular level, in animals responding to physiological or environmental changes. In vivo imaging modalities that are non-invasive have become especially important to study animal models longitudinally. Broadly speaking, these imaging systems can be categorized into primarily morphological/anatomical and primarily molecular imaging techniques. Techniques such as high-frequency micro-ultrasound, Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are usually used for anatomical imaging, while optical imaging (fluorescence and bioluminescence), Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT) are usually used for molecular visualizations. These technologies require advanced engineering and scientific skills in order to develop, use and optimize them.

As a leading institute for the convergence of science and technology in the field of preclinical imaging, TPCF organizes annual symposiums. Despite the difficult time we are experiencing due to the pandemic, Preclinical researches continues to grow in many areas. The 6th International TPCF preclinical imaging symposium is a key scientific and networking event yielding new partnerships that accelerate preclinical research and translation across all therapeutic areas. Preclinical imaging symposium (TPCF) is an annual event that focuses on newest trends and frontline technologies in drug discovery and translational research. In the TPIS 2022 we had 15 keynote speeches by brilliant scientists. These talks cover various aspects of preclinical imaging.

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 6th annual TPIS (for more information visit our website on: www.TPCF.ir).

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Assessment of Contrast to Noise Ratio of Folic Acid Targeted Gold Nanoparticles versus Gold Nanoparticles in Cancer Cells by CT

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Abstract

Background: Molecular imaging is a field of medical imaging that focuses on imaging molecules of medical interest within living patients. A clear benefit of molecular imaging is to enable noninvasive, repetitive monitoring of intrinsic signals within tumor cells as a means to identify the lesions as malignant or to assess the ability of treatment to perturb key pathways within the tumor cells. Due to the promising utility of molecular imaging in oncology, preclinical research to refine molecular imaging techniques in in vitro is a blossoming field.

In this study, we aimed to identify the benefits in image contrast enhancement of Folic Acid-Cysteamine conjugated gold Nanoparticles (FA-Cys-AuNPs) using measuring Contrast to Noise (CNR) compared to gold Nanoparticles (AuNPs). The CNR was assessed in different tube voltages, concentrations, and incubation times in nasopharyngeal KB cancer cells.

Materials and Methods: FA-Cys-AuNPs and Omnipaque suspension were scanned at different concentration ranges (500-2000 µg/ml) and energy ranges (80- 140 kVp) with CT imaging modality. FA-Cys-AuNPs and AuNPs were incubated in nasopharyngeal cancer cells at different incubation times (6, 12, and 24 h) and concentration ranges (200-500 µM). Finally, the contrast enhancement was assessed using CNR value at different tube voltages.

Results: Results showed that the formed FA-Cys-AuNPs with an Au core size of 15 nm in all concentrations and tube potentials from 80 to 140 kVp display greater CNR than Omnipaque. The CNR value was increased by increasing concentration and energy. At 140 kVp and 2000 µg/ml, the CNR value of FA-Cys-AuNPs was 2.25 times greater than Omnipaque. At 140 kVp, 500 µM and 24 h incubation, the CNR value of targeted cells were approximately 1.5 times higher than non-targeted cells. At 140 kVp, and 500 µM, the CNR value of targeted cells with 24 h incubation time was 2.66 times greater than the targeted cells incubated with 6 h.

Conclusion: These findings suggested that the designed FA-Cys-AuNPs could be a good candidate contrast agent for molecular CT imaging.

Keywords: Computed Tomography; Gold Nanoparticles; X-Ray Attenuation; Folic Acid.

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Gold Nanoparticle Parameters Play an Important Role as CT Imaging Contrast Agents

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Abstract

Background: Computed Tomography (CT) is extensively used in clinical imaging modalities. There have recently been many reports of novel contrast agents for CT imaging. In particular, the development of gold Nanoparticles (AuNPs) as CT contrast agents is a topic of intense interest.

AuNPs have favorable characteristics for this application such as high payloads of contrast generating material, strong X-ray attenuation, excellent biocompatibility, tailorable surface chemistry, and tunable sizes and shapes. However, there have been conflicting reports on the role of AuNPs size on their contrast generation for CT.

Materials and Methods: In this paper, the effects of parameters related to gold nanoparticles (sizes, shapes, concentrations, and surface chemistries) on X-ray attenuation beam in human nasopharyngeal cancer cells were investigated. Hematoxylin and Eosin (H&E), Colony, and MTT assays were applied to measure the compatibility of the NPs in cells.

Results: Our findings indicated that the GNPs with Au core sizes of ~13 nm and ~60 nm and polyethylene glycol covering on gold nanorods (PEG-GNRs) are non-cytotoxic and GNRs with an aspect ratio of 2.4 and 4.2 are toxic in a concentration range. At 80 kVp, GNPs (13 nm) enables 3.03–times higher contrast than iodine at a concentration of 5000 μM. The GNPs (13 nm) X-ray attenuations were 2.55-times and 1.63-times higher than PEG-GNRs and GNPs (60 nm) in cancer cells, respectively. X-ray attenuation highly increased when the concentration of mass (measured by ICP-OES) of NPs was elevated.

Conclusion: In sum, smaller spherical GNPs can be proposed as an excellent possibility to Omnipaque for CT imaging of nasopharyngeal cancer cells.

Keywords: Computed Tomography; Gold Nanoparticles; X-Ray Attenuation; Omnipaque.

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Volumetric Study of the Frontal, Maxillary and Palatine Sinus in the Ile De France Sheep

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Abstract

Background: The Computed Tomography (CT) scan imaging technique provides a situation for Clinicians to give the fastest and best diagnosis of many diseases of the skull and body without causing changes in the body. Some skull bones have hollow cavities called paranasal sinuses. These cavities are different in different species and sometimes they are directly and indirectly related to each other. The upcoming research will provide researchers in this field with comprehensive information about the volume of the different parts and sinuses of the skull of the Ile de France sheep.

Materials and Methods: 5 adult Ile de France sheep head, which was mature ages (above 10 month) and sex, were included in this study. The volume calculation was performed automatically using the software available on the CT scan system (Syngo MMWP VE40A software). For this purpose, the study area was introduced to the software in the bone window and the software automatically showed the boundaries of the study area in three available views (cross, sagittal, and coronal sections) if approved the Volume per cm^3 was displayed to the nearest three decimal places. To increase the accuracy of the measurement, the average volume in all three existing views was examined.

Results: The frontal sinus lies from the level of the second pre-molar tooth and continues along the frontal bone in the roof of the cranium to 1.5 cm posterior to the orbital cavity. The maxillary sinus in Ile-de-France sheep starts from the upper part of the first pre-molar tooth and continues in parallel with the maxillary teeth to about 1.3 cm caudal to the last molar one. Also, the palatine sinus, which in this breed is completely connected with the maxillary sinus, starts at the level of the first molar tooth region and continues to the third molar region.

The paranasal sinuses observed in this breed included Frontal, Maxillary, palatine, lacrimal and ethmoidal sinuses. Among these sinuses, Frontal, Maxillary, and palatine were the largest paranasal sinuses in the skull of Ile de France sheep, with an average volume of 57.5 ± 2.33, 34 ± 4.66, and 2.6 ± 0.50 cm^3, respectively. The ratio of the frontal sinus, which was the largest sinus in the skull, to the maxillary and palatine sinus was 1.67 and 21.9, respectively.

Statistical studies on the results of measuring the volume of different sinuses of the head of Ile de France sheep showed that there is no significant difference between males and females in all the investigated parameter (Table 1).

Conclusion: Using the above data will help to achieve the best diagnosis of diseases related to the sinuses and other areas of the skull of this sheep breed, which is one of the best meat breeds in the world.

Keywords: Computed Tomography Scan; Ile De France Sheep; Paranasal Sinuses; Volumetric Study.

Table 1. Volumetric study of skull sinus (unit of measurement is cm^3) in the Ile de France sheep. F Female, M Male

No	Frontal sinus volume	Maxillary sinus volume	Palatine sinus volume
F1	57	39	2
F2	59	34	3
F3	54	37	2.5
M1	56	32	2.3
M2	61	29	3.4
Mean and SD, F	56.6 ± 2.05	36.6 ± 2.03	2.5 ± 0.40
Mean and SD, M	58.5 ± 2.52	30.5 ± 1.55	2.8 ± 0.55
Mean and SD, F&M	57.5 ± 2.33	34 ± 4.66	2.6 ± 0.50

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Anatomy of Mandible and Hyoid Apparatus in Iranian Native Sheep (Afshari) Using Computed Tomography

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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. In this study, we tried to provide a comprehensive anatomy of the mandible of this breed of sheep along with the relevant CT scan cross-sectional images.

Materials and Methods: The 500 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: The two halves of the mandible develop in the cranial mesoderm of the first branchial arch and articulate firmly at the mental angle forming the median mandibular synchondrosis rostrally. Each half in this breed can be divided into Body of the mandible and ramus. The length of the mandible was 18.55 centimeter on average and the widest part this curved bone was 6 cm at level of third molar tooth. Its height was about 6.52 cm at level of Temporomandibular Joint (TMJ) and 10 cm at level of coronoid process. The body of the mandible can be subdivided into a rostral part, that contains 4 incisor teeth and a caudal part, that contains the 3 pre-molar and 3 molar teeth. The tooth-free rostral part of the dorsal margin between the canine and the first cheek tooth is termed the interalveolar margin or diastema, which Its average length was 4 cm. The temporomandibular joint is the synovial joint between the mandibular ramus and the squamous part of the temporal bone. It was 1.5 cm long and 2 cm wide. It was 1.2 centimeter cranial to the opening of external acoustic meatus. The mandibular canal has its caudal opening in the mandibular foramen on the medial surface of the mandible, which is approximately at a height of 4 cm from the mandibular body and 2.5 cm in front of the end of mandible. It passes rostrally, ventral to the dental alveoli and ends in the mental foramen. The hyoid bone develops from parts of the second and third branchial arches; its separate cartilagenous components ossify early in life and unite forming firm synchondroses. The hyoid bones are situated between the rami of the mandible at the base of the tongue and acts as a suspensory mechanism for the tongue and larynx. It can be divided into two parts. The first part connects to the tongue and larynx and is regarded as the hyoid apparatus, equivalent to that of man. The second is directed dorsally, articulating with the temporal bone and is termed the suspensory apparatus. The major part of hyoid corresponds to that of man and consists of three components: Basihyoid or body, Thyrohyoid and Ceratohyoid.

Conclusion: According to the study, the anatomy of the studied mandible was completely structurally similar to the other breeds studied. Also, the difference in the location of the declared important structures between the breeds is natural and expected.

Keywords: Computed Tomography Scan; Afshari Sheep; Mandible; Morphometric Study.

Frontiers in BIOMEDICAL TECHNOLOGIES

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Determination of seizure zone in Temporal Lobe Epilepsy using Perfusion MRI (Arterial Spin Labeling)

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Abstract

Background: Epilepsy is a disease that manifests itself with recurrent seizures over a period of time. Temporal lobe epilepsy originates in the part of the brain that is involved in processing emotions and short-term memory. In most cases, surgery can stop the seizure. Therefore, determining the exact location of the seizure area for critical surgery in patients with temporal lobe epilepsy is crucial. Imaging in epilepsy patients also plays an important role in diagnosing and deciding on their type of treatment. In the intraictal phase, the amount of cerebral blood flow and metabolism in the affected area decreases. Therefore, in addition to structural Magnetic Resonance Imaging (MRI), functional Magnetic Resonance Imaging (fMRI), including calculating cerebral blood flow and monitoring metabolism, can be effective. Arterial Spin Labeling-MRI (ASL-MRI) is MRI techniques that can, non-invasively, define the regions of cerebral perfusion.

The aim of the current study was to recognize the location of temporal lobe epilepsy in patients with ASL-MRI technique.

Materials and Methods: For this purpose, 20 patients with definitive diagnosis of temporal lobe were evaluated by EEG method with Arterial spin labeling-MRI (ASL-MRI) technique.

Results: In this study, we sought to use perfusion imaging to magnetically mark pulsed arterial blood spins as a non-invasive, non-radioactive and inexpensive method compared to other methods to detect cerebral blood flow asymmetry and Changes in metabolism in the temporal lobe can be seen in magnetic resonance imaging and clinical implementation of this technique. According to the results and analyzes performed on patients, the results indicate that about 60% (12/20) of patients in the identified area according to the EEG to the conflict area according to ASI is consistent and coordinated.

Conclusion: The use of ASL-MRI can be considered as in-vivo proficient bio-marker for proper identification of epileptogenic zone in patients with final diagnosis of drug-resistant temporal lobe epilepsy.

Keywords: Arterial Spin-Labelling; Drug-Resistant Temporal Lobe Epilepsy.

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Ex-vivo Imaging of GFP-Labeled Human Placenta Mesenchymal Stem Cell for Characterization and Validation of Hepatocellular Carcinoma (HCC) Xenograft Tumor as a Suitable Liver Cancer Model for Preclinical Studies

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Abstract

Background: Hepatocellular Carcinoma (HCC) is the fifth most diagnosed cancer and the third leading cause of cancer-related death. sorafenib is used as a standard therapy to treat HCC. Mesenchymal Stromal Cells (MSCs) have also been used to suppress HCC. Here we investigate the development of a xenograft model of liver cancer to study the homing of hpMSC-GFP cells, tumor kinetics and molecular characterizations of HCC. Animal models are one of the most important means of evaluating cancer treatment by cell therapy or novel drug candidates in cancer treatments. In this study we aimed to firstly validate that the tumors are all composed of HCC cells, secondly to make sure that our treatment would not harm the animals' liver or kidneys and finally to verify if more hpMSC have been implanted in site after 72 hours as compared to the systemic injection.

Materials and Methods: To create xenograft models of HCC, HepG2 cell lines were inoculated into the flanks of 9 nude mice bilaterally. Animals were then divided into three groups: the first group received hpMSC-GFP systemically, the second received intra-tumoral hpMSC-GFP and the third received PBS. The first two groups were sacrificed after 72 hours of MSCs injection but the third group was followed up for forty days. One tumor from each animal was then transferred to formalin buffer for H&E staining and the other tumor was used for ex-vivo imaging. Blood samples were taken from all subjects before sacrificing them.

Results: Histopathological fidelity of heterotopic HePG2 xenograft models to human HCC tumors was demonstrated. Biochemical evaluation suggested the health of the animal's liver and kidneys. Ex-vivo imaging illustrated homing of more hpMSC-GFP cells in tumor tissues derived from the group receiving intra-tumoral hpMSC-GFP.

Conclusion: This study represents a comprehensive model of HepG2 xenograft for in vivo and ex vivo imaging studies that enable researchers to assess new therapeutical approaches for treatment of liver cancer with hpMSC. A standard method was used to inoculate tumor cells and the intervention was shown to be safe to liver and kidneys. Local injection of MSCs can be used as cell therapy to fight neoplasms.

Keywords: Hepatocellular Carcinoma; Sorafenib; Human Placenta Mesenchymal Stem Cells Green Fluorescent Protein; Animal Model.

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Evaluation of Ultrasound Images of Glioblastoma Tumor with Conventional MR Images in Rat Animal Model

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Abstract

Background: Magnetic Resonance Imaging (MRI) is essential for characterizing brain tumors. It guides the surgical strategy and is necessary to monitor treatment response. It is possible to use transcranial ultrasound for periodical follow-ups. In addition to causing little stress to the patient, this type of imaging is cost-effective and can be monitored in the patient's bed. Ultrasound waves pass through the skull's delicate areas called acoustic windows. The detection rate of brain tumors with conventional transcranial ultrasound is between 40 and 80%, depending on the tumor type and the acoustic window quality. Glioblastoma is one of the most aggressive and difficult cancers to treat. Patient life expectancy after diagnosis is only 12 to 18 months and 5-year survival is less than 10%. In this research, the images of glioblastoma tumor in male Wistar rat is compared using MRI and sonography.

Materials and Methods: The animals were anesthetized by intraperitoneal injection of the combination of two drugs Ketamine and Xylazine. Using a stereotaxic machine and a Hamilton syringe, C6 GBM cell lines were injected into the brain of rats. After two weeks of tumor induction, the brain sample of an animal was sent for histology and the formation of a glioblastoma tumor was confirmed. Another animal was imaged using MR. On the same day, the animal was anesthetized, the hair on its head was shaved, and then the tumor was imaged using high-resolution ultrasound. For ultrasound images, an imaging device (Sonix Touch ultrasound system, Ultrasonix Medical Corporation, Richmond, ON, Canada) was used at Tarbiat Modares University with probe settings at a frequency of 14 MHz, 13 frames per second, and a depth of 3 cm. For MR images, a 3 Tesla Siemens Magnetom Prisma scanner and an animal head coil with a holder in the Iranian National Brain Mapping Laboratory (NBML) were used and images were taken with T2 Weighted settings from coronal and axial directions.

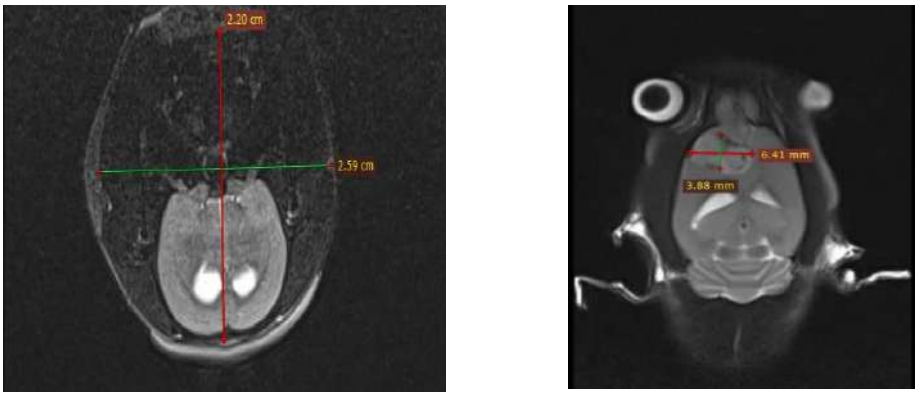
Results: As shown in Figure 1a in the ultrasound image, the sizes of the rat skull are 25.42 mm and 21.00 mm in the longitudinal and transverse directions with the largest cross-sectional area, respectively. The most significant dimensions of the tumor are given in Figure 1b. These dimensions are 6.04 mm and 3.71 mm in length and width, respectively. In Figure 2a on the MR image, the size of the skull in the longitudinal and transverse directions is 25.9mm and 22.0 mm, respectively. The dimensions of the tumor in Figure 2b in the longitudinal and transverse directions are 3.88 mm and 6.41 mm, respectively. Correlation analysis shows a 0.99 percent correlation between skull and tumor dimensions in ultrasound images compared to MR images. Figure 3 shows the linear regression analysis along with the regression function and correlation coefficient.

Conclusion: The difference percentage of skull dimensions in ultrasound and MR images in longitudinal and transverse directions is 1.88% and 4.7%, respectively, and in the case of tumor dimensions, it is 6.12% and 4.5%, respectively. Although the exact shape of the tumor is not completely clear in the ultrasound images, it can be useful to detect the presence of the tumor and its approximate dimensions.

Keywords: High-Resolution Ultrasonography; Magnetic Resonance Imaging; T2 Weighted; Glioblastoma Multiform Tumor.

a b

Figure 1. Ultrasound images of rat skull. a) Internal dimensions of the skull; b) Tumor dimensions



a b

Figure 2. MR images of rat skull. a) Internal dimensions of the skull; b) Tumor dimensions

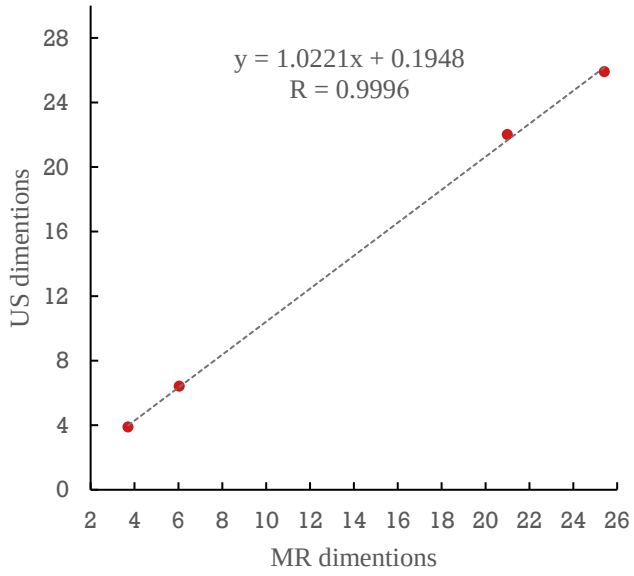


Figure 3. The linear regression analysis between between skull and tumor dimensions in ultrasound images and MR images

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A Review of the Study of the Anatomy of the Respiratory System of Turtles Using CT-Scan

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Abstract

Background: Turtles are one of the types of reptiles that, due to having shell, anatomically, their coelomic cavity structures have differences from other reptiles and other animals. One of these systems is the respiratory system, especially the lungs. Computed Tomography (CT) scan is one of the best techniques that is widely used for studies related to the respiratory system.

The purpose of this article is to review the studies conducted by the authors on two species of pond turtles in Iran and to compare some characteristics of their lungs, trachea and bronchi.

Materials and Methods: Regarding the materials and methods of the studies whose results we have reviewed here, these things are worth mentioning: In these studies, two species of turtles Emys Orbicularis and Mauremys caspica were examined. All the samples were anesthetized for the CT scan and regained consciousness after the study. It should be noted that no turtles were killed for these studies. Siemens Somatom spirit Dual Slice CT scan machine has been used. The samples were fixed in ventral recumbency to take CT-scan images. In each sample, the CT-scan was done in both fixed limb and neck and extended form.

Results: In both turtle species, trachea passing a short distance in the midline of the neck, and deviated to the left; then, it entered to the coelomic cavity. The tracheal bifurcation site was movable and move to caudal parts with neck flexion. The entrance site of the bronchi to the lungs was fixed. With the consideration of coelomic cavity volume and various parts of that in the neck extended position.

Conclusion: According to the observations, we can say the flexion of the neck leads to some alterations in the tracheal bifurcation site and locating posteriorly to the lung's hilum. As a result, the way of the bronchus changes to inter the lungs. The branches of bronchus in these turtles also are like other reptiles, and it's not similar to a bronchial tree and it contains just limited small branches. The CT-scan is applicable for alive animals, so this is one of the best choices for anatomical studies in animals who are in danger of extinction.

Keywords: Turtle; Anatomy; Computed Tomography Scan; Lungs.

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High-Resolution Ultrasound Imaging for Non-Invasive Characterization of Acute Wound Healing in a Radiation-Induced Skin Damage Guinea Pig Model

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Abstract

Background: High-resolution ultrasound imaging is a non-invasive and objective assessment. Ultrasound imaging accomplishes a target assessment and follow-up of radiation-induced skin injury.

The purpose of this study is to investigate the anatomical, structural and functional changes of the irradiated skin after cell therapy.

Materials and Methods: In this study, Female guinea pigs (250 gr) were divided into 3 groups: (a) controls, consisting of nontreated guinea pigs; (b) radiation-treated; (c) radiation-treated receiving adipose-derived mesenchymal stem cells. Mesenchymal stem cells were isolated from the neck adipose tissue. Acute radiation-induced skin injury is caused by a single fraction of X-ray irradiation of 60Gy to a 3.0×3.0 cm area with 1.3 cm bolus on 100 cm SSD in abdominal skin tissue. Ultrasonic imaging of the depth and quality of healing in the skin tissue will be performed by processing ultrasound images with a frequency of 40 MHz and a resolution of 0.01mm. Evaluation of the thickness and Young's modulus on days 7 and 14 of irradiation were investigated with the software ImageJ and Matlab.

Results: Skin thickness indicated a significant difference between the treatment and control groups on day 7 and 14 after 60 Gy irradiation ($P < 0.05$). The thickness of the control group was 0.89 ± 0.04 mm with dermis 0.73 ± 0.03 mm and epidermis 0.13 ± 0.05 mm. The highest skin thickness was observed in the irradiated group and the lowest skin thickness was in the stem cell treatment group. Increased elastic modulus (Young's modulus) in the irradiated group with $19/56 \pm 0/74$ kPa represents a significant increase in the stiffness of the skin. In the treated group the elasticity was $14/56 \pm 1/2$ kPa after 14 days ($P < 0.05$). This increase in stiffness can be due to biochemical changes and degeneration of the elastic fibers of the collagen of the skin tissue.

Conclusion: Measurement of skin thickness, wound depth, scar formation and elasticity are important for the proper assessment and management of the healing wound in stem cell therapy of radiation-induced skin damage. Currently, these measurements require repeated biopsies that necessitate the removal of a portion of the wound to assess biomechanics, morphology and biochemical properties. High-resolution ultrasound applications of non-invasive methods involving ultrasonic measurements can be widely applied to studies involving the skin, particularly in the context of wound healing.

Keywords: High-Resolution Ultrasound Imaging; Radiation-Induced Skin Injuries; Stem Cell Therapy.

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Efficient Algorithm for Distinction Mild Cognitive Impairment from Alzheimer's Disease Based on Specific View FCM White Matter Segmentation and Ensemble Learning

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Abstract

Background: Alzheimer's Disease (AD) is in the dementia group and is one of the most prevalent neurodegenerative disorders, approximately 50 million people were affected in 2018 and are expected to get tripled by 2050. Several demographic properties, neuroimaging such as MRI, functional MRI (MRI), neuropsychiatric symptoms, and cognitive performances are used to predict AD. Between existing characteristics; White Matter (WM) is known as a good marker for AD tracking, and MRI image segmentation by WM can be a good choice for decreasing the volume of data. In order to predict AD, many algorithms have been developed, but most studies are concentrating on the distinction of AD from Cognitive Normal (CN), and fewer on the distinction of AD from Mild cognitive impairment (MCI) level, which has an important position in AD progression. In addition, there aren't efficient algorithms with low computational costs and sufficient features in clinical use.

In this study, we provided a new simple, and efficient methodology for classifying patients into AD and MCI patients, and evaluating the effect of the view dimension of Fuzzy C Means (FCM) in prediction with ensemble classifiers. This work was based on the segmentation of WM and extracting two groups of features.

Materials and Methods: We proposed our methodology in three steps; first, segmentation of WM from T1 MRI with FCM according to two specific viewpoints (3D, and 2D). In the second step, two groups of features are extracted, approximate coefficients of Discrete Wavelet Transform (DWT) with three-level decomposition, and statistical (mean, variance, skewness) features. In the final step, an ensemble classifier that constructs with three simple classifiers, K-Nearest Neighbor (KNN), Decision Tree (DT), and Linear Discriminant Analysis (LDA) were used for distinct MCI from AD.

Results: The proposed method has been evaluated by using 1280 T1- weighted MR imaging from 62 patients of MCI (32) and AD (32) for the ADNI dataset. The best performance is for the 3D viewpoint, and the accuracy, precision, and f1-score achieved from the methodology are 94.22%, 94.45%, and 94.21% respectively by using a ten-fold cross-validation strategy.

Conclusion: Experimental evaluation shows that 3D view segmentation FCM is better than the 2D view, and according to the results, the proposed methodology has comparable performance with state-of-the-art methods for distinction MCI from AD. By the low computational cost algorithm, we used three classifiers for generalization that can be used in practical application by physicians in pre-clinical.

Keywords: Alzheimer's Disease; Fuzzy C Means; Ensemble.

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Super-Critical Bone Defect Healing Acceleration by a Growth Factor-Releasing Allo-Hybrid Graft

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Abstract

Background: Bone can recover itself after an injury. However, a serious bone deficiency necessitates external intervention. Bone tissue engineering has used a range of materials, including artificial and naturally derived auto/allo/xenografts as scaffolds to help damaged areas. Despite being the gold standard for treating bone abnormalities, autografts have several drawbacks, like the morbidity of the harvesting site. Allografts and xenografts present acceptable biological features similar to autografts, such as desired chemical and mechanical properties, biocompatibility, and an excellent osteoconductive surface. However, insufficient osteogenic properties of bone allografts, particularly in the case of critical size defects, could potentially inhibit regeneration and lead to therapy failure. Growth factors have been found to accelerate tissue recovery in a variety of tissues. Similarly, the importance of Growth Factors (GFs) in bone repair is well known, especially for the Bone Morphogenic Proteins (BMPs), fibroblast growth factors (FGFs), Insulin-like Growth Factors (IGFs), Platelet-Derived Growth Factors (PDGFs), Transforming Growth Factors (TGFs), and Vascular Endothelial Growth Factors (VEGFs). Several ECM components can be found in the Human Amniotic Membrane (HAM). The PDGFs, TGF-b1, and FGFs are only a few of the numerous substances found in HAM. Additionally, natural bone-derived Demineralized Bone Matrixes (DBM) possess BMPs. Current study has been focused on the delivery of a GF mixture into the site of bone repair in the form of a hybrid DBM/HAM to decrease bone remodeling time.

Materials and Methods: In this study, DBM was prepared by a detergent-free method. Alongside, human placentas were taken with full consent from Caesarean operations and decellularization was performed to obtain freeze-dried amniotic patches and then solubilized to prepare Amniotic Membrane Jelly (AMJ). The allo-hybrid grafts were prepared by coating the AMJ on the surface of allografts and subsequently underwent in vitro studies, such as alkaline phosphatase activity, MTT assay, and SEM analysis, before being evaluated in vivo. Next, critical calvarial bone defects were created in twenty-four male Wistar rats and treated with DBM, allo-hybrid, and AMJ. The treatment groups were as follows: DBM implanted, allo-hybrid implanted, AMJ injection, and a Negative Control (NC) group in which the defect was left unfilled. Bone regeneration was assessed using Computed Tomography (CT scan) and histological analysis at 1, 2, and 3 months after surgery.

Results: CT scan analysis clearly showed improved new bone growth in the allo-hybrid group compared to the NC group. Histological staining revealed immature bone in the allo-hybrid and DBM groups, along with the creation of a medullary cavity and bone marrow two months after surgery. Three months after surgery, the allo-hybrid group showed signs of mature new bone creation, while the NC group showed no signs of healing at any of the three time points.

Conclusion: Collectively, according to analysis of histological sections and computer tomography images, our data indicates the maximum amount of bone regeneration is achieved in vivo using allo-hybrid scaffold after 90 days.

Keywords: Bone Tissue Engineering; Allografts; Human Amniotic Membrane; Critical Bone Defect.

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Quantitative Evaluation of SPECT/CT Image Based on SUV of Y-^{90} Activity Distribution in Liver

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Abstract

Background: In nuclear medicine, the radionuclide ^{90}Y is used for treatment of malignancies due to high localized dose rate in the target organ. The Standard Uptake Value (SUV) quantity, which has a vital role in the diagnosis and treatment planning, is used to evaluate radiopharmaceuticals distribution in the patient body. The quality of activity distribution images in the patient body has an important role in this evaluation which affected by attenuation, scattering, system sensitivity, etc.

The aim of this study is evaluation of spatial resolution of distribution of ^{90}Y radiopharmaceutical in the liver based images resulted from bremsstrahlung radiation, and also SUV calculation

Materials and Methods: The simulation of the Single-Photon Emission Computed Tomography/ Computed Tomography (SPECT/CT) imaging system was done using the Monte Carlo GATE code. The GE Infinia device and the MEGP collimator were simulated. The simulated phantom is derived from the data of the abdominal CT images. The SPECT images were reconstructed using OS-EM method in the STIR software. The average and the maximum of counts in the region of interest were extracted using the AMIDE software and the standard uptake value was calculated. The validation of simulation performed based on system sensitivity and spatial resolution parameters using Point Spread Function (PSF) of a point source filled with ^{99m}Tc.

Results & Conclusion: The resolution values at 10, 15, 20, 25, and 30 cm distances from the collimator surface were 9.1, 12.9, 14.1, 16.8, and 18 mm, respectively. The system sensitivity at distances of 10, 15, 20, 25, and 30 cm from the collimator surface were calculated 66, 63, 64, 65, and 65 cps/MBq, respectively. The standard uptake value was calculated based on the calibration factor obtained from the ^{90}Y point source. In the next step, the effect of the number of iterations and subsets on the activity concentration was investigated. It was observed that with increasing both the number of iteration and subsets, the percentage difference between the values of actual activity concentration and the calculated activity concentration was reduced. This study shows that the standard uptake value decreases with increasing radius in a constant activity.

The Results of activity concentration and SUV calculation are shown in the Table 1.

Keywords: Standard Uptake Value; Simulation Monte Carlo; Radiopharmaceutical Y^{90}; Single Photon Emission Computed Tomography/Computed Tomography.

Table 1. The Results of activity concentration and SUV calculation

Tumor volume 33.5 ML			
Activity	18.5 Mbq	37Mbq	55.5Mbq
Activity Concentration calculated with 5 subset and 6 iteration	0.449 ± 0.08	0.896 ± 0.16	1.34 ± 0.24
Activity Concentration calculated with 5 subset and 9 iteration	0.460 ± 0.07	0.950 ± 0.12	1.44 ± .17
SUV calculated with 5 subset and 6 iteration	36.40 ± 3.20	36.32 ± 3.30	36.27 ± 3.16
SUV calculated with 5 subset and 9 iteration	37.29 ± 3.17	38.51 ± 3.31	39.08 ± 3.27
Tumor volume 113.04 ML			
Activity	18.5 Mbq	37Mbq	55.5Mbq
Activity Concentration calculated with 5 subset and 6 iteration	0.124 ± 0.02	0.271 ± 0.04	0.41 ± .06
Activity Concentration calculated with 5 subset and 6 iteration	0.134 ± 0.01	0.278 ± .03	0.43 ± .05
SUV calculated with 5 subset and 6 iteration	10.05 ± 0.96	10.98 ± 1.03	11.16 ± 1.02
SUV calculated with 5 subset and 9 iteration	10.86 ± 1.01	11.27 ± 1.00	12.63 ± 1.00
Tumor volume 267.95 ML			
Activity	18.5 Mbq	37Mbq	55.5Mbq
Activity Concentration calculated with 5 subset and 6 iteration	0.055 ± 0.01	0.111 ± .02	0.016 ± 0.02
Activity Concentration calculated with 5 subset and 9 iteration	0.057 ± 0.008	0.115 ± 0.018	0.018 ± 0.02
SUV calculated with 5 subset and 6 iteration	4.50 ± 0.44	4.50 ± 0.46	4.57 ± 0.44
SUV calculated with 5 subset and 9 iteration	4.62 ± 0.44	4.66 ± 0.44	4.92 ± 0.45

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An introduction to the Comparison Shape of Some Cranial Structures in Boleophthalmus Dussumieri and Periophthalmus Waltoni (Teleostei: Oxudercidae) in the Persian Gulf: An Exploratory Analysis with Micro-CT Scanning

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Abstract

Background: Knowing the osteological characteristics of fish, especially the head structure, is important in understanding the biological characteristics. Also, from the point of view of evolutionary ecology, it is important to describe the adaptation of different populations of a species to environmental conditions. Periophthalmus waltoni and Boleophthalmus dussumieri are among the mudskippers, that belong to the Oxudercidae family. They are distributed along the coasts of the Oman Sea and the Persian Gulf (Iraq to Mumbai). Mudskippers like early tetrapods are an independent cause of amphibian living standards that are Unparalleled among other fish. We anticipate that the morphological detail and analytical power that come with the technique we here employed will assist us in this task. The skeletal structure of mudskippers is still poorly understood. Hence, there may be a possible link between the skeletal structure of the skull and their amphibious life.

Materials and Methods: The study was conducted on 3 specimens of B. dussumieri and P. waltoni collected from the shores of Musa estuary. Specimens were fixed in ethanol (96 %). The samples were then sent to the preclinical laboratory (Lotus-InVivo) micro-CT scanning (TPCF, in Tehran university of medical sciences) for imaging. Micro-CT or Micro-Computed Tomography is a three-dimensional imaging device using X-rays.

Results: The skull of mudskippers is very variable and consists of 5 parts, neurocranium, its appendages (suspensorium), jaws, gill cap bones, and branchiohyoid). The neurocranium forms the brain compartment. In *B. dussumieri*, the skull skeleton is rudimentary. As it is still cartilaginous-osseous, a high percentage of the skeleton is still cartilaginous. This state is in such a way that the mass in the middle remains cartilaginous and the surrounding area is becoming ossified. In this species, despite the larger head size, the brain is small. In *P. waltoni*, the brain area is larger, but the skull tissue is completely bony and has very little cartilaginous. The floor of the skull is spongy. The connection between the neurocranium and the jaws is made through a row of bones (hyomandibular, symplectic, quadrate, pterygoids, etc.). In terms of shape, size, and position, these bones have undergone more severe changes in *P. waltoni* than in *B. dussumieri*. The jaws have also undergone drastic changes, corresponding to the change from a nearly fixed biting mouth to a flexible sucking mouth. In both species, the teeth are sharp and in two parts in the jaws. In *P. waltoni*, there are two pairs of sharp teeth for hunting in the upper jaw, the number of these teeth in *B. dussumieri* is one pair and it is less curved.

Conclusion: In this report, for the first time, the skeletal structure of the mudskippers of the Persian Gulf has been studied. According to the observed changes in the skeletal structure of mudskippers compared to other bony fishes, It can be inferred that the Mudskippers have developed special adaptations to live in mud in terrestrial and aquatic conditions. These adaptations are greater in P. waltoni, which shows greater degrees of terrestrialization, and requires detailed studies in this field.

Keywords: Cranial Skeleton; Neurocranium; Mudskipper; Micro-Computed Tomography Scanning; Persian Gulf.

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Cellulosic Scaffolds for the Repair of Bone Defects in Preclinical and Future Clinical Studies

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Abstract

Background: Using natural bio-inspired extracellular matrix for tissue engineering, drug delivery, and medical devices has been suggested to have a significant impact on future healthcare technologies. Exploiting them for regeneration of fractures caused by trauma, osteoporosis or tumors has been considered a solution in our super-aging modern societies considering the limitations of autograft and allograft in bone graft.

The present study has investigated various herbal-derived cellulosic scaffolds with different structures combined with human Adipose Derived Mesenchymal Stem Cells (h-ADMSCs) to study the relationship between the physical architecture of the scaffold (fibrillary or porous) on stem cell adhesion, proliferation, and induction of osteogenic differentiation.

Materials and Methods: Several plants first decellularized using detergent-based and detergent-free protocols and their physiochemical and biological characteristics such as hydrophilicity, surface roughness, chemical composition, surface morphology, porosity, toxicity, swelling behavior and biodegradability were assessed using SEM, AFM, Spectrophotometer and etc. Additionally, osteo-inductivity of obtained scaffolds has evaluated by culture of h-ADMSCs on top of them and cellular activities including cell adhesion, calcium secretion, and Alkaline Phosphatase activity (ALP) as well as expression levels of bone-related genes were examined.

Results: Natural cellulosic scaffolds exhibited a hydrophilic nature due to the presence of hydroxyl groups on the surface, which affect cell adhesion and growth. Based on SEM images and molecular analysis, different micro-structure of the herbal scaffolds (fibrillary and porous) has been shown to affect stem cell fate and regulate cellular behaviors. Cell culture and in vivo evaluations confirmed that herbal-derived scaffolds provide a proper niche for cell migration and osteogenic differentiation. Moreover, significant increased expression levels of bone marker genes, cell's ALP activity and mineralization showed high potentials of these scaffolds to safe repair osteochondral defects without the risk of toxicity or an immunological reaction.

Conclusion: Present study demonstrated that the various herbal-derived cellulosic scaffolds are capable of promoting osteo-inductive signals in h-MSCs and could be considered as a new feasible platform for treating bone tissue defects in vitro and in vivo and future clinical applications.

Keywords: Regenerative Medicine; Tissue Engineering; Plant Scaffolds; Bone Defects; Human Stem Cells.

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Parameters Affected MTF in Spatial Resolution Evaluation of Computed Tomography Scanners: A Review Study

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Abstract

Background: Spatial resolution is a parameter to show the ability of the imaging system to distinguish adjacent objects in an image. By developing Computed Tomography (CT) systems and their important application in diagnosis, therapy, and preclinical studies, evaluation of CT spatial resolution gets more important. The Poor spatial resolution of a system can cause many crucial effects on the result of diagnosis so it is important to evaluate the effects of different parameters on it. As Modulation Transfer Function (MTF) has been widely used to measure image spatial resolution of computed tomography systems, it is necessary to study image spatial resolution using MTF and find what may influence it.

The purpose of this study is to review articles that assess the effects of different parameters on MTF and spatial resolution.

Materials and Methods: The present review is based on Pub Med online database using these keywords: computed tomography AND modulation transfer function AND MTF AND spatial resolution AND effect. 28 of 51 articles were selected based on inclusion criteria.

Results: Many studies show that types of image reconstruction algorithms and filters can cause effects MTF measurements. Iterative Reconstruction (IR) is challenging as MTF is influenced by many parameters such as methods used for MTF calculations, IR strength level, and different system settings like tube current when IR is used. With the advancement of technology, Deep learning is used to find better results. In some studies, different convolutional filter algorithms show effects on spatial resolution results and they may differ by field of view size. Slice thickness, Region of Interest (ROI) size, and some system design factors like the number of detectors, sampling rate, and others can influence spatial resolution. Moreover, some artifacts and noise are effective which can cause the necessity of calibration operation before the measurement procedure. As was reported before, focal spot blooming has a noticeable effect on spatial resolution in CT imaging. By further research, it was found that spatial resolution is adversely affected by the non-ideal focal spot size, but with a deep learning-based strategy, this problem can be reduced to obtain high spatial resolution CT images even in the case of a non-ideal x-ray source. Image assessment in both the x-y plane and z direction shows spatial resolution in the x-y plane was not affected by image filter processing in the z direction but may influenced by the reconstruction kernel used. It has been found that the spatial resolution in the z direction does not depend on the reconstruction kernel used but it can be affected by filter in the z-direction. Research showed spiral pitch (z-axis reconstruction algorithm) had a slight effect on in-plane(x-y plane) spatial resolution of asymmetric-type detectors in Multi-Slice CT (MSCT).

Conclusion: Many studies evaluate parameters affecting MTF but, by system development and the vast application of CT scanners, it is necessary to study more in this field. Deep learning in image quality may be effective and useful and hope to work more.

Keywords: Modulation Transfer Function; Spatial Resolution; Computed Tomography; Image Quality; Quality Control.

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Imaging Applications of Tc-^{99m} for Labeling Different Cells and their Products

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Abstract

Background: The use of cells or their byproducts is a promising approach to treating a number of diseases. A number of cells, including stem cells, islet cells, immunological T cells, NK (Natural Killer) cells, and CAR (Chimeric Antigen Receptor) T cells, or cells-related products such as exosomes have been investigated for a number of cancer types, cardiovascular diseases, and autoimmune disorders. The distribution, location, survival, and quantity of the therapeutic cells or its products used must be clarified in order to more accurately evaluate the safety and efficacy of this therapy approach. Cells, extracellular vesicles or any molecules may be tracked non-invasively and real-time to provide answers to these concerns using molecular and anatomical imaging, which is more effective than traditional methods like histology. Cells must be labeled with various agents or probes in order to be tracked and their fate determined using a variety of modalities. With a short half-life of just 6 hours, the popular radioactive tracer technetium-99m enables scanning operations that quickly capture data while limiting overall patient radiation exposure. Technetium-99m is used in a variety of cells and cell-related products. Macrophages, T-cells, B-cells, dendric cells, red blood cells, platelets, mesenchymal stem cells, leukocytes, granulocytes, etc. are some of the several types of cells that make up this variety. Exosomes, extracellular vesicles, and peptide bodies are additionally thought of as cell products, could be labeled with Tc-^{99m}. Exclusive tissue drug delivery is one of the purposes that was achieved by technetium labeling. Tc labeled cells and products can also be used for monitoring cell functions. Controlling a cancerous tumor's stage and cell uptake can be accomplished by labeling cells and products (esp. peptides) to target receptors on the target cells. This labeling can be done non-invasively in vitro or in vivo. The evolvement of this procedure can be followed up by modalities such as SPECT, CT, scintigraphy, PET, and other common modalities. This study focused on applications of Tc^{99m} labeling on different cells, exosomes, and biomolecules.

Materials and Methods: Cell labeling can be performed with different dosages of Tc-99m on various cells including T-cells, B-cells, macrophages, mesenchymal cells, etc., and their products such as exosomes and biomolecules. Tracing migration of these labeled cells and exosomes can be monitored using SPECT, CT, planar scan, and other modalities in use.

Results: Results showed that we can label different cells and extracellular vesicles(exosomes) via Tc-^{99m}. These labeled exosomes have stability in serum so they are used as radiopharmaceuticals. ^{99m}Tc-radiopharmaceuticals can be traced by SPECT, CT, etc. In addition, ^{99m}Tc labeled proteins like antibodies have application in fine-tuning the currently available radiopharmaceuticals.

Conclusion: In conclusion, different cells and their products like exosomes and peptide bodies are labeled by Tc-99m and become great tracers for noninvasive imaging. These tracers have applications in cell therapy, especially for the treatment of cancer and drug delivery.

Keywords: Technetium-99m; Labeling; Radioactive Tracer; Imaging; Cell Therapy; Exosomes; Peptide Bodies; Radiopharmaceuticals.

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A New Animal Model of Radiation-Induced Skin Damage Using Megavoltage Radiotherapy

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Abstract

Background: The most complication of radiation therapy methods is skin tissue damage. To describe this acute skin reaction and create modalities.

This study developed a novel model of acute skin radiation injury without internal organ damage.

Materials and Methods: On this study female guinea pig with an average weight 250 gr were used. Guinea pigs were exposed to a single fraction of X-ray irradiation of 20, 30, 50, 60, 80 Gy to a 3.0*3.0 cm area with 1.3 cm bolus on 100 cm SSD in the dorsal and abdominal skin. The control group did not receive radiation. Skin of the irradiated field area was isolated using a low pressure clamp. Guinea pig was followed for 4 weeks with serial photographic analysis and sonographic evaluation of the irradiated areas. The Kumar scale has been used to evaluate acute skin damage. Tensiometry was performed and achieved Young's modulus. Histological analysis was carried out on the healed skin damage.

Results: Loss of dermal integrity has appeared after a single dose of soft X-ray radiation at or over 30 Gy. Sonographic images indicate an increase in the thickness of skin tissue with increasing radiation dose. At 20 and 30 Gy healing was observed after the peak injury. At the dose of 60 Gy and higher, ulceration and full-thickness dermal injury was observed starting around day 14 and did not heal in the abdominal skin.

Conclusion: The guinea pig is a small animal model for the short-term screening of skin radiation injury. This technique can be used to study radiation induced injury and suggested to evaluated skin wound healing, cell therapy and transplant for these clinical issues.

Keywords: Radiation-Induced Skin Damage; Guinea Pig Model; Megavoltage Radiation Therapy.

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Effects of Gamma-Irradiation on Topographical and Osteogenic Properties of Seaweed Scaffold

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Abstract

Background: The goal of bone tissue engineering is to develop implantable graft substitutes for serious skeletal defects that are unable to heal on their own and it has sparked a lot of treatment hope. Fractures are the main issue caused by bone disease. The risk of a fracture increases with age. As people live longer, the lifetime risk of fractures will rise for all ethnic groups. In order to address bone loss caused by trauma, infection, tumor excision, orthopedics, and craniofacial surgery, it is critically essential to generate a biocompatible osteogenic implant combined with cells.

The aim of this research was to develop an efficient method for fabricating a sustainable natural-based scaffold as a framework to enhance cell adhesion, proliferation, and differentiation using gamma radiation on natural scaffolds.

Materials and Methods: In this study, decellularized algal tissue was created as a promising biomaterial for stimulating osteogenic development in human mesenchymal stem cells. The scaffold was then exposed to gamma radiation at 4 different dosages, and its chemical and biological characteristics were evaluated.

Results: Data presented here revealed that mechanical properties of the decellularized cellulosic seaweed scaffold increased with the enhancement of radiation doses from 10 kGy to 50 kGy, especially the irradiation dose of 250 kGy which imposed a remarkable effect on these properties. Moreover, the osteoinduction of human mesenchymal stem cells on irradiated scaffolds has revealed that alkaline phosphatase activity and calcium deposition in MSCs was significantly higher in irradiated matrixes than those cells differentiated on the non-irradiated scaffolds.

Conclusion: Exploring the interaction between therapeutic radiation and natural biomaterials revealed that not only Gamma-Irradiation has no adverse effect on the properties cellulosic scaffolds but it provides a unique opportunity to enhance their osteogenic property to treat bone defect. Preclinical evaluation of obtained result is necessary prior to introducing these approach for clinical purposes.

Keywords: Gamma Irradiation; Sea-Weed Scaffold; Tissue Engineering; Osteogenic Differentiation.

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Transcranial Electrical Stimulation Parameter Estimation Based on Deep Regression Method

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Abstract

Background: Neuromodulation is a promising method for the treatment of neurological abnormalities in patients resistant to common treatments, as well as discovering the functional secrets of the brain through brain mapping. However, one of the challenges of neural modulation is determining the stimulation parameters with appropriate accuracy. Transcranial electrical stimulation is one of the common methods of neuromodulation, and various techniques have been proposed to improve its performance. Temporal Interference (TI) method, which has been introduced in recent years, has made it possible to stimulate the deep areas of the brain without affecting the superficial areas. In the TI method, the use of an array of electrodes increases the spatial accuracy in stimulating the desired area of the brain.

In this article, a method is proposed to determine the amplitude of the signal applied to each pair of electrodes in the array of stimulation electrodes to achieve the desired stimulation pattern. In this way, by adjusting the amplitude of the signal applied to each electrode and without moving them, it is possible to stimulate the desired area in the brain.

Materials and Methods: First, the simplified model of the head is considered as multi-layer concentric spheres and the electric current density at different points of the head model has been calculated by the finite element method and injected into a neuron model (Hodgkin-Huxley model) as the excitation current. The action potential created by the neuron model in different places of the head is considered as a stimulation pattern. In the following, a large number of these stimulation patterns have been created by changing the amplitude of the applied signal to the electrodes. The features of these stimulation patterns were extracted by a pre-trained deep neural network (Inception V3) and using machine learning algorithms (different regression methods), the amount of potential needed to stimulate different areas of the brain has been determined.

Results: Different methods have been used to estimate the potential of each pair of electrodes, the best result is obtained by the ε-SVM algorithm with the non-linear RBF kernel. For this algorithm, the average MAE and RMSE errors are 2.1 and 2.67, respectively.

Conclusion: The method proposed in this paper estimates one of the most important parameters of the stimulation signal, i.e. the amplitude of the voltage applied to the electrode for a large number of electrodes in the transcranial electrical neuromodulation using the TI method with appropriate accuracy and is a step towards facilitating the process of neuromodulation. This method is also applicable for other neural modulation techniques with different modalities.

Keywords: Neuromodulation; Transfer Learning; Deep Regression.

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Dosimetric Assessment of Four Most Commonly-Used Radionuclides in Radionuclide Therapy of Bone Metastases

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Abstract

Background: Bone metastases are common in a large number of malignancies, resulting in a worsened prognosis and a multitude of complications, including pain. Radionuclide therapy in order to relieving bone pain is now well-established method and several radionuclides are available for this purpose.

The aim of this study is the dosimetrically assessment and comparison of four most common radionuclides including ^{89}Sr, ^{166}Ho, ^{177}Lu, and ^{188}Re, used to treat and relieve pain caused by bone metastases in a femur model using the Monte Carlo N-Particle extended (MCNPX) code.

Materials and Methods: The absorbed radiation dose patterns of four radionuclides, including ^{89}Sr, ^{166}Ho, ^{177}Lu, and ^{188}Re, were obtained in a femur model based on the MCNPX Monte Carlo code. To calculate the absorbed dose in different tissues, we used RAdio Detection And Ranging (RADAR) Decay nuclear data on gamma and beta radiation energy, emission probability, ICRU, and ICRP data relating to different tissue components.

Results: Absorbed dose profiles based on the radius of the phantom for various beta and gamma rays of the aforementioned radionuclides showed a high dose variation in bone tissue compared to normal tissues. In terms of total absorbed dose, ^{188}Re showed to have a higher radiation dose on soft tissue (= 779.5 pGy/disintegration) and bone tissue (= 488.2985 pGy/disintegration), while ^{89}Sr had greater radiation dose on the bone marrow (= 58.25 pGy/disintegration) compared to other investigated radionuclides. Regarding the gamma ray absorbed dose, ^{89}Sr showed to have the highest radiation dose on all the tissues (soft tissue = 116.155 pGy/disintegration, bone = 54.5775 pGy/disintegration, bone marrow = 58.25 pGy/disintegration), whereas based on beta ray radiations, ^{188}Re had the highest impact on all the three types of tissues (soft tissue = 709.865 pGy/disintegration, bone = 451.855 pGy/disintegration). In addition, ^{89}Sr and ^{166}Ho presented the highest and lowest radiation toxicity to bone marrow (58.2 and 13.565 pGy/disintegration, respectively). Furthermore, ^{188}Re showed had the best results in terms of cost-effectiveness, theranostic value and effective half-life.

Conclusion: To select the proper radionuclide for treatment, many factors have been reported in some studies. Considering the diversity in the desirable characteristics of radionuclides, our suggestion is that further researches are essential to investigate conjugate radionuclides in order to achieve the best therapeutic effect and reduce side effects. According to our study, 188Re may be a desirable candidate for the treatment of bone pain caused by bone metastasis.

Keywords: Radionuclides; Bone Metastases Pain; Radionuclide Therapy; Palliative Therapy.

Frontiers in BIOMEDICAL TECHNOLOGIES

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Radioprotective Agents: Past, Recent Advances and Future Perspectives

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Abstract

Background: Cancer is one of the most important causes of death in the world, according to the estimates of the World Health Organization. Approximately 50% of patients with cancer require to receive radiation therapy, which may cause severe and late toxicities. Under these situations, radioprotective agents, a group of synthetic or natural compounds that can selectively protect or decrease damage to normal cells against ionizing radiations, can be used to prevent secondary malignancies. Preliminary studies focused on 4400 synthetic structures led to the discovery of Amifostine as the first US FDA-approved radioprotectant. However, due to several difficulties with this compound, more ideal radioprotective agents with low toxicities were sought. Natural compounds such as Herbal medicine, Flavonoids, vitamins, Melatonin, etc. are another group of radioprotectors that have been investigated due to their antioxidant, anti-inflammatory, and free radical scavenging properties. Nitroxides such as JP4-039, Superoxide dismutases, and superoxide dismutase mimetics such as M40403 and AEOL 10150 have attracted wide attention due to their free radical scavenging effects. Among the numerous older agents, a recent strategy can be focused on cell pathways through inhibiting cell apoptosis or Modifying cell signaling using targeted compounds including cytokines, growth factors, or some small molecules such as peptides. These discussed agents may also improve the health of normal cells under the previous approach.

Although Amifostine and Palifermin have US FDA approval for the prevention of severe Oral Mucositis (OM) caused by radiotherapy, both compounds have also some adverse effects. Thus, further agents that have general protective effects on the human body are required. In addition, these radioprotective agents should have less toxicity and more selectivity for normal cells. This study aims to review the well-known radioprotectors that can reduce harmful radiation effects in various situations such as radiation therapy, Occupational radiation exposures, or Non-Occupational radiation exposures.

Materials and Methods: A literature search in five databases was carried out: Ovid, PubMed, Scopus, ScienceDirect, and Google Scholar. Appropriate data from 1991 to 2022 was collected and compiled in this study.

Results and Conclusion: Nowadays, The Development of radioprotective agents is an important issue, considering the side effects of radiotherapy. Synthetic sulfhydryl compounds such as Amifostine can provide good local radiation protection through free radical scavenging. On the other hand, despite natural products being generally safe compared to synthetic compounds, they have the disadvantages of having low to mild efficacy. Among New approached compounds, some peptides including Bowman-Birk protease inhibitor peptide, mitochondria-targeted peptides, CBLB613 and CBLB502 peptides have shown the potential for radioprotection. For example, CBLB502 is an engineered derivative of the Salmonella flagellin protein that binds toll-like receptor-5 and activates a signal pathway. This pathway modulates the expression of several genes that can affect scavenging reactive oxygen species and inhibiting apoptosis. Currently, FDA has granted this compound as an Investigational New Drug (IND) and orphan drug for radiation countermeasure. Future horizons of radioprotectors will be more selective and specific compounds through designing novel small molecules and improving their formulation.

Keywords: Radioprotective Agents; Radiation Therapy; Antioxidants; Free Radical Scavenging.

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γ-Radiation Changed Stem Cell Response and Differentiation on Cellulosic Plant Scaffolds

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Abstract

Background: Nowadays, various tissue engineering approaches have been developed to repair damaged tissues using biomaterial implants in order to induce the regeneration of stem cells or induce directed differentiation. Plant tissue decellularized scaffolds might overcome availability issues, high costs, and ethical and environmental concerns related to the use of animal sources and synthetic methods.

This study investigated the effect of gamma irradiation on the chemical and physical properties of decellularized plant scaffolds. Two gamma radiation doses (25 and 50 kGy) were applied to scaffolds for modification followed by assessment of crystallization behavior, and mechanical properties of cellulosic scaffolds.

Materials and Methods: The irradiated polymers' microstructural and physical changes were evaluated using Scanning Electron Microscopy (SEM). BET analysis was used for the measurement of the specific surface area and porosity of materials. Component changes were assayed by using the FTIR technique. The MTT assay and DAPI staining are used to measure cell viability, proliferation, and cytotoxicity. Gene expression were performed to verify the effect of irradiation on differentiation of the cells.

Results: Irradiation dose of 50 kGy led to a remarkable effect on physical properties of plant derived scaffold while adverse effects have been found in high dose irradiation (100 kGy) was applied. Moreover, changes in nanostructure of the irradiated scaffolds have a significant effect on stem cell response and inducing differentiation.

Conclusion: This study proposes using appropriate radiation to improve the properties of the scaffolds to achieve an adequate response in cell culture.

Keywords: Scaffold; Tissue Engineering; Radiation.

5th International TPCF Preclinical Imaging Symposium

Potential of Decellularized Ponytail Palm and Haworthia Fasciata Decellularized Leaves for Stem Cell Differentiation Revealed by Image Analysis

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Abstract

Background: What is known is that the damaged tissues of the human body do not recover completely in many cases and can even be irreversible. Though new approaches of tissue engineering improve regeneration of stem cells for repair damaged tissues, the challenge of finding the superlative substrate to support stem cell growth, proliferation, and differentiation still remained.

Nowadays, the use of accurate imaging devices to examine the microstructures on the surface of various scaffolds and identify the elements can pave the way to facilitated the engineering of optimal scaffolds and create a suitable platform for cell growth, proliferation or differentiation. The use of cellulose scaffolds derived from nature in tissue engineering has been considered due to their high biocompatibility, non-toxic structure, and the lack of immune response of the host environment. Here we aimed to assess mechanical properties of ponytail palm and *Haworthia fasciata* decellularized leaves such as hydrophilicity, three-dimensional structure, angles, tensile strength and biodegradability. Further, their ability to provide appropriate environment for growth and maintenance of human mesenchymal stem cells considering their chemical functional groups as well as physical architecture.

Materials and Methods: In this study, the physical and chemical structures of the surface of the decellularized scaffolds of Ponytail palm and *Haworthia fasciata* have been investigated in order to evaluate the adhesion, migration, differentiation, and growth of the stem cells using various analytical and imaging measurements.

Results: Analysis of obtained Scanning Electron Microscope (SEM) images of prepared scaffolds showed their potentials for mimic the niche of the stem cells and are capable of inducing cell differentiation due to their high biocompatibility, proper wettability, the wide surface containing hydroxyl functional groups, and homogeneous and appropriate porosity as well as their chemical structure. Further, it was confirmed their proper 3D structure with interconnected pores, and moderate surface roughness are the key factors for directing cell fate.

Conclusion: According to our data, these plant-derived scaffolds have promising potential for use in regenerative medicine as a novel cost-effective and tailorable scaffold for stem cell culture and novel platform for preclinical research mainly in drug screening and disease modeling.

Keywords: Tissue Engineering; Cellulosic Scaffolds; Stem Cells; Preclinical Researches; 3Dimentional Culture.

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A Comparison between Electrical Impedance Tomography and Conventional Methods in Breast Cancer Screening and Detection

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Abstract

Background: Breast cancer is the most common cancer among women and the second leading cause of cancer deaths worldwide. The prevalence of breast cancer is predicted to have a 50% rise by 2040. Therefore, screening and early diagnosis are the key to effective breast cancer treatment and lead to a 15%-25% reduction in the mortality rate. Conventional diagnostic methods include mammography and ultrasound. Mammography has limitations in examining dense breasts and breasts that have undergone surgery, and ultrasound does not show lesions smaller than 1 cm with high accuracy due to low image contrast. Electrical Impedance Tomography (EIT) is an innovative imaging technique recently used in the early detection of breast cancer. EIT is a non-invasive modality based on permittivity and electrical conductivity differences between malignant and non-malignant tissues through surface electrodes (16 electrodes). Advantages of EIT include portability, low cost, 3D imaging capability, quantitative assessments, and non-ionizing radiation, which is suitable for pregnant women and women under 40. EIT provides information on physiological and metabolic changes. Contrary to the structural characteristics, functional features are detectable in the early stages of cancer imaging. 3D-EIT (128 electrodes) improves tumor localization by receiving depth information. The purpose of this study was to compare electrical impedance tomography with mammography and ultrasound in breast cancer screening and diagnosis.

Materials and Methods: The present review article was performed by searching "Pubmed" and "google scholar" by different combinations of the terms "breast cancer" and "electrical impedance tomography". 25 articles were obtained. After removing the reiterative and reviewing abstracts, 15 articles were selected and reviewed in full text.

Results: There was no significant difference between the sensitivity, specificity, and accuracy of ultrasound, mammography, and EIT alone. 3D-EIT performs better on dense breasts than mammography. 3D-EIT, along with mammography and ultrasound, improves the sensitivity of these methods and increases the early detection of breast cancer, especially in examining microscopic lesions. In a study of 1,200 women, sensitivity, specificity, positive predictive value, and negative predictive value for EIT were 85%, 96%, 12%, and 99%, respectively. In another study of 808 women, EIT, mammography, and ultrasound showed a sensitivity of 87%, 89%, and 91% and specificity of 85%, 91%, and 84%, respectively. In combination EIT with mammography and EIT with ultrasound, sensitivity and specificity increased. EIT can be used as a screening method in young women with dense breasts and high-risk breast cancers. However, EIT is limited in detecting tumors in the nipple-areola region because this region has high conductivity and is difficult to distinguish from the tumor. It is also unable to distinguish benign lesions from each other.

Conclusion: EIT is an effective and affordable method for the early assessment of breast cancer and provides additional beneficial information about metabolism and tissue function. By EIT techniques development, it might be possible to improve breast cancer diagnosis in the future. With all the advantages and diagnostic advances in this imaging technique, EIT is still not a substitute for conventional modalities, and it is recommended to be used as a complementary diagnostic method alongside mammography or ultrasound.

Keywords: Breast Cancer; Electrical Impedance Tomography; Mammography; Sonography.

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A Review on the Role of Non-Contrast Computed Tomography-Based Radiomics in Intracranial Hemorrhage Patients for Hematoma Expansion Prediction

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Abstract

Background: Spontaneous Intracerebral Hemorrhage (sICH) is responsible for 10%-30% of all strokes. Early Hematoma Expansion (HE) occurs in 30% of ICH patients and is an autonomous and adjustable predictor of poor outcomes in ICH patients. HE usually appears in the first 24 hours after the initial bleeding. Consequently, evaluation of prognostic factors in patients with a high risk of HE is necessary for quick and early diagnosis. Spot sign is known as the most effective prognosis of ICH, with a sensitivity of 51%, but its evaluation is possible only by the CT Angiography method. It is also limited in evaluating patients with renal failure or allergies to iodinated contrast materials. Hence, to investigate ICH patients with a high risk of HE, researchers turned to the markers that can be obtained through Non-Contrast Computed Tomography (NCCT). Radiomics is a non-invasive quantitative analysis method of radiological images that can extract hundreds of features from each image and supply more information for the prognosis and treatment. Machine learning is a set of complicated mathematical algorithms automatically modeling based on images' information. Using radiomics models with machine learning strategies based on NCCT images has significantly helped early HE prediction. The prediction by the radiomics model is fast and equal to 2.5 minutes per patient.

This review aimed to assess the role of radiomics through NCCT images to predict HE in ICH patients.

Materials and Methods: The present review article was performed by searching "Pubmed" and "google scholar" by different combinations of the terms "radiomics" and "intracranial hemorrhage" and "hematoma expansion" and "prediction". 21 articles were obtained. After removing the reiterative and reviewing abstracts, 10 articles were selected and reviewed in full text.

Results: To compare the methods of discriminating early HE after sICH, (I) the clinical-radiologic model, (II) the radiomics model, and (III) the combined model (clinical information, image signs, radiomics, and machine learning algorithm) were prepared in training (n=182) and validation (n=79) cohorts. The specificity was (I) 0.775, (II) 0.914 in the training cohort and 0.818 in the validation cohort, (III) 0.952 in the training cohort, and 0.881 in the validation cohort, respectively. The sensitivity was (I) 0.645, (II) 0.818 in the training cohort and 0.761 in the validation cohort, (III) 0.844 in the training cohort, and 0.804 in the validation cohort, respectively. The early prediction performance of radiomics models with machine learning was better than the clinical-radiologic model. However, the performance of the combined model has been significantly more effective than all other models. In another study, clinical, radiomics, and hybrid models were compared in the derivation cohort (n=864) and the validation cohort (n=289). In both groups, the clinical model had the lowest discrimination, and the hybrid model had the highest sensitivity (87% in derivation and 88.1% in validation) for the diagnosis and discrimination of HE.

Conclusion: In conclusion, radiomics as a fast and objective approach may improve treatment guidelines for patients with ICH. Modeling based on NCCT images, radiomics features, and machine learning algorithms makes it possible to improve the early diagnosis of HE after sICH, which ultimately reduces the mortality caused by it.

Keywords: Intracranial Hemorrhage; Hematoma Expansion; Radiomics.

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Decellularized Coleus Amboinicus and Echium Vulgare Leaves: A Potential Natural Nanostructure Matrix for Stem Cell Tissue Engineering

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Abstract

Background: Conventional medical treatments such as organ transplantation are limited due to constraints such as lack of organ donors or graft rejection of the transplanted tissue. Despite recent advances, almost biomedical technologies and tissue engineering are uncapable of the regeneration and repair of damaged tissues or have low efficiency due to the toxicity. Natural scaffolds such as plant leaves can be used as proper scaffold for stem cell culture and regenerative purposes owing to their inspired microenvironment.

Nowadays, imaging devices have given us a great help in examining the three-dimensional microstructures of scaffolds and the materials that are using for tissue engineering. Recently, natural polymers have received much attention in regenerative medicine due to their outstanding characteristics such as low cost, bioactivity, biocompatibility, non-toxicity of bio-products of degradation in addition to their unique three-dimensional structure. Analysis of nanostructure of cellulose-based scaffolds as a novel green matrix for stem cell culture can solve current issues for industrial production considering their porous structure and vascular network.

Materials and Methods: In this research, the leaves of Coleus amboinicus and Echium vulgare were decellularized, and their physical and chemical properties were investigated by Atomic Force and Scanning electron microscopes, Infrared spectroscopy and Brunauer-Emmett-Teller, tensile, and contact angle tests as well as evaluation of their supportive properties for human mesenchymal stem cell maintenance or differentiation.

Results: The topographical characterization of aforementioned scaffolds implied their ability to mimic stem cell microenvironment, whereas their regenerative potential was validated for two-week cell culture. In vitro and in vivo analysis showed that their great repair inductive potential without no major inflammatory response. The results confirmed a great potential and promising option for scaffolds in cell culture applications.

Conclusion: Altogether, decellularized scaffolds were revealed to provide a biomimetic microstructure for stem cell proliferation and directing differentiation through their unique physical and chemical properties combined with human mesenchymal stem cells for producing tailorable scaffolds and clinical regenerative purposes.

Keywords: Tissue Engineering; Natural Scaffold; Decellularized Plant Tissue; Stem Cells; Imaging Devices.

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Role of Machine Learning and Computer-Aided Diagnosis of Micro Calcification Lesions in Mammograms

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Abstract

Background: In mammography, many Computer-Aided Diagnosis CADx techniques have been developed for the classification of suspicious breast tumors in mammogram images, including both masses and clustered Micro Calcifications (MCs). Because of the subtlety of MCs in appearance in mammogram images, accurate diagnosis of MC lesions as benign or malignant is a very challenging problem for radiologists. Studies show that a false-positive diagnostic imaging study leads to unnecessary biopsy of benign lesions, yielding a positive predictive value of only 20–40%. There has been intensive research in the development of CADx techniques for clustered MCs, of which the purpose is to provide a second opinion to radiologists in their diagnosis to improve performance and efficiency. This review aimed to present the application of machine learning algorithms in CADx systems in the diagnosis of microcalcification lesions in mammograms.

Materials and Methods: The present review article was performed by searching "Pubmed" and "google scholar" by different combinations of the terms "Machine Learning" and "Computer-Aided Diagnosis" and "Algorithms" and "Mammography." 33 articles were obtained. After removing the reiterative and reviewing abstracts, 12 articles were selected and reviewed in full text.

Results: Various machine learning methods such as Linear Discriminant Analysis (LDA), logistic regression, Artificial Neural Network (ANN), and Support Vector Machine (SVM) have been used in developing CADx classifiers for clustered MCs. in a study, an LDA classifier was used for the classification of benign and malignant MCs based on their visibility and shape features. This approach was subsequently extended to morphology and texture features in another study. It was demonstrated that an ANN-based approach could improve the diagnostic performance of radiologists for MCs. Feature Kernel Distillation (FKD), ANN, SVM, Relevance Vector Machine (RVM), and committee machines were explored in a comparison study, wherein the SVM yielded improved performance over the others. Collectively, the reported research results demonstrate that CADx has the potential to improve the radiologists' performance in breast cancer diagnosis. In the development of CADx techniques in the literature, various features have been investigated for characterizing MC lesions. These features are defined to characterize the gray-level properties (e.g., the brightness, contrast, and gradient of individual MCs, the texture in the lesion region) or geometric properties of the MC lesions (e.g., the size and shape of the individual MCs, the number of MCs, the area, shape, and spatial distribution of a cluster). They are extracted either from the individual MCs or the entire lesion region. The features of individual MCs are often summarized using statistics to characterize an MC cluster. While research and development have led to improvement in CADx performance, as a diagnostic aid, the accuracy level achieved by CADx classifiers is relatively moderate for specific tumor types due to the inherent difficulty of the problem (e.g., MC lesions).

Conclusion: We conjecture that with the integration of a retrieval system and a CADx classifier, the retrieved images could serve as supporting evidence to the CADx classifier, which may facilitate the interpretation of the likelihood of malignancy by the radiologists in clinical practice.

Keywords: Machine Learning; Micro Calcification; Mammography.

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Application of Imaging Techniques for Preclinical Models of Placental Disorders

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Abstract

Background: The development and maturation of a fetus depend heavily on the placenta. Throughout pregnancy, it keeps the blood flow between the mother and fetus physically distinct but functionally connected. The functional evaluation of the placenta, which controls almost all exchanges of nutrients, waste products, and breathing gases between the maternal and fetal compartments, is a significant challenge in prenatal treatment. Although the etiologies and pathogenesis of utero-placental disorders are poorly understood, and placental function is still difficult to assess and quantify in routine clinical practice, we now need both animal models and noninvasive functional imaging tools to better understand the mechanisms underlying placental pathologies. Imaging can diagnose abnormal placentation, monitor uterine blood flow semi-quantitatively to determine the health of the fetus, and recent developments in imaging technology allow for the in vivo visualization of the uterine contents during pregnancy. Retrograde femoral angiography, X-ray computed tomography, radionuclide scintigraphy, ultrasonography, and, more recently, Magnetic Resonance Imaging (MRI) are some of the methods used. The purpose of this review article is to show the advantages and disadvantages of different imaging modalities in animal models of placental dysfunction.

Materials and Methods: A comprehensive search for pertinent studies was conducted in PubMed, Scopus, web of science, and Embase databases using the terms "preclinical imaging", "animal model", and "placental abnormality" The relevant articles published up to 31st of January 2022 were assessed.

Results: Emerging MRI methods like SPEN (soild psedopapillary epithelial neoplasm) offer robust imaging various for the investigation of anatomical and dynamic options even underneath the difficult conditions arising in vivo MRI of mice at high magnetic fields. Equipped with this tool, diffusion-based studies capable of enhancing our understanding of placental structure and performance become attainable. High-Frequency Ultrasound may be a powerful technique for observing and measuring mice's embryonic improvement from exceptionally early stages of pregnancy. HFUS (high frequency ultrasound) is performed in real-time and is both simple and fast. This strategy is favorable for animal well-being, permitting serial ultrasound examinations on consequent days. HFUS is a critical phenotyping instrument for embryonic mouse research and can be utilized to reply to vital questions in developmental science. CE-CT gives a strategy to accurately evaluate placental parameters (i.e. volumes, volume division, the proportion of distinctive placental layers, and volumes of particular cell populaces) that are vital for factual comparison studies. Doppler ultrasound (Doppler-US) has the ability to evaluate unusual placentation and to semi-quantitatively degree uterine blood flow for the assessment of fetal well-being. However, this method is restricted to characterizing major maternal blood vessels supporting the placenta and isn't capable of assessing blood glide in the inter-villous space, the site of nutrient exchange with the fetal vasculature. These limitations lead to multi-modality imaging to increase our knowledge of placental disorders.

Conclusion: Preclinical imaging is crucial in enhancing animal models and allowing a noninvasive and clinically translatable way to track the progression of disease in real-time. Various imaging modalities are used to investigate placenta disorders in multiple conditions such as intrauterine growth restriction, placental insufficiency, and inappropriate placental function related to glucose, etc. The integration of imaging methods with each other, helps us in early diagnosis and reducing the number of stillbirth and maternal and perinatal mortality and morbidity.

Keywords: Placental Disorders; Preclinical Models; Imaging.

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Live Imaging Determination of Blood Cells during Neurovascular Thrombosis Mediated by Intranasal Inoculation of MVA, IgA-based vaccines in Mice against SARS-CoV-2 Infection

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Abstract

Background: Immune complexes are formed in systemic disorders such as rheumatologic, autoimmune and allergic diseases or in response to infections or drugs. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) adenovirus vector vaccines are associated with rare but serious thrombotic events in the brain due to the formation of immune complexes that activate platelets. The current vaccines have greatly reduced the severity of the COVID-19 (Coronavirus disease-2019) epidemic, even they do not completely prevent the infection and transmission of this virus due to insufficient immunity in the upper respiratory tract. Here, we compared and investigated intramuscular and intranasal administration of Ankara-based replication-deficient Modified Vaccinia virus Vaccine (MVA) to enhance protective immune responses in the hACE2 mouse model. This study aimed to determine live imaging of blood cells during neurovascular thrombosis by intranasal inoculation of MVA, IgA based vaccines in mice against SARS-CoV-2 infection.

Materials and Methods: This research, as a review study of the type of secondary studies with a narrative review approach with the aim of collecting and presenting information, is about neurovascular thrombosis mediated by intranasal inoculation against COVID-19 infection with the main coverage of articles in this field has been published until June 2022. This research was conducted by searching keywords such as Blood Cells, Intracranial, Thrombosis, Intracranial, MVA vaccine and SARS-CoV-2 variants, in reliable databases such as Science Direct, Scopus, PubMed and Web of Science.

Results: According to the studies from the articles, the results obtained are that, using a recombinant MVA expressing firefly luciferase for tracking, live imaging, it showed the luminescence of the mouse respiratory tract within 6 hours and for 3 days after it remained from intranasal inoculation, while luminescence remained at the site of intramuscular vaccination. Intramuscular vaccination induced S-binding-Immunoglobulin G (IgG) and neutralizing antibodies in the lungs, while intranasal vaccination also induced immunoglobulin A (IgA) and higher levels of CD3+CD8+IFN-γ+ cells. It induced a specific gene. Currently, there are no data showing the interaction of platelets with leukocytes and brain vascular endothelium in response to immune complexes. This is partly due to the absence of FcgRIIA in mice, a receptor for immune complexes involved in these thrombotic events. Here, we describe and demonstrate the events at the cellular level that occur in the cerebral vasculature in response to systemic administration of alternative immune complexes. We used Ly6gCre1/2: Rosa26-TdT1/2: CD41-YFP1/2 mice expressing the FcgRIIA gene and fluorescence in neutrophils and platelets. Similarly, IgG and neutralizing antibodies were present in the blood of mice immunized intranasal and intramuscularly, but IgA was detected only after intranasal inoculation. Intranasal boosting increased IgA after intranasal or intramuscular priming. Whereas intramuscular vaccination prevented disease and cleared SARS-CoV-2 from the respiratory tract within days of challenge.

Conclusion: According to the results, we observed transient and stable platelet-neutrophil interactions, platelets forming thrombus, and neutrophil adhesion to the blood vessel wall. This imaging approach in the quadruple transgenic animal model can be used to study the pathogenic role of immune complexes in disease.

Keywords: Blood Cells; Intracranial Thrombosis; Intracranial; Modified Vaccinia Virus Ankara; Severe Acute Respiratory Syndrome Coronavirus 2 Variants.

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Determining the Preparation Mechanism and Applications of Photodynamics and Phototherapy in the Treatment of Hepatocellular Carcinoma

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Abstract

Background: Photothermal Therapy (PTT) has been widely used in cancer treatment due to its non-invasive, local treatment and good therapeutic effect. The final therapeutic effect of PTT mainly depends on the photothermal materials, which can be further determined by the photothermal conversion efficiency, biocompatibility, and photothermal stability of the photothermal materials. Although there have been advances in the treatment of HCC, the prognosis of HCC patients is still poor, with a 5-year survival rate of only about 18%. Hepatocellular Carcinoma (HCC) is the most common primary liver tumor. It is the sixth most common neoplasm and the third most common cause of cancer death. The most common treatment for HCC is surgery, but the 5-year recurrence rate remains high. Patients with early stage HCC with few nodules can be treated with resection or Radiofrequency Ablation (RFA). While for multinodular HCC, Transarterial Chemoembolization (TACE) has been the first line of treatment. Based on biomedical engineering collaborations, nanotechnology has been increasingly applied in cancer treatment. Photodynamic therapy and photothermal therapy are effective for cancer. This article summarizes the latest advances in photodynamic therapy and photothermal therapy for HCC with the aim of providing new ideas for the treatment of HCC.

Materials and Methods: This research, as a review study of the type of secondary studies with a narrative review approach with the aim of collecting and presenting information, is about the mechanism of photodynamic and phototherapy applications in the treatment of hepatocellular carcinoma with the main coverage of articles published until June 2022. This research was done by searching keywords such as Photo chemotherapy, Phototherapy, Antineoplastic, Protocols Carcinoma, and Hepatocellular in reliable databases such as Science Direct, Scopus, PubMed, and Web of Science.

Results: Cancer is the second most common cause of death among all diseases. HCC is a common gastrointestinal tumor and the sixth most common type of cancer worldwide. Treatment includes radical surgery, molecular targeted therapies and neoadjuvant therapy. Therefore, new treatment methods are urgently needed to change this situation. HCC is a malignant tumor with poor prognosis and high mortality, and it is difficult to diagnose in the early stages, which endangers human health. Research efforts have focused on effective treatment. Surgical treatment and chemotherapy as well as targeted therapies and current immunotherapy have curative effects on HCC. Combining medical and engineering methods as a treatment strategy for liver cancer is beginning to yield results. Most current studies are based on basic research, and there are still few HCC clinical studies based on PTT or PDT. At the same time, accelerating the transformation of basic research into clinical research and promoting clinical research into clinical application are effective approaches for the treatment of HCC. With the advancement of science and technology and the deepening of research, the effective treatment of liver cancer will improve.

Conclusion: PTT and PDT have played an important role in the treatment of tumors and are used for the treatment of HCC.

Keywords: Photo Chemotherapy; Phototherapy; Antineoplastic; Protocols Carcinoma; Hepatocellular.

Frontiers in BIOMEDICAL TECHNOLOGIES

5th International TPCF Preclinical Imaging Symposium

Fundamentals and Profound Developments in Cancer Tumor Surgery with Ionizing Radiation for Imaging in Cancer Treatment

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Abstract

Background: Fluorescence-guided surgery using tumor-targeted imaging agents has emerged as a promising and effective method for intraoperative cancer diagnosis in the last decade. The higher doses required for technologies such as Computed Tomography (CT) and the increasing use of these technologies further increase medical radiation exposure for the population. In addition, the use of CT for population-based cancer screening for common malignancies such as lung cancer and colorectal cancer continues to be investigated. Given the known carcinogenic effects of ionizing radiation, this assessment ensures a balance between the benefits of early cancer detection and the risk of malignancy from screening. Limited experimental studies using cell lines and primary cells exposed to low and high doses of radiation have been performed to help determine the radiosensitivity associated with DNA mismatch repair gene deficiency, a defining feature of Lynch syndrome. Collectively, these studies suggest that mismatch repair-deficient cells may be relatively radioresistant (especially for low-dose exposures) with higher mutation rates, although no definitive conclusions can be drawn.

The purpose of this study is to determine the fundamentals and profound changes in the surgery of cancer tumors with the presence of ionization rays for imaging in cancer treatment.

Materials and Methods: This research is a review of the type of secondary studies with a narrative review approach with the aim of collecting and presenting information about the basics and deep developments in cancer tumor surgery for imaging in cancer treatment with the main coverage of articles in this field. Published by June 2022. This research was conducted by searching keywords such as surgery, cancerous tumors, ionizing radiation, imaging and cancer treatment in reliable databases such as Science Direct, Scopus, PubMed and Web of Science.

Results: Studies of different mouse models showed an increased risk of developing colorectal tumors in mismatch repair deficient mice that were exposed to a radiation dose of about 2 Gy. With appropriate ethical approval, further studies investigating the radiation risks associated with CT imaging and the doses associated with radiation therapy have been developed. This report provides an overview of the process of radiation carcinogenesis and the literature on CT-induced malignancy risk assessment, focusing on the risks and benefits of CT for cancer screening. In high-risk patients, CT colonography for colorectal cancer may significantly outweigh the risk of radiation. Future studies evaluating the benefits of CT screening should consider the potential risks of radiation.

Conclusion: Using cells/tissues derived from confirmed Lynch patients or genetically modified animal models is essential for future clinical guidance.

Keywords: Surgery; Cancerous Tumors; Ionizing Radiation; Imaging and Cancer Treatment.

5th International TPCF Preclinical Imaging Symposium

Investigating the Relationship between the Roles of Imaging in the Discovery of Biomarkers in Cancer Treatment

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Abstract

Background: Targeted cancer imaging, design and synthesis of Nano platforms based on tumor biology, categorizes imaging and targeting approaches based on cancer type. It highlights new and safe approaches that include membrane-encapsulated nanoparticles, tumor cell-derived extracellular vesicles, circulating tumor cells, free DNA cells, and cancer stem cells with the aim of showing the way to develop precision and nanotechnology-based imaging probes. A cancer biomarker indicates the presence of cancer in the body. Genetic, epigenetic, proteomic, glycemic, and imaging biomarkers can be used for cancer diagnosis, prognosis, and epidemiology, and ideally, these biomarkers can be measured in noninvasive biological fluids such as blood or serum. A biomarker may be a molecule that helps doctors detect abnormalities in tissues prone to cancer and prevent its spread by applying cancer treatment methods. Imaging tests work by sending different types of energy into the body, such as sound waves, X-rays, magnetic fields, or radioactive particles. Body tissues change these energy patterns to create an image.

The purpose of this study is to determine the relationship between the roles of imaging in the discovery of biomarkers in cancer treatment.

Materials and Methods: This research is a review of the type of secondary studies with a narrative review approach with the aim of collecting and presenting information about the affected roles of imaging in the discovery of biomarkers in cancer treatment with the main coverage of articles in this field. Published by June 2022. This research was conducted by searching keywords such as imaging, marker, cancer, tumor biology and cancer stem cells in reliable databases such as Science Direct, Scopus, PubMed and Web of Science.

Results: The results show that biomarkers are proteins that can be identified and measured in blood or urine. This term covers any molecular, biochemical, physiological or anatomical property that can be quantified or measured. The National Cancer Institute (NCI) defines a biomarker as a biological molecule expressed in blood, tissue fluids, or tissues. This molecule can be a sign of a normal or abnormal process, a disease or condition. A biomarker can also be used to check how the body responds to a treatment for a disease or condition. It is also called molecular marker and effector molecule. In cancer and medical research, there are three main methods of using biomarkers: first, to help diagnose conditions, such as identifying cancers in the early stages, second, predicting the aggressiveness of the condition, such as determining the patient's ability to compensate in the absence of treatment, third, predicting Patient response to treatment.

Conclusion: Cancer is a disease that affects society globally. By imaging biomarkers, early diagnosis can be made to prevent death and progression of the disease.

Keywords: Imaging; Marker; Cancer; Tumor Biology; Cancer Stem Cells.

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Application of Imaging Techniques in the Diagnosis and Treatment of Pancreatic Cancer

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Abstract

Background: The most common type of pancreatic cancer is Pancreatic Duct Adenocarcinoma (PDAC). Pancreatic cancer is a heterogeneous and malignant disease. This cancer is the second leading cause of death from cancer. Lack of early diagnosis of the disease and lack of biomarkers is one of the main reasons for the high mortality rate of this disease, and increases treatment limitations. There is currently no effective method of prevention or early detection, and patients refer to the advanced stage of disease. One of the most effective treatment methods is surgery to remove the tumor, but few patients have the condition to do surgery. Imaging approaches play an important role in identifying PDAC patients in the early stages of the disease and their treatment.

Materials and Methods: The imaging techniques that are utilized for this purpose include: CT, MRI, PET, Ultrasound and photoacoustic imaging.

Results: Nanoparticles are widely utilized as a contrast agent in imaging techniques to detect PADC, gold nanoparticles play the role of contrast agent in several imaging techniques. These nanoparticles are first coated with a layer of mesoporous silica and then coated with a layer of gadolinium oxide carbonate (AuNR−SiO_2−Gd). These nanoparticles accumulate in the soft tissues surround the tumor, these compounds act as negative contrast in CT/PAI imaging modality and as positive contrast in MRI modality. For PET imaging, the radiotracer 18F-FDG is utilized in a large number of studies. The uptake of this substance in chronic pancreatitis is lower compared to pancreatic cancer. Iodine contrast agent is also utilized in CT imaging modality. Utilizing this method, it is possible to detect the tumor when its size is less than 1 cm and it has not started metastasizing yet.

Conclusion: Unlike other imaging modalities, the ultrasound technique is highly dependent on the operator. A panoramic view of the pancreas is not sometimes possible due to the presence of stomach gases. when the transabdominal ultrasound imaging method is utilized to diagnose pancreatic cancer, the sensitivity of this method is very different, so that up to 50% of tumors smaller than 1cm and 90% of tumors smaller than 3cm can be detected by the method. Contrast agents that are approved by the FDA and utilized in the ultrasound technique to produce microbubbles and nanobubbles include: octafluoropropane, perfluorohexane and perfluorobutane. Therefore, non-invasive imaging techniques have different sensitivity and accuracy in tumor detection during the disease progression process.

Keywords: Pancreatic Cancer; Ultrasound; Positron Emission Tomography; Magnetic Resonance Imaging.

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Hierarchical Design of "All in One" TME-Responsive Nanoplatform for Theranostics Application

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Abstract

Background: The word "Theranostics" was coined by the US consultant John Funkhouser, in August 1998. In the last two decades, "Theranostics" has become the heart of cancer research in the field of nanomedicine. Theranostics can be defined as a smart "all in one" package that combines one or more diagnosis modalities with therapeutic agents. The purpose of designing this package is to gain correct diagnosis in the early stages of the malignant pathological tumors and prognosis of tumor metastasis, in order to treat efficiently. Design and development of tumor microenvironment-responsive (TME-responsive) theranostic nanoplatforms as a cohesive unit enabled to address unmet medical need and creates a promising solution to deal with one of the most important causes of death (cancer) in the world. The microenvironment of cancer tumor is an intricate and heterogeneous system with a set of characteristic features such as high concentration of H_2O_2 and intracellular glutathione (GSH) and H+ (low pH), low level of pathological pressure of O_2 (pO_2) and lactate, vascular abnormalities, glucose deprivation. An "all in one" smart theranostic nanoplatform must have unique features such as: (1) high surface area to load considerable amount of therapeutic payload, (2) TME-responsiveness to release of payload correctly in the target tissue, (3) nanoscopic size to escape from Reticuloendothelial Systems (RES) of body and enhanced permeability and retention (EPR) effect (4) functionalize easily to couple of the imaging modality to monitor the therapeutic process or link targeted moiety or hydrophilic parts to enhance circulation time, (5) biodegradability and dispersibility to reduce toxic side effects. Therefore, the integration all of these factors in one system is promising. Design and development of MnO_2-based theranostic nanoplatform to introduce several unique features that are important in diagnosis, monitoring, drug loading and releasing, prognosis of metastasis, and proper noninvasive therapy of pathological tumors.

Materials and Methods: We successfully synthesized high specific surface area and O_2-generating GdxMn1-xO_2@TPP-Chit (X: 0, 0.03, 0.06, 0.09, 0.12) multifunctional and multimodal nanoplatform and well characterized through FT-IR, FE-SEM, TEM, XRD, BET, LDI-TOF, EDX, Elemental mapping, PSD, Zeta-potential, VSM techniques.

Results: Highly surface area GdxMn1-xO_2 nanoplatforms had an excellent performance in catalytic generating of molecular O_2 in vitro upon reaction with TME condition of cancers. Good dispersibility and biocompatibility can be obtained with surface modification of nanoparticles with chitosan polymer that cross-linked with tripolyphosphate. Further, this nanoplatforms specifically released Doxorubicin (DOX) and paclitaxel (PTX) as a chemotherapeutic drug upon an endogenous stimulus (H+, H_2O_2, Glutathione (GSH), Temperature in the TME). GdxMn1-xO_2 with optimum amount of Gd3+ ion doping shown an excellent candidate for MRI and fluorescence imaging.

Conclusion: This study not only demonstrated the great potential of GdxMn1-xO_2@TPP-Chit TME-responsive nanoplatforms for targeted therapy of cancer but also provided a new therapeutic strategy to overcoming tumor hypoxia with in-situ catalytic O_2 production reactions.

Keywords: Theranostics; Nanoplatforms; Tumor Microenvironment; Manganese Dioxide.

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Development of New CT/MRI/Optic Trimodal Lanthanide-based Nanosystems for Theranostics Application

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Abstract

Background: In recent years, implementation of new concepts and equipment derived from nanoscience has made a lot of progress and solve problems of conventional techniques for diagnosis and therapy. The combination of diagnostic modalities and therapeutic functionalities into one "package" at nanoscopic size, namely nanotheranostics. Nanotheranostic as a progressive paradigm probably demonstrates the highest level of technological advance in the nanomedicine field. The use of lanthanides in the field of nanotheranostics brings unique features to these systems. Lanthanides refer to 15 rare earth elements placed at the 6th period and IIIB group in the periodic table. The unrivaled attributes of lanthanides relate to their 4f orbitals. The number of unpaired electrons in 4f orbitals have strong unquenched angular momentum can be up to seven in Gd3+ ion, inducing impressive spin-orbit coupling and significant paramagnetic properties which introduces these elements as a suitable candidate for magnetic resonance imaging (MRI). In addition, the lanthanides are marvelous for optical imaging due to the large quantum numbers (n = 4, l = 3). Furthermore, recent research has shown introducing Nd^{3+} ions have a direct constructive influence on Mass Attenuation Coefficient (MAC) and also the Linear Attenuation Coefficient (μ, LAC). On the other hand, in CT imaging different tissues have distinctive μ values; thus, contrast occurs when an X-ray beam traverses different tissues and the larger the difference in μ values between tissues, the greater will be the contrast. Therefore, the design of Nanotheranostic system with Nd+3 ion is very attractive.

Synthesis and development of multimodal lanthanide-doped Gd_2O_3 theranostic nanoplatform in order to substantiation of the objective of personalized medicine "the right dose of the right drug for the right patient at the right time".

Materials and Methods: We successfully synthesized highly porous hollow sphere $NdxGd_2$-xO_3@PEG (X: 0, 0.05, 0.10, 0.15) nanotheranostic platforms and well characterized through FT-IR, DRS, PL, FE-SEM, DLS, XRD, BET, Rietveld refinement, EDX, Elemental mapping, PSD, Zeta-potential, VSM techniques.

Results: Hollow sphere $NdxGd_2$-xO_3 theranostics nanoplatforms had an excellent performance in loading and releasing of DOX drug and also combine three complementary of imaging modalities (CT/MRI/Optic). PEGylation of this nanosystem reduced the toxicity of the naked nanocarrier. The presence of micro and mesopores alongside the main macroporous structure of H- $NdxGd_2$-xO_3 not only increases the drug loading capacity but also induce a smooth drug release pattern.

Conclusion: The results demonstrate H-$NdxGd_2$-xO_3@PEG@DOX with optimum amount of Nd+3 ion doping agent has a good efficacy for trimodal CT/MRI/Optic imaging and also shows an excellent potential for targeted drug delivery.

Keywords: Nanotheranostics; Hollow Sphere; Gadolinium Oxide; Doping Agent; Trimodal Bioimaging.

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5th International TPCF Preclinical Imaging Symposium

Necessity and Need of Ethic in Clinical and Preclinical Trials

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Abstract

It can be taught that after writing "Nicomachean Ethics" by Aristole, necessity of intention to ethics in interaction between human and other creatures arrive to the fields of life and research. There is no doubt that any wise, intellectual and reasonable person accept the necessity of responsibility and accountability in interaction with other peoples, animals and nature not only in researches even in an ordinary life. Unfortunately, we had to accept the shames of non-ethical manners which happened by owners of power and capitals in history.

After the RENAISSANCE, ethics arrive to different branches of life and scientific activities and now a day we can not find no field with special ethical topics for any kind of interactive actions between different creatures. Fortunately, arriving the law into the scientific fields and development of social media power reduce the chance of violence of the right by researchers

Adherence to ethic in clinical and preclinical researches in human and animal fields is very important. The probability of even an unwanted injury to the population of study can be very high according to designed material and methods of study. Some kinds of these injuries have been announced by Frans de Waal (2018) for animals and Vodkher Brahman (2019) for human in research. Both authors have this opinion that passing time can not reveal the pains and discomforts which arose by non-ethical procedures of aforementioned research.

Some examples for compliance of ethic in clinical and preclinical activities are: prevention from suffering of case, no preference of scientific expediency to the reality and truth, ability of case of study (person) or responsible person for animal in ending the study in any time, clarifying all stages of clinical and preclinical trials for case of study (person) and responsible person for animal, full responsibility and accountability of researcher for any wanted and unwanted corresponding injuries to case of study (person or animal) during or after ending of study.

Keywords: Preclinical Research; Scientific Research; Ethical Research; Discover the Truth.

5th International TPCF Preclinical Imaging Symposium

PET Scan Ability in Evaluating, Interpretation and Diagnosis of Heart Disease

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Abstract

Heart is one of the vital, important and sensitive organs in most creatures. Diseases of this organ is situated in first row of the list of the reason of death in word. Prevention and diagnosis of heart diseases are the valuable procedures in all branches of medicine and using of sophisticated and high-quality techniques in this field is very important and valuable. PET SCAN (Positron Emission Transfer) is one of these aforementioned techniques. Unfortunately acquisition of PET SCAN is not acceptable now a day in Iran.

PET SCAN is an accurate quantitative procedure with some degrees of invasivity. In this technique by using a radioactive agent, functions of tissues and organs will be evaluated in cellular and intracellular levels in patients. By using this method for evaluating the heart, valuable anatomical and physio-pathological information will be achieved. Evaluation of myocardium in patient with systolic dysfunction, patient who candidate for heart transplantation, coronary heart disease, atherosclerosis, thrombosis, differentiation of ischemic and non-ischemic conditions and differentiation between malignant and non-malignant tumors is possible in this diagnostic procedure.

PET Scan shows the metabolic changes of heart. Fatty acids are the source of the heart metabolism and most of the ATP is acquired via oxidation of fatty acids. Heart has the ability of using Glucose, Lactate and ketone bodies as sources of energy with adequate mechanisms for controlling on these different sources. PET SCAN has marvelous ability for detecting changes in these different routes with enough ability in evaluation the level of pathologic and underling heart condition for choosing best treatment procedures.

There is no doubt with all of these abilities, trying for finding essential biomarkers and accurate new sophisticated mechanisms are very important for development of PET SCAN usage in all field of medicine.

Keywords: Pet Scan; Heart Disease; Diagnostic Imaging.

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Importance Intrauterine Adhesions and Its Induction in the Rat Model

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Abstract

Background: Intrauterine Adhesions (IUA) or Asherman's Syndrome, are a type of more common gynecological disease. This syndrome associated with amenorrhea, hypomenorrhea, infertility and recurrent miscarriage. The most common and most important cause of IUA is trauma or infection, especially after pregnancy. Animal models are alternative to experimental systems for biomedical research to obtain information about drugs and new I treatment. Severe IUA can cause serious harmful damage to female reproductive system. Therefore, the discovery of modern therapeutic strategies to enhance the acceptance of endometrium tissue and prevent infertility are very important in this syndrome. Importance and treatment of IUA and its induction in the rat model.

Materials and Methods: In this review article, the articles indexed in various databases were used. The collection of articles was evaluated without time constraints using keywords inducing Intrauterine adhesions, rat model, treatment and endometrial acceptance. The selected articles were evaluated according to the inclusion criteria.

Results: Endometrial receptivity is Considered as a short period when the endometrium is acceptable to embryo implantation. IUA can affect the acceptance of endometrium through different aspects of morphological and molecular biology. Therefore, acceptance of endometrium tissue is a decisive prognosis factor for fertility to evaluate the effectiveness of IUA treatment. On the other hand, although none of the animal models are completely ideal, rat models are the most widely and most commonly used in studies related to midwifery, gynecology, theriogenology and pregnancy.

Conclusion: Animal models can act as a maquette of real systems and easily imagine them. In order to create IUA in rat model, the animal must be in the diestrous stage of estrous Cycle, which can be determined by vaginal cytology. Then, following the anesthesia induction and preparation of the surgical site, the rat is placed in the dorsal recumbency and the abdominal area is exposed with a cut of 2 to 2.5 cm in the middle line. The endometrial lining is then scratched in the middle and upper two-thirds of the uterus using an endometrial curette of 2.5 mm. The curettage stops when the uterine cavity stopped feeling uneven and the uterine wall is rough. Since a week after the surgical intervention, the various effects of the drugs on the model can be examined. The IUA is referred to as an endometrium trauma that causes adhesion to the uterine cavity. IUA eventually causes complete or incomplete obstruction of the uterine cavity and/or cervical canal. The acceptance of the endometrium tissue of the uterus, the function of the blastocyst tissue, and the synchronization of the interactions (dialogues) between the embryonic and maternal tissues are essential for successful embryo implantation. The purpose of IUA treatment is to regeneration uterine endometrium tissue to achieve successful pregnancy, which treatments are: 1- hysteroscopic surgery to restore the normal size and shape of the uterus; 2- Use hyaluronic gel or Foley catheters to prevent recurrence of adhesion; 3- Using high doses of estrogen to stimulate uterine endometrium tissue regeneration and 4- insertion of an IUD in uterus.

Keywords: Intrauterine Adhesions; Rat Model; Treatment; Endometrial Acceptance.

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Importance Fungal Vaginitis and Its Induction in the Rat Model

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Abstract

Background: It is well accepted that the microbiota in the human body can affect the immune system, health and physiology. Vaginal microbiota has evolved uniquely to play its dual role, resistance to diseases and pregnancy protection. Vaginal Microbiota imbalance is primarily caused by Candida, which is considered the second common vaginal infection. The disease causes discomfort and pain in the vulva area. Vulvovaginal candidiasis is often caused by Candida albicans and is a common mucosal infection. The disease affects a large population of women of fertility age. It is recommended to use of rat models of gynecology because of the benefits such as minor changes in physical properties, pathophysiological and mechanical properties among animals, comfortable handling capability, good cost efficiency and availability.

Importance and method of inducing fungal vaginitis in the rat model.

Materials and Methods: In this review article, the articles indexed in various databases were used. The collection of articles was evaluated without time constraints using keywords inducing fungal vaginitis, rat model, genecology and Candida albicans. The selected articles were evaluated according to the inclusion criteria.

Results: Upregulation of proinflammatory cytokines (IL-17 and IFN-γ) by Candida albicans suggests proliferation of T cells and activation of these cells. In addition to, successful fungal vaginitis can be induced in the rat model.

Conclusion: The suggested animal species to create these models have benefits such as low cost, repetition of results and management during testing, and minimal ethical/social consequences. To create an experimental vaginitis candidiasis, the Candida albicans are first incubate in the Sabouraud Dextrose Agar (SDA) environment at 37 ° C for 72 hours. Animals received subcutaneous injection of 0.5 mg estradiol benzoate at 2-day intervals until the end of the experiment to induce immunosuppression. Rats with a 1×10^8 yeast/ ml fungal suspension (in 150 ml of sterile saline solution) are inoculated intravaginal. Four days after inoculation but before treatment, samples were obtained from the vaginal cavity to confirm candida albicans infection by Gram staining of the yeast/hyphae-like form and vaginal cells observed under light microscopy. It is widely accepted that local immune system plays a more vital role in systemic immune system. The pathological infection caused by Candida albicans does not only stimulate immune cells but also induce significant Ultrastructural changes in the host body cells. For example, we can refer to the inhibition of the accumulation of desmosomes, which ultimately leads to a decrease in adhesion power. Desmosomes are a preadult type of intracellular adhesive in tissues that fight various factors such as toxins, inflammatory and pathological factors that potentially cause damage to body tissues. It is recommended that standard treatment for vaginal fungal infection caused by Candida albicans is an antifungal therapy including the use of azole or triazole drugs orally or intravaginal.

Keywords: Fungal Vaginitis; Rat Model; Genecology; Candida Albicans.

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Importance of Controlled Release Drug Delivery Systems Based on Chitosan

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Abstract

Background: One of the drug delivery systems is implant systems. The main purpose of these drug shapes is to release local drug release to increase the presence and absorption of the drug to the desired location, which can be controlled release. Since these compounds is necessary to perform continuously and repeatable to the target site during the repair period Therefore, a controlled or slow implant system is designed to be effective in site and prolonged release of the drug. Chitosan is prepared by chitin deacetylation (natural polysaccharides in the external skeleton of crustacean such as crabs and shrimp). This cationic polysaccharide has been widely considered in biology, medicine and pharmacology due to its high availability, unparalleled adhesion, appropriate pharmacological properties and other beneficial biological properties such as biocompatibility, biodegradability, lack of toxicity and low immune system. Importance of controlled release drug delivery systems based on chitosan.

Materials and Methods: In this review article, the articles indexed in various databases were used. The collection of articles was evaluated without time constraints using keywords inducing controlled release drug delivery systems, chitosan, implant systems and biocompatibility. The selected articles were evaluated according to the inclusion criteria.

Results: With the development of science, the researchers are trying to create a slowdown of the drug by making controlled release drug delivery systems, while reducing the number of medications and reducing its side effects to create a certain level of blood during treatment in the body to provide a more effective treatment for the patient. Implant systems is that they are able to even provide drugs for more than a year. The longest drug delivery can be achieved by using biodegradable or non -biodegradable implant systems.

Conclusion: Long effect formulations compared to common formulation of the same compound show many benefits, including: 1- Predictable profiles of drug release in defined time period following each injection; 2- Better adaptation of the patient with treatment; 3- Easy use; 4- Less injections without endangering the effectiveness of treatment; 5- Reducing the incidence of side effects and 6- Reducing the total cost of medical care. Chitosan is biodegradable polymers, which, due to its unparalleled physicochemical and biological characteristics, has many motivations for healthy and effective development of the drug delivery system. The physicochemical and biological properties of chitosan are heavily affected by molecular weight and degree of deacetylation. Chitosan is decomposed by lysozyme, lipase, protease, chitinase, chitin deacetylase, collagenase and chitonic enzyme to N- acetyl -glucosamine units. Chitosan biodestruction occurs much more commonly when it less than 70% of deacetylation. Also, if the molecular weight of the chitosan is low, its toxic effects will be reduced. On the other hand, the chitosan is able to attach to the mucosal surfaces inside the body, which makes it a focus on mucosal delivery. In addition, biocompatibility and low toxicity of chitosan have made it used to transmit large molecules such as peptides, proteins, antigens, oligonucleotides and genes.

Keywords: Controlled Release Drug Delivery Systems; Chitosan; Implant Systems; Biocompatibility.

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The New Anti-Estrogens with Anti-Cancer Properties for Breast Cancer

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Abstract

Background: Considering the high prevalence of breast cancer and radiation sensitivity of breast tissue, it is necessary to optimize the treatment process of this tumor, especially when using radiation therapy methods. The present study was conducted to investigate the effect and Complications of new anti-estrogens on the effectiveness of breast cancer treatment.

Materials and Methods: Articles were searched in PubMed, Science direct, Embase, Cochran and Scopus databases using the keywords Cancer AND Anti-estrogen, Breast Cancer AND anti-estrogen AND mice, Breast cancer and anti-estrogen AND rat. The authors reviewed the abstract and full text of the articles and the relevant studies were selected for systematic review.

Results: The anti-estrogens used in the reviewed studies included TAM, RAL, SS1020, SS1010, GW5638, OSP, 4-OHTAM and TOR. Anti-estrogen related side effects included liver and uterine complications especially in the case of using TAM anti-estrogen (54%). Moreover, uterine hypertrophy was observed using GW5638, RAL, and SS1010 anti-estrogens. While it happened with a lower percentage than TAM, 16%, 14%, 13%, respectively. Side effects were significantly reduced by reducing the prescribed dose. So that this reduction for TAM is from 54% to 33%. In relation to the effect of antiestrogens on tumor treatment, the most effective and least complications were related to the antiestrogen "SS1020".

Conclusion: Based on the results of reviewed studies, SS1020, which has no estrogenic and genotoxic activity, it was safe and the most effective anti-estrogen against breast cancer in animals.

Keywords: Breast Cancer; Anti-Estrogen; Rat; Mice.

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Exploring Olfactory Dysfunction as a Biomarker in Neurodegenerative Disease with MEMRI by Using Animal Models

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Abstract

Background: Olfactory dysfunction generally happens earlier than the common motor and cognitive symptoms in many neurodegenerative diseases. Alzheimer's Disease (AD) is clinically characterized by cognitive impairments, such as declines in memory. Over the years, many studies have demonstrated the impairment in odor identification in AD patients. Nowadays it is known that olfactory deficits are observed in 85%–95% of AD patients, and therefore, such deficits can be considered as a sensitive marker of AD. It also occurs in other degenerative diseases, such as Parkinson's disease, Huntington's disease, and MS, therefore it can be an early symptom in these diseases, and this has made it important to examine the olfactory system and its function. Olfactory dysfunction can be probed using animal models, as the neural mechanisms of odor processing in rodents are well understood. Additionally, olfaction has similarities between humans and mice in the organization of the olfactory pathways. MEMRI is a powerful tool to study the olfactory system in animal models of neurodegenerative diseases. We aim to probe the olfactory system in neurodegenerative diseases by using MEMRI and mouse models.

Materials and Methods: Literature search was conducted in PUBMED, ScienceDirect and Google Scholar using terms "olfactory dysfunction"," Alzheimer's disease", "MEMRI" and "neurodegenerative diseases". Half of the articles were identified appropriate considering the title of this article and were reviewed.

Results: In a study Jieun Kim and colleagues explored axonal transport impairment in the olfactory system of a triple transgenic mouse model of AD which is similar to human AD neuropathology, by utilizing fast multi-sliced T1 mapping with manganese-enhanced MRI, they investigated that impairment in axonal transport in the olfactory system is an early event in AD pathology and data suggests that accumulation of intra-neuronal Amyloid-beta(Aβ) lead to the axonal transport impairment, and in a study conducted by Wesson DW and colleagues found a clear correlation between the decrease in the olfactory perception and the increase in Aβ the deposition in the olfactory system and observed that accumulation of Aβ in the olfactory bulb is earlier than other brain areas. In another study, Galir Saar and co-workers followed the progression of neural pathology and the recovery of it in amyloid based on a reversible olfactory induced AD transgenic mouse model.

Conclusion: Exploring the olfactory system as a clinical marker in neurodegenerative diseases can be helpful for early diagnostic strategies, differential diagnosis, and prediction of treatment success. Manganese-Enhanced MRI (MEMRI) provides a unique contrast in the mouse brain. Following systemic administration of manganese, it can detect, in vivo, layers in different areas of the brain, including the Olfactory Bulb (OB), cortex, hippocampus, and cerebellum, MEMRI can also exhibit anatomical features. According to the articles reviewed it can serve as a unique in vivo approach to exploring and detecting the changes in the olfactory system of the mouse. Moreover, it can enable assessment of the ability of different pharmacological reagents to block olfactory neuronal loss.

Keywords: Olfactory Dysfunction; Neurodegenerative Diseases; Mouse Models; Manganese-Enhanced Magnetic Resonance Imaging.

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Effect of Partially Purified Cyclotide Rich Fractions from Viola Odorata on Peripheral Blood Cells

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Abstract

Background: Plant cyclotides are mini plants proteins comprising 28–37 amino acids with an extraordinary structure in which they are popular for a head-to-tail macrocyclic structure with six conserved cysteine residues and three disulfide bonds with six inter-cysteine loops called Cyclic Cysteine Knot (CCK). Due to their particular structure, they are resistant to the degradation by extreme thermal and pH conditions or chemical or enzymatic reactions. Cyclotides have displayed a variety range of biological activities including uterotonic, anti-HIV, cytotoxic, immunosuppressant, antiviral and antimicrobial effects. Mentioned activities of cyclotides made them as a target to be studied by researchers with possible applications in both medicine and agriculture fields. Cyclotides are existed in different plant families such as Violaceae, Rubiaceae, Cucurbitaceae and Fabaceae. Specially, the Violaceae family is rich in species for producing cyclotides. In this study, the existence of cyclotides in different hydro-alcoholic fractions of Viola odorata (one of the species of Violaceae family) has been studied and after the extraction process, the possible effects of semi-purified cyclotides as an immunosuppressant agent has been investigated. So, the main aim of this study was to determine and introduce new immunosuppressant agents.

Materials and Methods: The plant materials were subjected to the maceration in methanol: dichloromethane (1:1; v/v) at controlled room temperature for 3 days. This procedure repeated three times. Then, the extract was partitioned by 0.5 volume of double-distilled water. The aqueous phase separated and freeze-dried. Finally, the crude extract passed through C18 column by vacuum liquid chromatography method. After loading the sample solution, the column was washed with 30%, 50% and 80% of ethanol. The obtained fractions were analyzed by High Performance Liquid Chromatography (HPLC) analysis. Finally, the 50% and 80% fractions were injected to the female C57BL/6 mice intraperitoneally at different dose of 5, 50 and 100 mg/kg. The lymphocyte and White Blood Cell (WBC) counts of whole blood in different groups were compared before and 24 hours after the injection.

Results: The cyclotides were isolated from the Iranian plant *Viola odorata* by fractionation methods and semipurified on a C18 column chromatography. The results confirmed the presence of cyclotides in *Viola odorata* based on their retention time and the composition of mobile phase in HPLC. The 80% fraction at all doses reduced the number of lymphocytes and WBC. On the other hand, interestingly the 50% fraction increased them at dose of 50 and 100 mg/kg. So, the 80% fraction could be considered as an immunosuppressant agent.

Conclusion: *Viola odorata* as a remedy represents different therapeutic activities, which may not be unrelated to its cyclotide content. So, from this study, it could be concluded that *Viola odorata* is a rich source of cyclotides in which they could be extracted by an easily available process and also they could be used as an immunosuppressant agent. Also, the effectiveness of cyclotides may also change because of their synergism, natural structure and bioactivities, the amount of purified content, and the way they were assayed.

Keywords: Cyclotide; Extraction; Isolation; High Performance Liquid Chromatography; Peripheral Blood Cells.

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Comparison of Mechanical Properties of Diseased and Healthy Erythrocytes: Molecular Dynamics Study

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Abstract

Background: Erythrocytes are the key to life and are surrounded by a membrane made up of lipids and proteins. In general, cell membranes are an attractive example of equilibrium interfaces that show different functions by changing structure. Much of their function depends on the membrane structure. Therefore, recognizing the physical and chemical properties and behavior of erythrocyte membranes will play a vital role in resolving the challenges in the field of diagnosis and treatment. It should be noted that a lot of research has been done in the field of experimental knowledge, but no significant research has been done on the simulation approach. Due to the lack of research on erythrocyte cell membranes with different percentages of lipids and cholesterol in a simulated manner, the aim was to calculate the mechanical properties of erythrocytes in healthy individuals and patients who have different properties due to differences in lipid and cholesterol percentages. A better understanding of the structure of the erythrocyte membrane and its distinction between diseased and defective ones opens a new window for researchers in various fields including but not limited to smart drug delivery and theranostics.

Materials and Methods: In this study, the mechanical properties of different human Red Blood Cell (RBC) membranes of healthy individuals and patients of PKAN (Pantothenate Kinase-Associated Neurodegeneration) were studied using all atom molecular dynamics simulation. PKAN is a neurodegenerative disease caused by the accumulation of iron in the brain. With different percentages of lipids and cholesterol in healthy individuals and patients, the required atomistic models were created. Considering appropriate force field and structure data, a series of all-atom simulations were performed in NAMD using the equilibrium approach. Post-processing the simulation outputs with the help of appropriate scripts, the mechanical properties of the models were calculated. In order to validate the results, the obtained results were compared with the available experimental reports.

Results: Analyzing the outputs, the mechanical properties of the membrane such as surface compressibility modulus, elastic flexural modulus and Young's modulus for healthy individuals and patients were calculated 115 ± 35 ($\frac{mN}{m}$), 1.04 ± 0.01 (k_B k°), 24.9 ± 0.1 (MPa) and 351 ± 38 ($\frac{mN}{m}$), 3.09 ± 0.01 (k_B k°), 76.6 ± 0.2 (MPa), respectively. Performing reliable statistical standard tests indicates the difference between the mechanical properties of erythrocytes in healthy individuals and patients are significant. This trait can cause differentiation and even somehow invasion of diseased cells (such as cancerous cells).

Conclusion: The findings of this study, which indicate a significant difference in the mechanical properties of healthy and defective cells, can be considered a criterion for the field of diagnosis and even treatment of diseases and the fight against cancerous cells.

Keywords: Molecular Dynamics; Mechanical Properties; Erythrocytes; Pantothenate Kinase-Associated Neurodegeneration; Nanoscale Molecular Dynamics; Cell Membrane.

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Optical Coherent Tomography in Dentistry: A Science Mapping Approach

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Abstract

Background: Optical Coherence Tomography (OCT) is a high-resolution non-invasive cross-sectional imaging technique. This imaging technique that uses light and eliminates the risk of radiation exposure. Therefore, OCT is a safe diagnostic method for dental diseases.

The aim of this study is a brief report on the use of OCT in the researches in various fields of oral and maxillofacial imaging.

Materials and Methods: Scopus database was searched in Jun 17, 2022 with the following query TITLE-ABS-KEY (optical AND coherence AND tomography) AND (LIMIT-TO (SUBJAREA , "DENT")). Bibliometric data of 321 results analyzed via VOSviewer software using author keyword co-occurrence, co-citation and co-authorship network analysis.

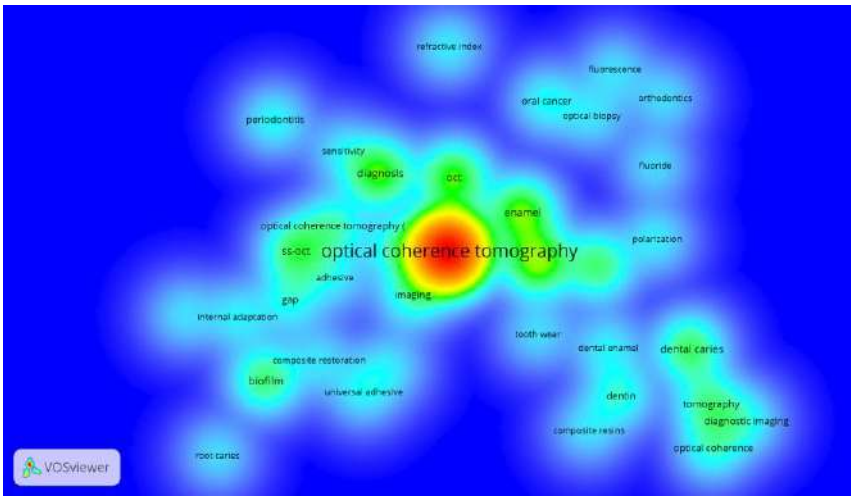
Results: Dental diagnosis, Enamel defects, adhesive and dental caries were the hottest topics. the dental material journal and Journal of dentistry had the most influence on the network. Among countries the united states, Japan, the United kingdom and Brazil had the most influence on the network.

Conclusion: Due to this imaging technique that uses light and eliminates the risk of radiation exposure, it is very important to use it for detection, especially instead of the high-dose imaging technique.

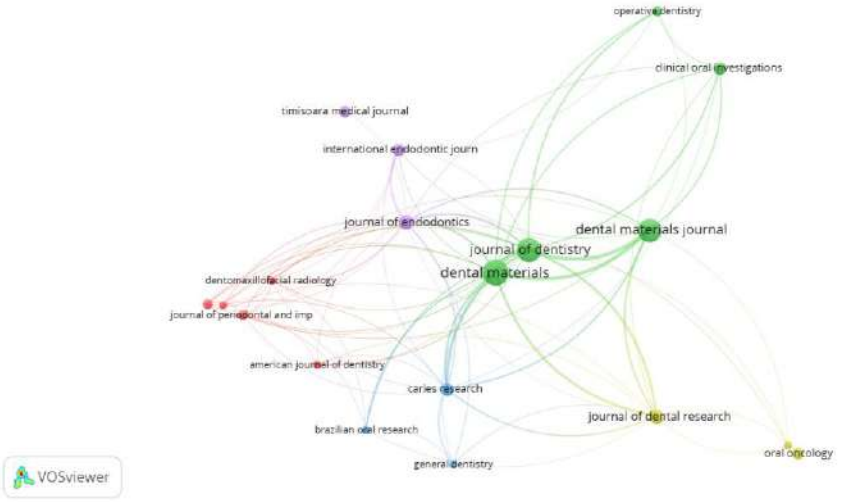
In this study, we did not find few article in the field of the application OCT in dentistry in iran.

Therefore, we suggest multidisciplinary research in related sciences in our country is supported by research centers and research institutes. And thus we can benefit from this technology in the clinical and preclinical fields.

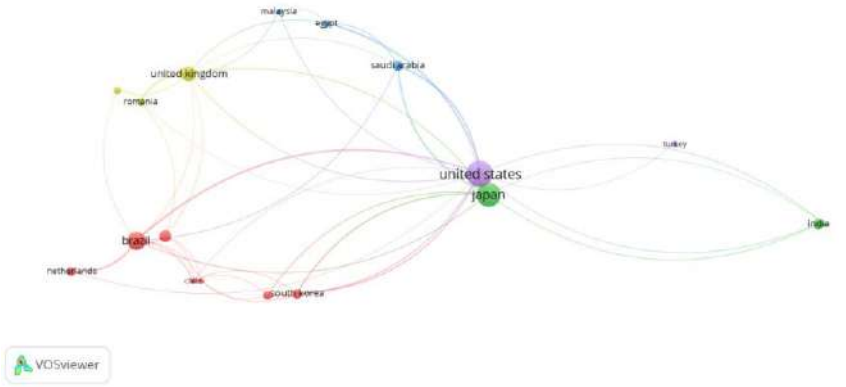
Keywords: Optical Coherent Tomography; Dentistry; Mapping Approach.



Hot topics based on subject. Red-yellow-green-blue colour scheme was used; red corresponds to the highest keyword and blue to the lowest density



Network visualisation of bibliometric coupling among journals



Network visualisation of bibliometric coupling among countries

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The Welfare of Laboratory Animals in Preclinical Research Imaging Considering the Classic 3R Principle and Its Modifications

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Abstract

Background: Numerous scientific achievements are beholden by animal testing; therefore, animal welfare serves as a cornerstone for every research. Any method without considering the ethical codes is unqualified. The effects of disregarding animal welfare are not limited to its inflection on the lab animals. An empathetic attitude toward animals is critical in any practice, particularly in the field of veterinary medicine, as the central role of a veterinarian is to heal them.

Imaging techniques are one of the most common methods used in preclinical research and have significant benefits, including monitoring information without interfering with the biological process. In 1959, William Russel and Rex Burch introduced the "3Rs: Replacement, Reduction, & Refinement" concept regarding laboratory animal welfare. Imaging techniques lead to a reduction in the number of animals required for an individual study, visualizing internal structures without injuring the animal and causing less pain, complying 3Rs policies. There are potential health risks associated with imaging procedures, and anesthesia is often required for image acquisition. Furthermore, specific imaging modalities employ ionizing radiation or use contrast agents or imaging biomarkers, which can result in undesirable health outcomes for the animal. The preparation of animals (e.g., fasting and premedication) and blood sampling that are also part of imaging procedures can also affect their physiological state and welfare. Therefore, some protocols are required to compromise the adverse effects, including proper anesthesia technique, monitoring cardiovascular and respiratory function and body temperature, appropriate handling, and providing animals' essential needs.

Recent debates add extensions to the classical 3R principle to meet ethical research and verify animal use. One consideration is that the research should have an acceptable scientific value. A question sufficiently investigated in previous works, unreliable answers, and selectively reported data enormously decrease the scientific value. Therefore, the modified principle has three new Rs: Robustness, Registration, and Reporting. This approach is also known as Refusal, meaning unjustified use of animals due to the low scientific value of the work. Other concepts, such as Responsibility, Respect, and Rehabilitation which refers to the animals' post-experiment care, lead to 4R, 5R, and 6R extensions of the classic 3R. As a step in preclinical research, imaging techniques should follow these codes to result in morally justified research work.

Materials and Methods: In this article, we will try to introduce the application of the classic 3R principle and its modern modifications to preclinical imaging techniques by reviewing articles from international databases such as PubMed, Google Scholar, Science Direct, Elsevier, etc., and the latest studies on animal welfare. The library method was also used in this study.

Results: While the classic 3R principle is an asset to animal welfare in research, it needs modifications and adjustments to the methods used, such as preclinical imaging, to verify their use and meet ethical codes.

Conclusion: Animal testing will be indispensable in research for some time. Accordingly, experiments must be conducted under stricter guidelines regarding animal well-being. Animal welfare policies need revisions, and scientific discoveries should result in alternatives and less invasive methods.

Keywords: Animal Welfare; Preclinical Studies; Imaging; 3R.

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Application of Magnetic Nanoparticles in Improving the Quality of MRI Images

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Abstract

Background: Nanotechnology is one of the new and attractive branches of research that offers significant opportunities for new developments in different branches of medicine. In the field of medicine, during the past decades, extensive research has been carried out in order to provide newer methods with the ability to diagnose diseases early. Among these, MRI imaging has a special place. The use of nanotechnology and the production of magnetic nanoparticles to improve image contrast and early cancer detection has been the achievement of nanotechnology over the past few decades.

The main purpose of this article is to investigate the use of magnetic nanoparticles in improving the quality of MRI images and trying to enter nanoparticles in the field of diagnosis.

Materials and Methods: This article is a type of review article, which has been written after searching in reliable sites such as Pubmed, Science Direct and Google Schoolar by selecting 10 selected articles from among 18 selected articles.

Results: The results of the studies show that by synthesizing magnetic nanoparticles, while taking into account the conditions and characteristics of use, they can be used as the basis for the production of contrast materials with high effectiveness. Among the studied nanoparticles, Superparamagnetic Iron Oxides (SPIO) Ultrafine Superparamagnetic Iron Oxide particles (USPIO) are the most widely used. Iron oxide nanoparticles are mostly used in the imaging of organs related to the reticuloendothelial system. Superparamagnetic superfine nanoparticles are suitable for imaging lymphatic systems due to their tendency to accumulate in lymph nodes. Superparamagnetic agents are composed of a central core of iron oxide surrounded by a coating of carbohydrates and polymers. Super paramagnetic agents consist of a central core of iron oxide surrounded by a coating of carbohydrates and polymers. Superparamagnetic iron oxide particles are often used as imaging probes for molecular imaging assays. These particles can shorten the T2 time of water protons more effectively.

Conclusion: Imaging at the molecular level relies heavily on the development of contrast agents for the biological detection of processes in cells. Contrast nanoparticles have significant advantages such as: high contrast, long circulation in the blood, high biocompatibility compared to other molecule-based contrast materials.

Keywords: Nanotechnology; Nanoparticles; Molecular Imaging; Magnetic Resonance Imaging.

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A Comprehensive Review of Optical Antennas in Biomedical Applications

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Abstract

Photonic technologies in healthcare (biophotonics) involve the interaction of light or electromagnetic radiation with living organisms or biological components. These methods are used to detect diffraction, refraction, scattering and/or absorption of light by tissue due to the high-speed movement of optical photons, fast time response, polarization dependence and the ability of light waves to penetrate various biological barriers (Without causing unwanted interactions and ionizing radiation.) This paper discusses the fundamental architectures of plasmonic, metamaterial and dielectric based waveguide antennas at optical frequency for biomedical applications. Optical antennas have the ability to increase the interaction between light and matter (due to the strong interaction between electromagnetic fields and the resonance of electrons in nanostructures and increasing the concentration of light fields in the deep subwavelength scale) to improve the accuracy of biochemical diagnosis. great metrological characteristics, low electromagnetic interference, electrical safety, the ability to record nanometer volumes and non-invasive performance, provide optical antennas as the suitable candidates in the biomedical fields such as bio-imaging, bio-sensing, neural interfacing, targeted drug delivery, intracellular exploration, and gene delivery. Considering the recent developments in the fields of optical antennas, this review article covers the state of this technology in biomedicine. This review article aims to inform and stimulate interdisciplinary research on the challenges and opportunities of biophotonics, and biomedical devices.

Conclusion: In this review article, we conducted a comprehensive review of optical antennas relevant to human physiology. Although we have only focused on selected and promising varieties. It is clear that the applications of optical antennas in medicine and especially in biomedical imaging systems as well as medical sensors are endless. However, it can still be carried forward.

Keywords: Optical Antenna; Plasmonic; Metasurface; Bio-Imaging; Bio-Sensing; Neural Interfacing.