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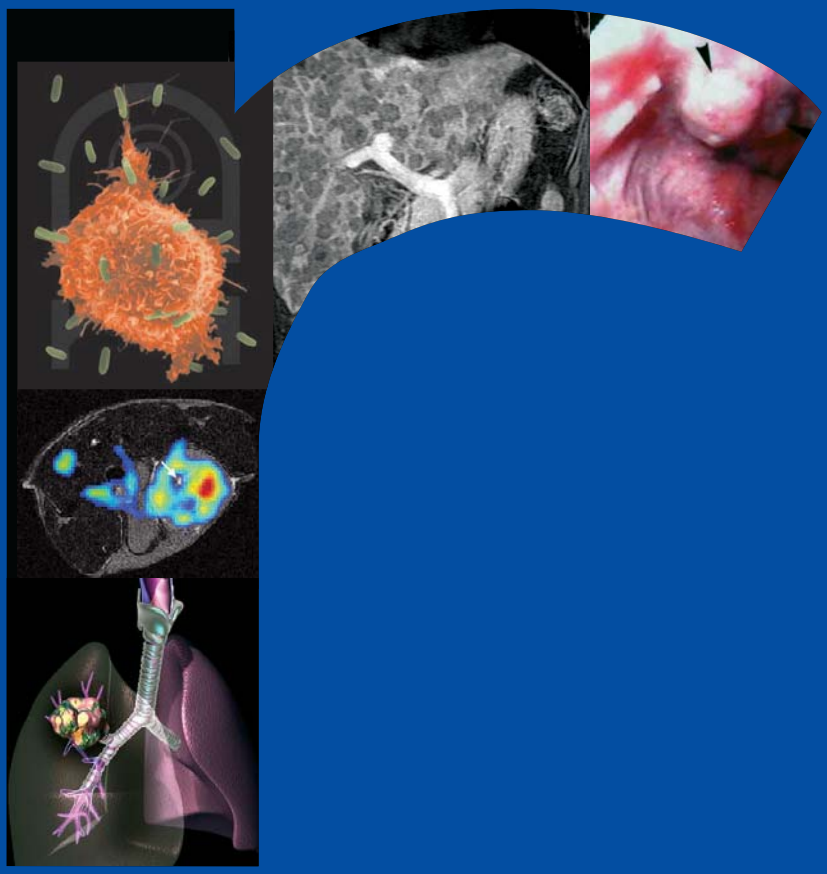

RAJIV GANDHI CANCER INSTITUTE AND RESEARCH CENTRE

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From the Desk of Director Research

Images are by far the most efficient way to obtain, interpret, and manage information about organ systems. Imaging Science has evolved considerably over the past 50 years, and one result of this evolution has been oncologic imaging. This field has endless horizons and need special expertise. Oncologic imaging uses multiple imaging modalities to detect tumors, stage lesions, monitor therapy, and perform surveillance for tumor recurrence. The imaging challenges presented by the patient with cancer encompass the entire technologic spectrum of radiologic sciences. By the very nature of the complex disease processes of cancer, planning the imaging algorithm for these patients requires many oncologic subspecialty disciplines and demand a thorough understanding of the disease entity, staging process, treatment options and tumor progression, as well as an appreciation of the potential complications of the disease and its therapy. Molecular imaging allows for the remote, noninvasive sensing and measurement of cellular and molecular processes in living subjects. Drawing upon a variety of modalities, molecular imaging provides a window into the biology of cancer from the subcellular level to the patient undergoing conventional, new or experimental therapy. As signal transduction cascades and protein interaction networks become clarified, an increasing number of relevant targets for cancer therapy and imaging becomes available.

Although conventional imaging is already critical to the management of patients with cancer, molecular imaging will provide even more relevant information, such as early insights to change in therapy, identification of patient-specific cellular and metabolic abnormalities, and the disposition of therapeutic, gene-tagged cells throughout the body all of which will have a considerable impact on morbidity and mortality. Molecular imaging has set a revolution and has become the main asset for 'personalized Medicine or treatment'. This issue of cancer news highlights molecular imaging in oncology, providing examples from a variety of modalities, with an emphasis on emerging techniques for translational imaging and the concept of 'Theranostics' as applied in this discipline.

The regular articles of Cancer News, "Perspective", "Research & Development", New Technologies", "Clinical Trials", "Watch Out", "Globe Scan", "In focus" are also covered in this issue.

The institute would like to acknowledge the contributions made by Dr. V Rangarajan, Professor & Head, Department of Nuclear Medicine & Molecular imaging, Tata Memorial Centre, Mumbai, India and Dr Sarah Schwarzenböck, Dr Bernd Joachim Krause, Department of Nuclear Medicine, Universitätsmedizin Rostock, Universität Rostock,GERMANY for providing us the "Special Feature" and "Guest article" respectively.

We would specially like to thank Dr PS Choudhury for his technical inputs and sincere efforts in bringing out this issue of Cancer News.

Dr D C Doval

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SPECIAL FEATURE

MOLECULAR IMAGING

Molecular Imaging has been recently defined as a technique which directly or indirectly monitors and records the spacio-temporal distribution of molecular and cellular processes for biochemical, biologic, diagnostic or therapeutic applications.

Radio-isotopes, soon after the discovery, were the earliest form of imaging due to their localization in specific organ systems. The uptake of 131-Iodine by the thyroid gland was discovered in the early part of last century and was largely attributed to the 131-Iodine uptake or localization by the thyroid follicles. It is in the recent past that this is recognized as the result of gene expression of the sodium iodide symporter. So the iodine visualization hallmarks the symporter gene expression and represents a classic example of molecular imaging. The bio-distribution of radiopharmaceuticals is currently the ideal example of molecular imaging. The physical properties of the isotope labelled classify them as positron emission tomography (PET) agents and single photon emission computerized tomography (SPECT) agents. The PET and SPECT have become hybridized with anatomical imaging scanner systems like CT and MRI, and this new hybrid image take the potential of molecular imaging to new heights. In India currently, ^{18}F-labelled FDG Fluoro-Deoxy-Glucose is widely available. Others like thymidine, misonidazole, fluoride, choline and acetate are very minimally utilized and that too in a research setting. Radiopharmaceuticals using SPECT/CT study fatty acid metabolism, blood flow, are a part of molecular imaging of the heart.

Molecular imaging has set a revolution and has become the main asset for 'personalized medicine or treatment'. It provides patient specific information that allows treatment to be tailored based on the biological or molecular attributes of both the patient and the disease. Advances in understanding the molecular biology of cancer, and the ability to translate these advances into therapeutic approaches, have led to a host of new targets and new drugs for anticancer therapy. And as cancer treatments become more individualized, there is an increasing need to characterize tumors and identify therapeutic targets, in order to select the therapy that's most likely to successfully treat an individual patient's cancer.

This personalized approach applies to both targeted loco-regional therapy, such as surgery and radiotherapy, as well as targeted systemic therapies, such as endocrine treatments for breast cancer, radioiodine treatment of thyroid cancer and I^{131} treatment of nueroblastoma to name a few. Till now tumor characterization has been accomplished by in vitro assay of tumor biopsy material. However, recent advances in functional and molecular imaging have laid the foundation for testing imaging as a cancer biomarker; namely, to help direct cancer treatment in a way that is complementary to plans based on tissue- and blood-based biomarkers. Molecular imaging has thus been termed as a surrogate marker.

When considering molecular imaging as a surrogate cancer biomarker, there are four major areas in which imaging can help guide management.

Prognostication

The imaging biomarker can help determine the aggressiveness of the tumor and thereby infer the likelihood of disease progression and cancer related patient death. This information can help guide how aggressive the treatment should be. A number of studies across a variety of tumour types have shown that rates of tumour glucose metabolism, reflected by PET imaging of ^{18}F-FDG uptake, are highly predictive of patient outcomes such as progression free and overall survival. The mechanisms underlying these findings are incompletely understood and complex. They include the association of increased glycolysis with other factors that are predictive of patient outcome, such as indices of cellular proliferation. They may also reflect a cellular stress reaction, also seen in normal non-tumour tissues, that enhance cellular survival and may mitigate the effectiveness of cytotoxic treatments. One such example in which FDG-PET is used to determine prognosis in clinical practice is the case of iodine-refractory differentiated thyroid cancer. Here the absence of FDG uptake indicates a quite favourable prognosis that often directs the patient away from further treatment towards close observation. During ongoing risk stratification studies during follow up, the presence of FDG uptake in refractory thyroid cancer identifies a relatively lethal form of the disease, indicating that further different therapeutic intervention is warranted.

Prediction

The imaging biomarker can help identify the presence or absence of therapeutic targets and therefore direct the

patient to the therapy that is most likely to be effective. Imaging can also help identify factors likely to mediate resistance to particular forms of treatment. When it comes to identifying therapeutic targets, imaging provides a method that is complementary to biopsy and in vitro assay like assay of tumor markers. Here the advantage of molecular imaging include the ability to characterize the entire disease burden (versus a small biopsied sample of the tumour or elevated tumor markers), measure the heterogeneity of the disease within or across disease sites, and measure the effect of treatment. ^{18}F-fluoroestradiol (FES) PET to image regional oestrogen receptor (ER) is one such example.

Studies have shown that the level of FES uptake in breast cancer predicts the likelihood of response to endocrine therapy. This is complementary to the current clinical practice of measuring ER expression on biopsy material to make treatment selections. Imaging may be particularly helpful in recurrent or metastatic disease, where biopsy can be challenging. PET hypoxia imaging, using compounds, such as ^{18}F-fluoromisonidazole (FMISO) and ^{64}Cu-ATSM is another example. Hypoxia imaging may be particularly important in radiotherapy treatment planning where it is likely that hypoxic regions will need different dosing schemes, given the well-documented association between hypoxia and radioresistance.

Response Assessment

Functional and molecular imaging can measure therapeutic response at a much earlier point of time than standard anatomic imaging. In addition, imaging the tumour's in vivo response to treatment may better predict the outcome in relation to important endpoints, such as disease-free and overall survival. Aberrant cellular proliferation is a characteristic of cancer cells and thus a decline in cellular proliferation is an early event that indicates successful cancer treatment. Work is on to develop thymidine analogues that can be labelled with ^{18}F for PET imaging, making them practical for more routine clinical use. The most promising to date is ^{18}F-fluorthymidine (FLT), which has undergone preliminary evaluation in patients. Early studies support serial FLT as a strong indicator of early response, including response to cytostatic and cytotoxic agents. This is a highly promising area of investigation, and multicentre trials of FLT-PET to measure early therapeutic response are warranted.

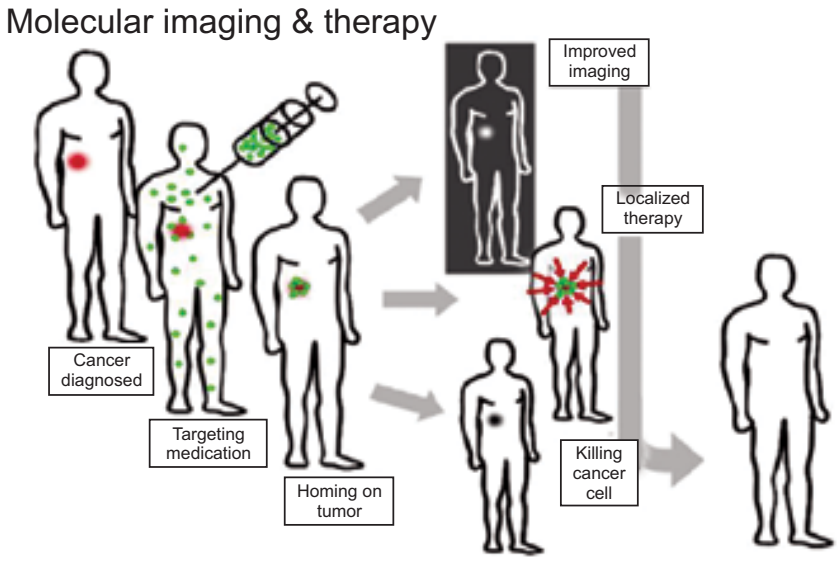
Biology

Molecular imaging provides a unique tool for characterizing the in vivo biology of cancer and its response to treatment. It may offer insights into factors that determine why some patients will response to a specific regime of anti-cancer treatments, while other apparently similar patients do not. The ability to measure in vivo cancer biology during treatment provides an unique opportunity to gain insights into factors underlying response and resistance. One interesting finding has been the association between mismatches in tumor metabolism and perfusion, and resistance to therapy.

For several tumor types, it has been seen that tumors that have high rates of glucose metabolism as compared to blood flow are less likely to respond to treatment, and that patients with tumors displaying such characteristics are more likely to have disease relapse. This same physiology has been seen in ischemic but viable myocardium, and is associated with functional recovery after revascularization.

While tissue viability is beneficial in the case of heart disease, a cellular response that promotes tumor survival is detrimental to the cancer patient. Identification of flow-metabolism mismatch as a marker of therapeutic resistance suggests the need for further studies to understand underlying mechanisms, and may identify alternative targets in tumors that are resistant to standard treatments.

Identifying and imaging the expression of various receptors is another important aspect of molecular imaging. ^{18}F-FDG uptake in PET imaging represents the expression of GLUT receptors. As GLUT over-expression hallmarks malignancy and is inversely proportional to the differentiation of the tumor. This directly refers to the outcome of the patient to the disease. Although FDG representing glucose metabolism appears to be a perfect overall answer when used as hybrid imaging for the staging, restaging and treatment response of a large number of malignancies, it is inadequate. Somatostatin receptor expression hallmarks neuro-endocrine tumors and agents like Gallium-68, DOTA-TOC is excellent in evaluating well-differentiated neuro-endocrine tumors. ^{18}F-DOPA images dopamine receptors and its uptake. It is very useful in neural disorders and multiple endocrine neoplasias. ^{18}F-Fluoride describes the calcium and fluoride metabolism in matrices of connective tissue and skeleton. Isotope labeled Annexin



has found to be effective in understanding apoptosis and this might have an effect on treatment plans in future. A few of the above mentioned cellular processes can also be described by functional MRI although the mechanism appears to be indirect unlike the direct mechanisms as mentioned above.

The diagnostic profile is equally supplemented by molecules that are labelled with I-131, Lu-177, Y-90 effectively strengthening the treatment strategy and the treatment options available for many tumors at least as an effective adjuvant option. Post-therapy scans represent uptake in areas where the molecular processes have been expressed demonstrating the adequacy of treatment. This is termed as 'Theranostics' and implies the use of same ligand for both diagnosis and therapy labeled with a diagnostic or therapeutic radionuclide as the case may be.

Molecular imaging systems like small animal multi-modality scanner shorten the drug discovery process and make these more cost-effective. Molecular imaging currently happens to be the fastest growing branch of imaging sciences. It is important to note that this approach is a departure from the standard paradigm for cancer imaging, which has largely focused on detection and staging. Imaging probes used for detection must have reliably higher uptake in tumors compared to normal tissue. For biomarker imaging, even a negative scan speakes volumes about a disease process. In this the absence of a particular feature, for example, tumor receptor expression may be equally, if not more, important than its presence to individualize treatment.

Molecular imaging as a cancer biomarker must therefore be able to go beyond simply detecting the tumor, to quantify tumor in vivo biology across a range of values. This requires the ability to localize and characterize tumors at the same time. Multimodality imaging techniques such as PET/CT, or pairs of imaging procedures, for example, using multiple PET imaging procedures with different probes may prove especially important for biomarker imaging.

Similarly, imaging as a biomarker requires image quantification and may entail detailed image analysis beyond standard clinical approach, incorporating kinetic analysis and parametric imaging, for instance. The implementation of molecular imaging as a biomarker in cancer clinical trials and clinical therapy will require efforts to develop rigorous, but clinically feasible, approaches for multimodality imaging and standardized image acquisition and analysis protocols.

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GUEST ARTICLE

CURRENT STATUS OF MOLECULAR IMAGING AND THERAPY

The hybrid imaging modality positron emission tomography/computed tomography (PET/CT) allows assessing molecular as well as morphologic information at the same time. PET/CT using tumor-seeking radiopharmaceuticals represents an efficient tool for whole body staging and re-staging within one imaging modality and has gained wide acceptance in oncology with many clinical applications. In oncology the glucose analogue 18F-fluorodeoxyglucose (FDG) is the most widely used radiopharmaceutical. Increased consumption of glucose is a characteristical feature of most tumour cells and is partially related to over-expression of the GLUT-1 glucose transporters and increased hexokinase activity.

FDG PET and PET/CT have been used for staging and re-staging of tumor patients in numerous indications[3]. The main clinical applications of FDG PET and PET/CT in oncology are lung cancer (fig. 1), colorectal cancer, lymphoma, breast cancer and esophageal cancer. A promising future indication of 18F-FDG-PET/CT imaging in clinical routine is the evaluation of therapy response, tumor control and prediction of prognosis.

PET and PET/CT, using 11C- and 18F-labelled choline derivates, are promising imaging modalities for imaging prostate cancer. Their value in primary as well as recurrent prostate cancer has been analysed in numerous studies.

Choline PET and PET/CT show a moderate sensitivity for the detection of primary prostate cancer. The detection rate depends on the tumor configuration: small and in part rind-like tumors often can not be visualized. Furthermore, the differentiation between benign changes like prostatitis, high-grade intraepithelial neoplasia (HGPIN) or prostatic hyperplasia is not always possible. Therefore, at present the routine use of PET/CT with 11C- and 18F-labelled choline derivates is not recommended as a first-line screening procedure for primary prostate cancer in men at risk.

For the diagnosis of recurrent prostate cancer (localized recurrence, lymph node involvement or distant metastases), several studies using PET- and PET/CT with 11C- and 18F-labelled choline derivates demonstrated promising results (for an overview see [6]) (fig. 2).The detection rate of PET and PET/CT using

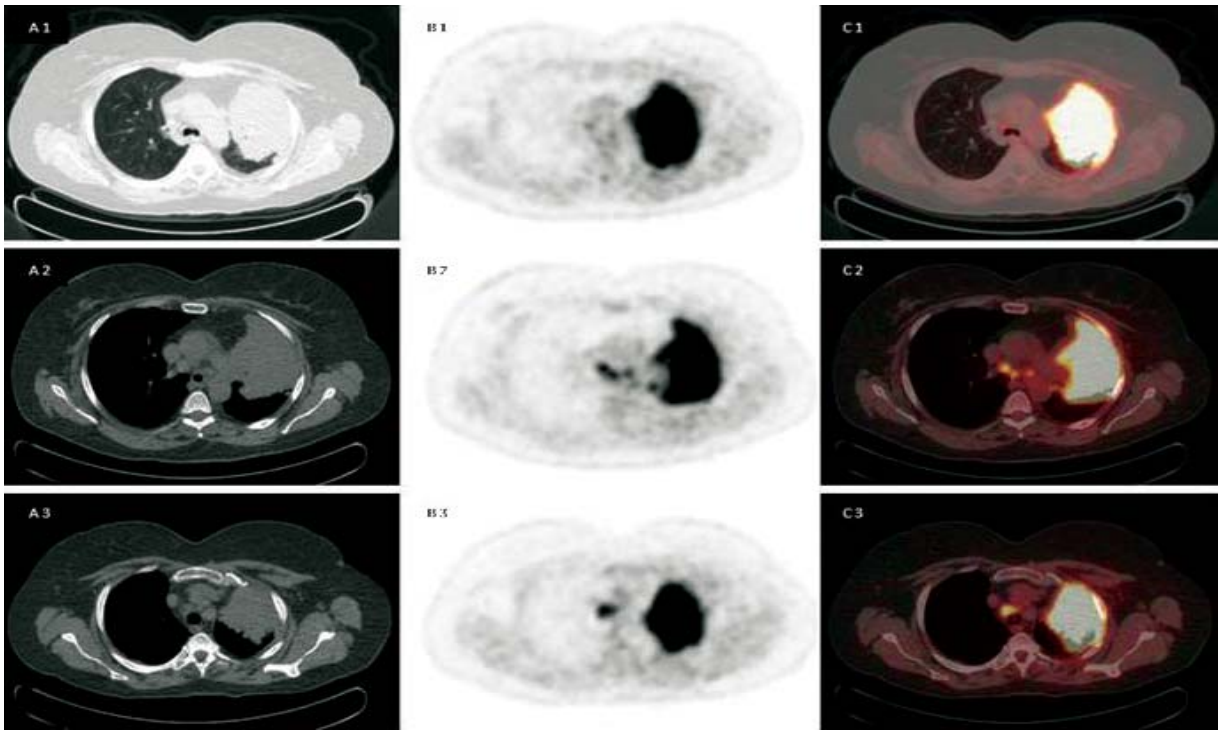

Fig. 1. 62-year old patient under suspicion of bronchial cancer of the left upper lobe referred for [^{18}F]FDG PET/CT for primary staging. [^{18}F]FDG PET/CT revealed FDG-positive primary tumor and contralateral lymph node metastases (N3); (A 1-3) CT scan, (B 1-3) PET scan, (C 1-3) PET/CT fused images

Fig. 2. 67-year old patient with prostate cancer after brachy therapy 04/02, referred for [^{11}C]choline PET/CT due to increasing PSA up to 1,3 ng/ml. [^{11}C]choline PET/CT at 08/11 revealed local recurrence and left inguinal lymph node metastasis, (catheter artefact) (A) CT scan, (B) PET scan, (C) PET/CT fused images

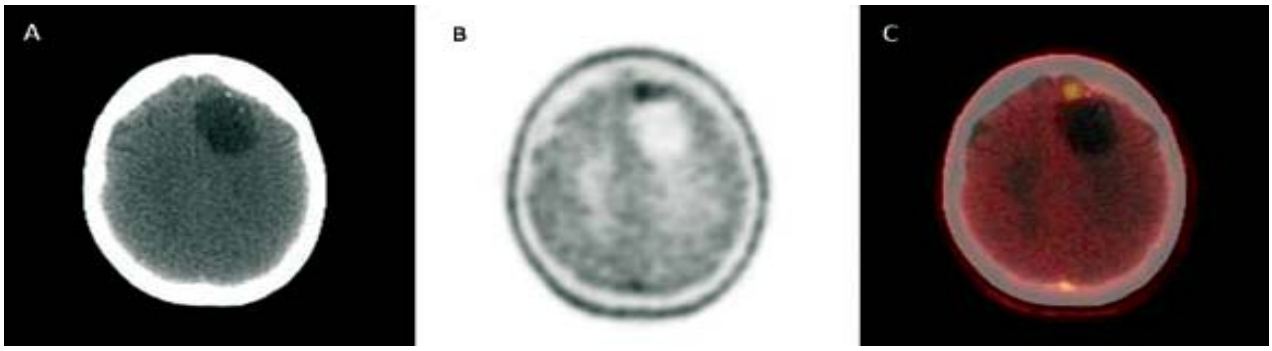

Fig 3. 34-year old patient suffering from recurrent astrocytoma grade III and condition after multiple resections referred for [^{18}F]FET PET/CT for re-staging. PET/CT revealed focal uptake left frontal indicating local recurrence. (A) CT, (B) PET, (C) PET/CT fused images

11C- and 18F-labelled choline derivates for local, regional, and distant recurrence in patients with biochemical recurrence shows a linear correlation with PSA value at the time of imaging. At PSA levels below 1 ng/mL, diagnosis of recurrence is possible in nearly one-third of the patients and reaches about 75% in patients with a serum PSA value >3 ng/mL. Since an early diagnosis of recurrent prostate cancer and the localization of the site of recurrence have important influence on the therapy regimen, choline PET and PET/CT can potentially be used for individualized therapy.

Besides increased glucose uptake, increased proliferation is a main characteristic of malignant cells. Non-invasive definition of proliferative activity to optimise oncological therapy strategies, especially with respect to regulation of increased proliferation, e.g. in therapy response assessment, is important. A promising PET tracer for imaging of proliferation is 3'-deoxy-3'-18F-fluorothymidine (18F-FLT), which is incorporated into the cell through nucleosidtransporters, phosphorylated by thymidine kinase-1 and accumulated in tumor cells[1]. Clinical studies showed proliferation dependent accumulation of 18F-FLT for a variety of solid and haematologic neoplasms, such as lymphomas, breast, lung, esophageal, gastric and colorectal cancers. For some entities, 18F-FDG PET/CT showed a higher sensitivity compared to 18F-FLT (e.g. in lung tumors)[2], however in some entities, 18F-FLT PET/CT performed better (e.g. in gastric cancer)[4]. 18F-FLT PET/CT showed a higher specificity in comparison to 18F-FDG, e.g. in differentiation between malignant and benign pulmonal lesions, such as tuberculosis. Furthermore, FLT has been suggested as surrogate marker for therapy response assessment[5].

For brain tumor imaging, the gold standard is magnet resonance imaging (MRI). However, MRI shows limitations with respect to the differentiation between tumor tissue and post-operative changes. For the diagnosis of primary brain tumor, recurrence and in the post-therapeutic setting PET/CT using radioactively labelled amino acids 11C-methionine und 18F-fluoroethyltyrosine (FET) shows higher sensitivity and specificity compared to MR imaging[7]. Amino acid PET/CT has the potential to optimize radiation treatment planning of brain tumors through accurate delineation of tumor tissue from normal tissue, necrosis and edema (fig. 3).

NETs are relatively rare tumors which mainly originate from the digestive and tend to be slow growing. The localization of NETs and the assessment of disease

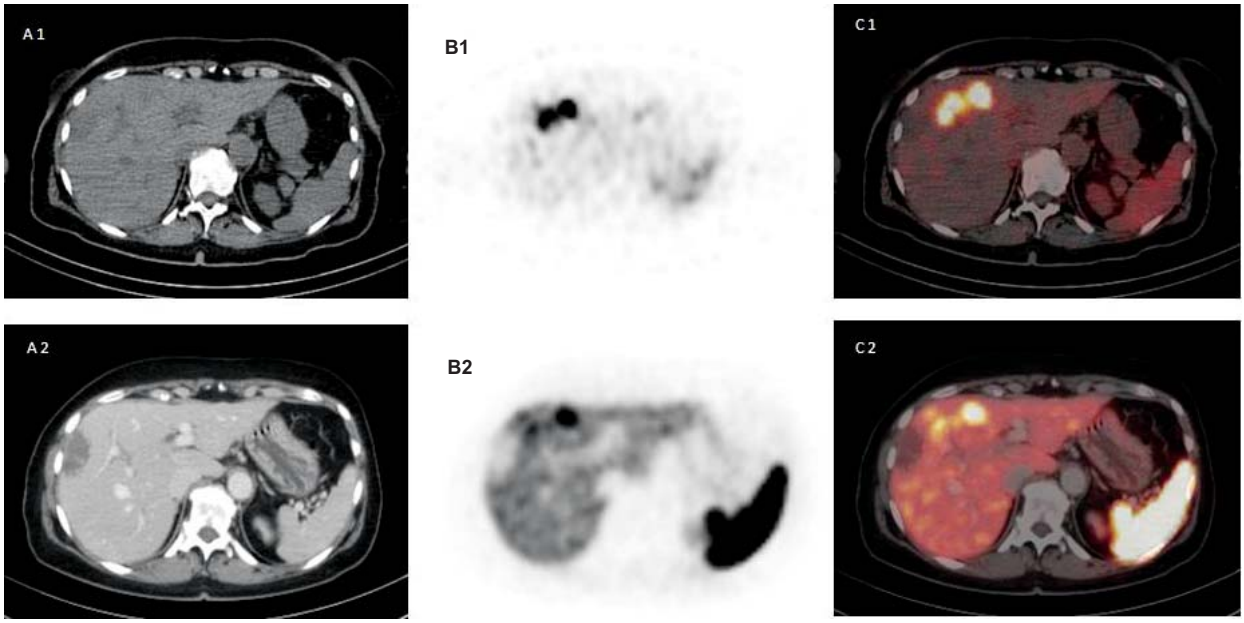

Fig 4.5 5 years old patient with somatostatin receptor positive gastrointestinal neuroendocrine tumour and hepatic metastases referred for Lutetium-177-DOTATATE therapy (radioreceptor nuclide therapy) and [^{68}Ga]DOTATOC PET/CT for re-staging after therapy . (A1) CT, (B1) SPECT, (C1) SPECT/CT fused images after Lu-177-DOTATATE; (A2) CT, (B2) PET, (C2) PET/CT fused images for restaging 6 weeks after Lu-177-DOTATATE therapy showing good therapy response.

extent are crucial for management. Commonly used diagnostic techniques include morphological imaging (ultrasound, CT, MRI) as well as functional imaging, such as PET/CT using radioactively labelled somatostatin analogues, e.g. 68Ga-DOTATOC PET/CT. Grade of differentiation is decisive for the sensitivity of 68Ga-DOTATOC PET/CT.

Treatment is multidisciplinary and should be individualized according to the tumor type, burden, and symptoms. Therapeutic tools include surgery, interventional radiology, medical treatments, such as somatostatin analogues, interferon, chemotherapy and new targeted drugs. NETs usually over-express somatostatin receptors, thus enabling the therapeutic use of radiolabelled somatostatin analogues in peptide receptor radionuclide therapy (PRRT), such as Lutetium-177-DOTATATE which has been explored in NETs for more than a decade. Present knowledge and clinical studies indicate that it is possible to deliver high-absorbed doses to tumors expressing somatostatin receptors, with partial and complete objective responses in up to 30% of patients. Side effects, involving the kidney and the bone marrow, are mild if adequate renal protection is used. Moreover, a consistent survival benefit is reported. As NETs may also express cholecystokinin 2, bombesin, neuropeptide Y or vasoactive intestinal peptide receptors even simultaneously, the potential availability and biological stability of radio-analogues will improve the multireceptor targeting of NETs.

Besides primary diagnosis and imaging of recurrent neuroendocrine tumors, 68Ga-DOTATOC PET/CT can also be used in therapy response assessment after radio receptor nuclide therapy (fig. 4).

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PERSPECTIVE

BEYOND ^{18}F-FDG: FOCUS OF MOLECULAR IMAGING IN THE NEXT DECADE

During the last decade, several PET radiopharmaceuticals entered the phase of clinical trial, promising to become an integral part of management of cancer patients. FDG PET found its way in different applications related to cancer management in India and is currently widely practiced.

Although time has come to look beyond metabolism and target other functions of a cancer cell like proliferation, hypoxia etc, not much has happened in the country in the last few years. It is highly essential that in the next decade we target newer ligands for PET imaging to bring them from the bench to the bed side. With the help of these tracers, knowledge is being acquired on the molecular characterization of specific tumors, their biological signature and post intervention response. The potential role of these imaging probes for tumor detection and monitoring is progressively being recognized by clinical oncologists, biologists and pharmacologists. The scope of information to be covered will certainly need to include the assessment of therapeutic response in a particular tumor type or a specific process in the biology of tumor. The focus will also be on different new treatment modalities/ targeted therapies and precise delivery of external beam radiotherapy targeted towards a particular process in tumor biology.

If we look into various aspects of tumor biology it is amazing to note that a tumor cell follows a particular pathway to grow and another process to die, whether undergoing a natural death or a death post intervention. The study of glucose metabolism is very well established by now as well as mapping of few receptor type with the help of molecular imaging and is used in routine clinical practice. Other processes are in the process of validation with encouraging results. Let us take a look into few of the ones which have the potential to be clinically relevant in day to day practice. At the same time these ligands, to be clinically useful, needs to be either prepared commercially or in a hospital radiopharmacy with a reproducible radiochemical purity and sterility. Amino acid and protein metabolism measured by 3-deoxy-3 (^{18}F) fluoro thymidine ^{18}F FLT measures tissue and tumor proliferation relying on enhanced proliferating activity which is more specific to a malignant tumor. This amino acid is rapidly incorporated into the newly synthesized DNA and 11-C thymidine could be produced. However, this being unsuitable due to short half life and rapid in vivo degradation, the more stable 18F labeled thymidine should be routinely used. The uptake of this tracer correlates with proliferation when compared with ki-67 index measurements in biopsy specimens 1-(2-deoxy-2 fluoro-B-D-a rabinofuranosyl) thymidine (FMAU) can also be labeled with ^{18}F and can be used to measure proliferative activity. (^{18}F) fluoro methyl and (^{18}F) fluoro ethyl tyrosine can also show amino acid metabolism of tumors. As stated previously, the technique of precise delivery of radiation to the target is becoming more and more possible so that more of tumor tissue is irradiated and normal tissue is spared. In this setting the biology of the tumor is also important in predicting outcome of radiation. Tumor hypoxia is considered an important factor for resistance to radiotherapy risk factor for tumor progression and thus imaging oxygenation of tumor is of great interest, especially for planning radiotherapy. Currently nitroimidazole derivatives like ^{18}F MISO & ^{18}F FAZA are the most common radiopharmaceuticals and the synthesis carried out via nucleophilic fluorination.

After ^{18}F fluorination protection groups are removed and the corresponding product is isolated via RP-HPLC, both tracers can be produced in high specific activity and radiochemical purity and the yield is much higher for ^{18}F MISO than ^{18}F FAZA. When oxygen is lacking in a tumor cell, however a second electron transfer reduces the nitroimidazole to a very reactive intermediate which binds to protein DNA with the cell and therefore becomes trapped intracellularly.

Thus ^{18}F MISO uptake is inversely related to the intracellular partial pressure of oxygen. The same mechanism mediates the accumulation of FAZA by hypoxic cells. Currently, most studies are being carried out by MISO and may be in the next couple of years we can use this compound for dose painting in radiotherapy. Imaging of lipid metabolism of tumor can be labeled achieved by synthesis of choline with either ^{11}C or ^{18}F. It was used to visualize a variety of tumor including prostate cancer. To benefit from the longer half life of the tracer and to promote its routine uses, more importance have been given to ^{18}F.

Ability to image dopamine transporter system has been of benefit in evaluation of primary and metastatic

NET's with usefulness also demonstrated in carcinoid tumors. It has highlighted more specificity in low grade gliomas thus helping in continued risk stratification in these patients. Similarly, somatostatic receptor imaging is establishing its role in routine clinical care. These radiopharmaceuticals pave the way for receptor based treatment labeled with a suitable radioisotope. ^{18}F-16 a fluoroestradiol ^{18}F FES has the potential to image oestrogen recptor status in breast carcinoma and has the potential to accurately predict response to modern breast cancer patients, especially those treated with aromalase inhibitors. Bench work to map angiogenesis is going on but will be a while before it comes to the bed side. Similar is the fate of radiopharmaceuticals for imaging of apoptosis.

Talking about the use of these molecular imaging agents in routine clinical practice, we are faced with a paradoxical situation especially in this country. Very few hospital based institutions have a radiochemist on their rolls for in-house synthesis of these compounds. The infra-structure of GMP is expensive and commercially not viable. Therefore, the concept of hospital based radiopharmacy for formulation of these compounds for its regular use needs to be standardized. Today some companies have standard synthesis modules which are fully automated and can be used for routine synthesis in GMP compliant environment. With one set-up it is possible to easily label different radionuclides without having cross contamination issues by easily replacing the sterile single use cassettes. This makes these modules an ideal equipment for routine clinical production. The sterile single use cassettes are assembled under GMP compliant clean room conditions, sterilized with gamma radiation and double vacuum packed. The manufacturer guarantees a shelf life of twelve months. It should be possible to use these in a hospital radiopharmacy as reconditioning, cleaning and sanitation routines are not necessary due to the cassettes one time use. It is presumed that routine use of other F^{18} based tracers will be possible in times to come and we here are certainly going to take a step forward to make this a reality.

Molecular imaging in discovery and development of drugs also plays a very important role. In core drug research focused imaging facilities, multiple imaging modalities are woven together in single studies to address numerous complementary aspects of the drug-target interaction and the degree of subsequent disease inhibition. Multi-modality imaging provides an opportunity to non-invasively generate simultaneous anatomical, functional and molecular end-points, with inherent spatial resolution. This approach leads to unique and powerful datasets that can be used for more effective decision making in drug research and development.

Bioluminescence imaging (BLI) is one of these imaging modalities which relies on detection of light from luciferase expressing cells in an animal. This is commonly achieved through implantation of cells engineered to express luciferase constitutively, or by use of transgenic animals that express luciferase in one or more tissues of interest. Emission of light from these cells or tissues occurs following systemic injection of the luciferase substrate, luciferin. Bioluminescence provides a convenient, quantitative means for assessing progression and treatment response in metastasis models, including those driven by cell injection as well as spontaneous metastasis models. Both intracardiac (e.g. to bone) and intravenous (e.g. to lung) cell injection-based models of metastasis and associated BLI and analysis protocols can be found. Spontaneous metastasis has also been an area of interest, particularly mammary fat pad implanted cells that

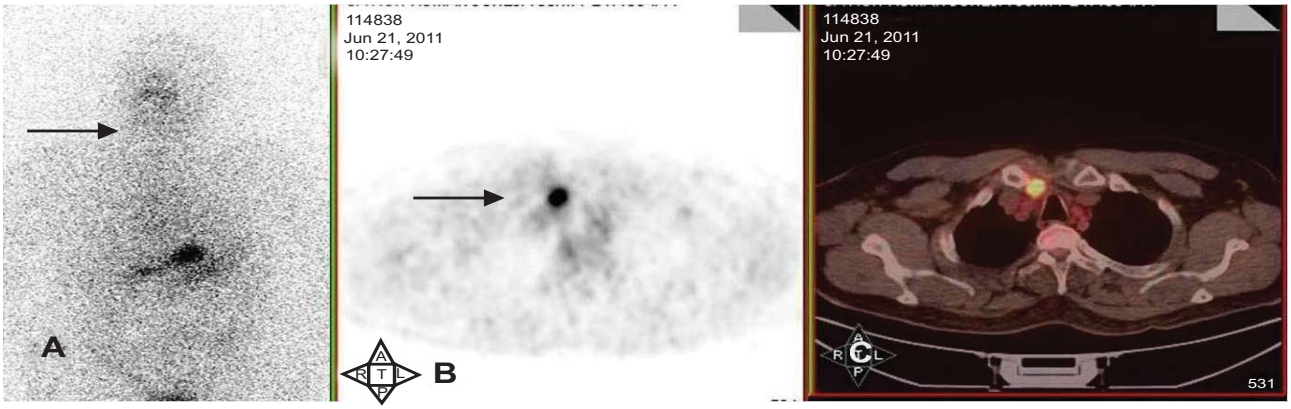


Figure: A case of radioiodine refractory thyroid cancer where I-131 scan is negative (A) & disease is seen in FDG PET (B & C)

metastasize to lymph nodes and lungs. Extensive work has also been undertaken to optimize the ability to image early-stage metastasis in the presence of more advanced primary tumors, where optical signals from the primary tumors can obliterate metastatic signals.

Fluorescence imaging (FLI) relies on light emission from a fluorophore or fluorescent protein after excitation by a light source at the appropriate wavelength for the fluorophore which is being imaged. It can be applied to cell lines or transgenics expressing fluorescent proteins, or by the use of exogenous probes labeled with fluorophores. A variety of targeted, activatable, and vascular probes have been developed to enable in vivo imaging of specific biological processes, molecular events, and tissue vascularity. Optical imaging and a panel of luciferase expressing cell lines for tracking the tumor burden in orthotopic systemic and metastasis tumor models can be utilized in glioma, neuroblastoma, leukemia, lymphoma, multiple myeloma, prostate, breast, lung and colorectal histotypes.

FMT technology enables quantitative imaging of the fluorescent probe, or marker concentration to the picomolar level with no tissue depth limitation. The increasing assortment of commercially-available NIR probes provides greater and more versatile access to fluorescent-imaging biomarkers that can be used to assess disease progression and drug response at the molecular, cellular and target levels. FMT can also be used as a discovery screening tool for assessing biologics biodistribution rapidly and cost effectively in the whole body.

NIR probes can be targeted to a variety of cell surface markers and receptors to enable imaging of target expression and modulation. Examples of commercially-available probes include those targeted to:

- **Hydroxyapatite :** It is a metabolite involved in bone turnover. Applications include imaging of bone metastasis, bone degradation in arthritis and osteoporosis.
- **$\alpha_v\beta_3$:** It is involved in vessel formation and allows the imaging of new vessel formation and tumor burden.
- **Hypoxia**: The HypoxiSense probe allows three-dimensional, FMT-based imaging of tissue hypoxia through targeting to the carbonic anhydrase 9 (CA IX) protein. This protein increases in hypoxic regions within many tumors, especially in cervical, colorectal, non-small cell lung tumors.
- **Annexin/Apoptosis:** This selectively binds phosphatidylserine exposed in the outer leaflet of the cell membrane during the early stages of apoptosis. This enables FMT-based imaging of apoptosis.
- **Her2:** Commonly over-expressed in human breast cancer and is the target of many breast cancer therapeutics. A Her2-targeted probe can be used for imaging of Her2 expression and therapeutic knockdown.

NIR-activated probes provide the opportunity to image the modulation of target-specific molecules. These probes are in a quiescent or quenched fluorescence state prior to activation and fluorescent activity. Commercially-available, activatable NIR probes exist for a variety of target molecules including:

- **Cathepsins:** Cathepsins are upregulated in a variety of disease states, including inflammation and cancer. They can also be used for tumor-burden tracking since tumors broadly produce high levels of cathepsins. Pan-cathepsin probes are available as well as probes specific to Cathepsin B and Cathepsin K (e.g. CatK FAST). Notably, Cathepsin K is commonly upregulated in the osteoblastic components of bone degradation and can be used to assess therapeutics targeted against this process in bone disease.
- **Matrix metalloproteinases (MMPs):** MMPs are active in inflammation diseases and cancer. MMP-activatable fluorescent probes can be used both for quantifying the early and mechanistic aspects of rheumatoid arthritis and other inflammatory diseases. They can also be used for tumor burden tracking since tumors commonly produce high levels of MMPs.
- **Neutrophil elastase:** Neutrophil elastase is a protease involved in a variety of indications, including acute lung injury, acute respiratory distress syndrome, as well as many other inflammatory processes, such as emphysema, cystic fibrosis, COPD, wound healing, rheumatoid arthritis, and ischemia-reperfusion.

PET imaging in the preclinical setting (micro-PET) is increasingly being used in drug discovery to study tumor biology. As applications of micro-PET imaging in cancer models have increased, preclinical micro-PET equipment design and sensitivity have also improved, allowing higher resolution and throughput.

Micro-PET studies utilize the same radiotracers used in clinical PET, and provide the same versatility in imaging in vivo molecular and cellular function.

(Dr PS Choudhury, Director Nuclear Medicine)

RESEARCH & DEVELOPMENT

Clinical Experience with Whole-Body PET/MR

A study at Technische Universität München, Germany, has evaluated the comparability of clinical performance between conventional PET/CT and PET/MR in patients with oncologic diseases. Thirty-two patients with different oncologic diagnoses underwent a single-injection, dual-imaging protocol consisting of a PET/CT and subsequent PET/MR scan. PET images of both modalities were reconstructed iteratively. PET/MR and PET/CT were compared visually by rating the number and location of lesions suspicious for malignancy, as well as image quality and alignment. Simultaneous PET/MR acquisition was feasible with high quality in short acquisition time (d"20 min). This study demonstrates that integrated whole-body PET/MR is feasible in a clinical setting with high quality and in a short examination time. The reliability of PET/MR was comparable to that of PET/CT in allowing the detection of hypermetabolic lesions suspicious for malignancy in patients with oncologic diagnoses.

(J Nucl Med, Apr 25, 2012)

Ghrelin Receptor Imaging Target

A team of researchers at Canada have assessed the specificity of a novel ghrelin-imaging probe for prostate cancer (PCa) over normal tissue or benign disease. Ghrelin is a natural growth hormone secretagogue (GHS) that is co-expressed with its receptor GHSR in human cells. A fluorescein-bearing ghrelin analogue was synthesized (fluorescein-ghrelin (1-18)), and its application for imaging was evaluated in a panel of PCa cell lines and human prostate tissue from 13 patients undergoing radical prostatectomy and signal was detected and quantified using hapten amplification technique. The ghrelin probe was taken up by GHSR-expressing LNCaP and PC-3 cells, and not in BPH cells that express low levels of GHSR. The ghrelin probe signal was 4.7 times higher in PCa compared to benign hyperplasia tissue (P=0.0027) and normal tissue (P=0.0093) and there was no significant difference in the signal of benign hyperplasia compared to normal tissue. This data suggests that ghrelin analogues may be useful as molecular imaging probes for prostatic neoplasms in both localized and metastatic disease.

(Prostate, June 2012)

GLOBE SCAN

MRI Based Scoring System

Malignant axillary lymph nodes are an important predictor for breast cancer recurrence, but invasive dissection or biopsy is required for the diagnosis. A study has determined whether and how malignant nodes could be diagnosed preoperatively with magnetic resonance (MR) imaging. MR images of all women evaluated for breast cancer were obtained and correlated with the image characteristics of each axillary node with the pathologic diagnosis of the same node. 251 nodes (117 benign; 134 malignant) from 136 women (mean age: 44years; range: 20-67) were analyzed. Mean diameter of the nodes was 18mm (range: 5-58mm). With pathologic diagnosis as the reference standard, MRI-based interpretations were 66.4% sensitive, 94% specific, and 79% accurate. An MRI-based lymph node scoring system based on various correlations had a specificity of 91%, a sensitivity of 93%, and an area under the ROC curve of 0.95 (P<0.001). So, metastatic axillary lymph nodes can be accurately diagnosed by MR in women with early breast cancer preoperatively and non-invasively. The scoring system appears to be superior to current methods.

(China: Eur J Radiol, Apr 2012)

Fast and Inexpensive Imaging

A fast and inexpensive new imaging technique, called digital chest tomosynthesis, is a promising method for lung cancer screening. Data was analysed from over 1,500 patients with no previous evidence of cancer, who were screened using the technique. The doctors identified abnormalities in the lungs of 268 subjects, of whom 16 (1.07%) were found to have lung cancer. Digital tomography takes about 11 seconds. The lung cancer detection rate using digital chest tomography is in line with the detection rate of previous studies using computed tomography. The 1% detection rate is adequate for lung cancer screening and the cost is by far lower than using low-dose CT scan. Compared to chest CT, patients who underwent digital chest tomography received a far lower radiation dose. Digital chest tomography seems to be a promising first-line tool for lung cancer screening. Further multicenter studies are needed to confirm the clinical role for the technique in the detection or evaluation of lung nodules.

(Italy: Science Daily, Apr 18, 2012)

NEW TECHNOLOGIES

Endorectal Ultrasonography Technique

Endorectal ultrasonography (ERUS) with sterile coupling gels filling the rectum improve the accuracy of T staging in rectal cancer was shown in a study from Cancer Hospital, Peking Union Medical College, China. A total of 189 patients with confirmed rectal carcinoma were recruited in the study. All underwent ERUS and surgery within the week following sonography. EURS was performed by introducing sterile coupling gel into the rectum. Two radiologists looked at the images at the same time and agreed upon staging. Rectal carcinoma was staged from Tis to T4. The accuracy of T-staging by ERUS was 89.95%. The sensitivity, specificity, PPV and NPV for ERUS at different stages were calculated. For early stage (Tis and T1), these values were 93.62%, 97.89%, 93.62% and 97.89%, respectively. ERUS filling with sterile coupling gel in the rectum overcomes the pressure effect from a water bath and the restriction caused by tumor stenosis, thus, greatly improving the accuracy of T-staging. The examination is real-time, safe and inexpensive.

(Ultrasound Med Biol, Apr 2012)

Mutations Detection in Brain Tumor Using Non-Invasive Imaging

Researchers at Winship Cancer Institute have developed a technique for detecting an "oncometabolite," a chemical produced by some brain tumors via non-invasive imaging. They used magnetic resonance spectroscopy (MRS) to measure a chemical, 2-hydroxyglutarate (2HG), that is scarce in normal tissues. 2HG is produced by some types of brain tumors carrying mutations in an enzyme called isocitrate dehydrogenase (IDH). Mutations in the genes IDH1 or IDH2 cause an accumulation of 2-hydroxyglutarate. The presence of the mutations means patients generally survive longer, but they don't respond as well to standard radiation and chemotherapy treatments. To verify the test as a diagnostic tool, DNA from 65 glioma biopsy samples was analyzed; 39 had mutations in IDH1 or IDH2. MRS analysis of the samples predicts the presence of the mutation with 98% accuracy. The technique offers the possibility of following the patient after surgery to see if the treatment is working, by monitoring the decline in levels of the oncometabolite.

(J Mol Med, Mar 17, 2012)

Novel X-ray Imaging System

Scientists at German Cancer Research Center, Germany, have made use of a novel linac-mounted kilovoltage x-ray imaging system for multileaf collimator (MLC) tracking. The unique in-line geometry of the imaging system allows the detection of target motion perpendicular to the treatment beam. The imaging system either alone or in combination with an external surrogate monitoring system was utilized using a Siemens ARTISTE linac with two flat panel detectors. A programmable phantom with an embedded metal marker reproduced three patient breathing traces. For MLC tracking based on x-ray imaging alone, marker position was detected at a frame rate of 7.1 Hz. For the combined external and internal motion monitoring system, a total of only 85 x-ray images were acquired prior to or in between the delivery of 10 segments of an IMRT beam. External motion was monitored with a potentiometer. Dosimetric accuracy for a highly modulated IMRT beam, assessed through radiographic film dosimetry, improved substantially when tracking was applied, but depended strongly on the respective geometric tracking accuracy.

(Phys Med Biol, Apr 21, 2012)

Ovarian Cancer - Best Imaging Technique

Researchers from the University of Cambridge, UK, have determined the best method "diffusion-weighted MRI" to monitor response to treatment in late-stage ovarian cancer. This technique measures the movement of water molecules within the tumor. CT scans only detect changes in the size of the tumor, not differences in its structure. Diffusion-weighted MRI can give a much better idea of the density of tumors, in addition to their size. Twenty-one study participants received an MRI of the pelvis and abdomen, they also underwent 3 additional MRI techniques on top of the standard scans. The researchers compared different parameters, including Apparent Diffusion Coefficient (ADC), which measure the movement of water molecules in tumors. They found that among individuals who responded to treatment, there was a larger increase in the ADC of the primary tumor, than in patients who didn't respond to treatment. In addition, they found no change in the sites of cancer spread. The increases in ADC seen in the primary tumor in patients who responded to treatment, is due to the chemotherapy killing cancer cells, which in turn increases the amount of space inside the tumor allowing water molecules to flow more easily.

(Medical News Today, Feb 16, 2012)

WATCH-OUT

Methods and Apparatuses for Thermal Ablation

Nields, et al. of Intio, Inc. (Broomfield, CO) have been assigned US Patent No. 8,155,416 on April 10 2012 for their invention entitled "Methods and apparatuses for planning, performing, monitoring and assessing thermal ablation". Thermal ablation involves the creation of temperature changes sufficient to produce coagulation necrosis in a specific volume of tissue within a patient, typically one or more benign and/or cancerous tumors. The present invention relates to thermal ablation systems and methods and, in particular, to improved systems and methods for planning, performing, monitoring and assessing thermal ablation. A thermal ablation system is operable to perform thermal ablation using an x-ray system to measure temperature changes throughout a volume of interest in a patient. Image data sets captured by the x-ray system during a thermal ablation procedure provide temperature change information for the volume being subjected to the thermal ablation. Intermediate image data sets captured during the thermal ablation procedure may be fed into a system controller, which may modify or update a thermal ablation plan to achieve volume coagulation necrosis targets.

(www.patentgenius.com, Apr 29, 2012)

PET Probes for Imaging Cancers

United States Patent No. 8,101,740, issued on January 24, 2012, was assigned to The Regents of the University of California (Oakland, CA) . "Positron emission tomography probes for imaging immune activation and selected cancer" was invented by Radu; Caius G. et al. The advent of molecular imaging approaches, such as Positron Emission Tomography (PET), has enabled measurements of molecular and cellular mechanisms throughout the body in preclinical and clinical settings. Various cell surface receptors and intracellular enzymes may potentially be imaged by PET using specialized probes. Recently, in a mouse model of autoimmune demyelination, it has been shown that a probe for glycolysis called [.sup.18F]fluorodeoxyglucose ([.sup.18F]FDG) enables PET-based monitoring of disease onset via distribution of the probe in organs and of immunosuppressive therapy.

(www.ukpmc.ac.uk, May 4, 2012)

Processing Mammographic Images

The inventors Choi; Hyung Sik (Seoul, KR), et al of PACSPLUS Co., Ltd. (Tokyo, JP) have been assigned US patent No. 8165380 on 24th April 2012 for "Method, apparatus and program for processing mammographic image". The present invention relates to mammography, but more precisely, to a method of automatically processing a digital mammographic image, an apparatus, and a program for executing the method. A controlling unit divides an original mammographic image into a breast portion and a background portion based on a predetermined value. It determines the breast boundary line between the breast portion and the background portion. It shifts and expands the breast portion upward, downward and forward to result in a secondary boundary line, wherein the breast portion side of the secondary boundary line has a size larger than that of the breast portion. In addition, the controlling unit cutting off the background portion of the mammographic image vertically and/or horizontally at the secondary boundary line so that the original breast portion side remains, thereby obtaining the finally processed mammographic image. Thus, the controlling unit generates the final image smaller in file size than the original mammographic image.

(www.patentstorm.org, May 7, 2012)

Robotic Localizing Aid for HIFU Delivery

Dogra, Vikram S. (Pittsford, NY, US), et al have filed an application No. 13/060673 in USPTO which was published on 19th April 2012. There have been many advances in the medical use of ultrasound, especially for high intensity focused ultrasound (HIFU). HIFU has been successfully applied in the treatment of cancers, particularly in destroying tumors found in the breast, prostate, kidney and pancreas. However, a need exists in the art for accurate placement of the HIFU transducer relative to the biopsy needle to allow HIFU hemostasis of the specific location of the biopsy. It is an object of the invention to provide such accurate placement in a form which can be conveniently used in an operating room or a biopsy room. The HIFU probe can track the biopsy needle entry site even when the needle has been removed with the help of the robotic arm. Targeting can be robotically controlled using data extracted from a conventional two-dimensional image taken via any suitable imaging technique. The area in which the biopsy is to be performed is imaged, and coordinates of the location of the biopsy are extracted and input into a processor.

(www.uspto.org, May 2, 2012)

RGCON-2012

The 11th International Conference of Rajiv Gandhi Cancer Instiute & Research Centre, "RGCON-2012", was organised from 6th to 8th April, 2012. The theme of the conference was "Prostate Cancer", the aim being to provide the latest updates on various aspects of prostate cancer, from screening and treatment options in early prostate cancer to newer advances in metastatic and hormone refractory prostate cancer. The program included Live Robotic Workshop and International Prostate Cancer Symposium. It was clubbed with "First National Conference on Men's Health" that addressed "Why men die earlier and suffer more".

On 6th April,there was live demonstration of Robotic Radical Prostatectemy by Rajiv Gandhi Cancer Institute at the Auditorium of Dr RML Hospital. It was performed by Dr Ashok Hemal in a difficult case of enlarged median lobe in Carcinoma Prostate. A Symposium on Prostate Cancer was conducted, which deliberated on the importance of various parameters in final pathology report by Dr John Davis from M.D. Anderson Cancer Centre, 'Prostate cancer genome' by Dr Chandan Guha from Albert Einstein School of Medicine, and 'Evolution of single port robotic surgery' by Dr Robert Stein from Cleveland Clinic.

Then the audience was greeted to another surgical feast in the form of telecast of live single port Robotic Radical Prostatectomy performed by Dr Robert Stein, which was being done for the first time in India.

In between the demonstration, there were panel discussions and symposia on matters related to Men's Health, like testosterone replacement therapy, metabolic and cardiovascular disorders related to obesity, and metabolic syndrome and erectile dysfuction. Discussion was also carried out on 'Bone and mental health,' including various topics like osteoporosis, depression and bone complications in prostate cancer.

Dr Andrew Vickers from Memorial Sloan-Kettering Cancer Centre delivered a guest lecture on 'How surgeon characterstics such as clinical experience affect the outcome of radical prostatectomy'. The scientific session concluded with a panel discussion on 'Treatment options for localized prostate cancer' which was moderated by Dr Ashish Kamat from M.D. Anderson Cancer Centre and the panel included renowned Urologists and Radiation Oncologists.

The scientific deliberations on 7th April were held in the comfort of the Sovereign Hall at hotel Le Meridien. The morning started with "Meet the Professor" session in which there was interaction with Dr David Mcleod, Director CPDR; Dr James Eastham from MSKCC; Dr Judd Moul, from Duke University; and Dr Ganesh Gopalakrishnan, Ex HOD Urology, CMC Vellore. It was ably moderated by Dr NP Gupta, Ex HOD Urology, AIIMS. It was an interactive session with the audience taking keen interest in the proceedings. This was followed by a brain storming debate on"Should Screening be Done". Dr Fritz Schroder from Netherlands spoke in favour of screening and Dr Nitin Kekre from CMC Vellore was very articulate in his talk against screening .There was a case-based discussion conducted by Dr Amlesh Seth, AIIMS, subsequent to this debate.

Dr David Mcleod's key note address on 'Hypes and Hopes in Carcinoma Prostate', covering the various trends of treatment presently followed in USA, was greeted with rapt applause. Dr Pramod Sogani from MSKCC discussed the 'Role of Survelliance in Treatment of Low Risk Prostate Cancer'. Some of the aspects regarding 'Role of PCA 3, MRI Histioscanning and PSA isoforms in prostate biopsy', were touched upon by Dr John Davis, and on 'ERG Oncogene' by Dr Shiv Srivastava, CPDR.

Whenever treatment for prostate cancer is discussed, radiotherapy is spoken of in the same league as surgery. Various lectures were delivered on the different techniques of radiation, like IGRT, Cyber knife along with their Indian experiences. The session was followed by a panel discussion on various radiation techniques which was moderated by Dr Sheh Rawat, RGCI.

After a finger licking lunch, there were talks which foretold the journey of radical prostatectomy from open surgery to robotic surgery. While Dr Judd Moul deliberated upon the future of open radical prostatectomy, Dr Ashok Hemal discussed 'Surgeon controlled robotic radical prostatectomy'.

The next session focussed on imaging modalities in prostate cancer. While Dr Vikram Dogra spoke on 'Photo-acoustic imaging of prostate cancer' and 'Pearls and pitfalls of TRUS guided biopsy','Molecular imaging of prostate cancer' and 'Choline PET/CT in diagnosis, staging and re-staging of prostate cancer' were discussed by Dr Bernd Krause, Germany.

(Dr Rajeev Sood, Chairman Conference; Shri Rakesh Chopra, Chairman, RGCI&RC; Shri Hamid Ansari, Honorable Vice President of India; Shri D. S. Negi, CEO, RGCI&RC, Dr Sudhir Rawal, Orginzing Secretary, RGCON- 2012)

Various experts discussed their approaches to the treatment options in hormone refractory metastatic prostate cancer. The molecular pathways involved in HRPC were discussed by Dr Shiv Srivastava, followed by treatment options like 2nd line hormone therapy and chemotherapy, including the recent advances. Topics like 'Role of nutrition'and 'MR guided focussed ultrasound ablation' were touched upon in brief before the session concluded for the day.

In the evening, there was formal inauguration of the conference.The chief guest of the evening was Hon Shri Hamid Ansari, the Vice President of India.The proceedings started with traditional welcome of delegates by Mr DS Negi, CEO, RGCI&RC. Mr Rakesh Chopra,Chairrman, RGCI gave an insight about the future plans of RGCI&RC to serve the society. Dr Rajeev Sood, Chairman of the Conference spoke at length about prostate health awareness program and its implications. RGCON Souvenir was released by the chief guest followed by his inaugural address. He lauded RGCI&RC for its efforts in diagnosing and treating cancer patients with empathy. "Dr PS Raman Memorial Award" for the best publication of the Institute in the year 2011 was presented to Dr Sheh Rawat, Senior Consultant, Dept of Radiation Oncology, RGCI&RC, for his paper entitled "Analysis of dose-volume parameters predicting readiation pneumonitis in patients with esophageal cancer treated with 3D-conformal radiation therapy or IMRT" published in *Jpn J Radiol*. Dr Chandra Gouda, DNB, Dept of Medical Oncology was conferred with the "Young Doctor's Award". Dr Sudhir Rawal, Organizing Secretary, gave his vote of thanks. It was followed by dinner and the audience was enthralled with a lively musical program.

The day on 8th of April also started early with 'Meet the Professor' session in which the delegates interacted with senior urologists, radiation and medical oncologists. Dr James Eastham shared his experience on 'Surgical Management of High Risk Prostate Cancer'. Dr Andrew Vickers enlightened the audience regarding the statistics of a reliable marker to detect prostate cancer. Various techniques on improving continence in robotic assisted laparoscopic prostatectomy were also elaborated.

After much deliberation on treating early prostate cancer with either surgery or radiotherapy, salvage

(Lamp lighting ceremony by Vice President of India)

options after radiation and radical prostatectomy were discussed in detail. Dr Chandan Guha and Dr Bernd Krause, respectively deliberated upon newer advances in focal therapy and radio isotope therapy. No treatment is without its ill effects, so ways were discussed to rehabilitate patients after radical prostatectomy, radiotherapy and androgen deprivation therapy.

After lunch, the proceedings shifted to Dr RML Hospital where another live robotic radical prostatectomy was transmitted. It was performed by John Davis whose surgical skills were demonstrated in a case of locally advanced prostate cancer. It was an apt end to this academic extravaganza and the audience stayed on till evening to witness this surgery.

At the end of the day it was an extremely gratifying experience for the delegates as well as organizers. Everybody found the meeting useful and was able to take away new ideas and pearls of wisdom which will help them to improve care of prostate cancer patients.

(Dr Samir Khanna, Consultant, Dr Sudhir Rawal, Director of Surgical Oncology)

IN FOCUS

DIFFUSION-WEIGHTED MRI IN ONCOLOGY

Introduction

Diffusion weighting is a powerful imaging tool unique to Magnetic Resonance Imaging (MRI) which provides image contrast through measurement of the diffusion properties of water within the tissue. It is highly sensitive to thermally driven molecular water motion over distances of 1-20µm, which in biologic tissue is modified and limited by cellular density, interaction with the cell membranes, the intracellular environment, and macromolecules. Signal is derived from the motion of water molecules in the extra and intracellular space, and the intravascular space which can be quantified in the form of an apparent diffusion coefficient (ADC), directly proportional to the degree of molecular motion.

Certain biophysical processes, like active transport, flow and perfusion, and macroscopic/bulk movements can potentially increase apparent water mobility. On the other hand, various pathological processes within the tissue such as edema, necrosis, or fibrosis change the tissue architecture, its water content as well as its diffusional properties. The motion of water molecules is more restricted in tissues with high cellular density with intact cell membranes whereas in areas of low cellularity or where the cellular membrane has been breached, the motion of water molecules is less restricted.

Technical Aspect of DWI

On clinical MR scanners, the diffusion sensitivity in tissue is easily varied by changing the parameter known as b value which is determined by the gradient amplitude. At least two b values are required for a meaningful interpretation. Large b values (e.g., b = 1,000 s/mm2) are usually required to perceive slow-moving water molecules or small diffusion distances because these show more gradual signal attenuation with increasing b values. Higher minimum b values are required to suppress the perfusion in vascular-rich tissues, indicating that appropriate minimum b values may vary across applications depending on intrinsic vascularity.

Interpretation of DWI

By observing the relative attenuation of signal intensity on images obtained at different b values, tissue characterization based on differences in water diffusion becomes possible. Quantitative analysis of diffusion involves plotting the logarithm of signal intensity against the b value as an exponential function, the slope of which described the ADC which can be calculated for every pixel according to the following equation:

$$ADC = \frac{1}{b} \ln \left(\frac{S_0}{S_b}\right)$$

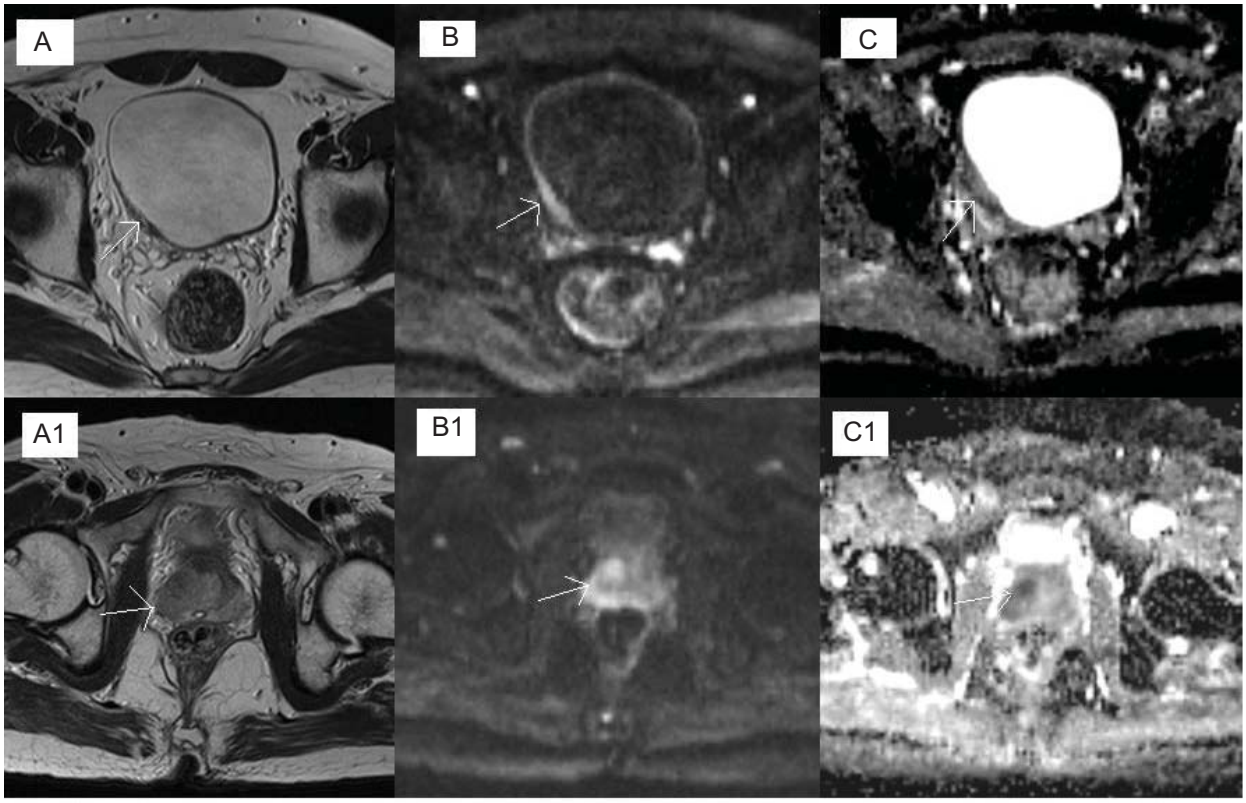
where S_0 is the signal intensity at b = 0 s/mm^2 image and S_b is the signal intensity at b= ~ 400-1500 s/ mm^2 image.

Clinical Applications in Oncology

Diffusion-weighted MRI has been incorporated into general oncologic imaging practice because of its many clinical advantages. A particular advantage of DW-MRI is that it does not require intravenous contrast media, thus enabling its use in patients with reduced renal function. Its clinical uses include improved tissue characterization (differentiating benign from malignant lesions), monitoring treatment response after chemotherapy or radiation, differentiating post therapeutic changes from residual active tumor, and detecting recurrent cancer. Potential additional roles include predicting treatment outcomes (before and soon after starting therapy), for tumor staging, and perhaps also for detecting lymph node involvement by cancer.

Tumor detection: DWI sequence is extremely sensitive for detection of small liver metastasis seen as high signal intensity foci, which are not visible on conventional MR sequences and CT. DWI has been reported to be more accurate than even superparamagnetic iron oxide (SPIO) enhanced MRI, for the detection of liver metastases. Small peritoneal deposits shine against a suppressed black background easing their detection. Prostate cancers, which appear as low-signal-intensity foci on ADC maps, typically show lower ADC values than the peripheral zone and the transitional zone and central gland. Small lesions in the oral cavity, like tongue & cheek and lesions especially in relation to urinary bladder in the higher 'b' value images that shine through the suppressed urine signal markedly improves detection (Figure 1).

Tissue characterization: Lower ADC values in malignant tissues have been related to a combination of higher cellularity, tissue disorganization, and increased extracellular space tortuosity, all contributing to reduced motion of water. A reliable differentiation between benign and malignant breast lesion, benign and malignant focal



A, A1-T2W, B,B1-Diffusion b1000, C,C1-ADC Map A,B,C- Lesion Urinary Bladder Arrow, A1,B1,C1-Lesion Prostate Arrow

liver lesions and benign and malignant nodes has been reported with DWI depending on the differences in their ADC values. Nevertheless false positive results are often encountered in abscess and infective processes and false-negatives occur with cystic, necrotic lesions and in well-differentiated neoplasms (particularly adenocarcinomas).

Predictive parameter for treatment outcome: Diffusion-weighted MRI has been shown to have the potential to prospectively predict the lesion aggressiveness and success of some treatments in a number of different tumors. Certain observations have led to the hypothesis that tumors with higher ADC levels are more likely to have areas of necrosis, which in turn predicts poor outcomes related to hypoxia-mediated radio-resistance. But this may not apply to all tumors and to all therapy types.

Monitoring treatment response: Because cellular death and vascular changes in response to treatment can both precede changes in lesion size, changes in DW-MRI may be an effective early biomarker for treatment outcome both for vascular disruptive drugs and for therapies that induce apoptosis. In most malignant tumors, successful treatment is reflected by increases in ADC values reported for several anatomic sites, including breast cancers, primary and metastatic cancers to the liver, primary sarcomas of bone and brain malignancies. Nevertheless, a transient decrease in ADC values has been reported in early phase of treatment related to cellular swelling, reductions in blood flow, or extracellular space.

Differentiating recurrence vs post treatment changes: The differentiation of post treatment changes and residual or recurrent tumor is a common diagnostic dilemma. In head and neck tumors, for instance, recurrent tumor and osteoradionecrosis are often impossible to distinguish clinically or by imaging. Diffusion-weighted MRI has the potential to distinguish post radiation changes from recurrent cancer based on ADC value differences. Higher ADC values likely represent post therapeutic extracellular edema, whereas lower values are suspicious for active disease. In this respect, DW-MRI may have advantages over fluorodeoxyglucose–positron emission tomography (FDG-PET) assessments, which can be limited shortly after radiation therapy because areas of inflammation often have high uptake on PET scans and can lead to false-positive results.

Tumor staging: There is early experience indicating that DW-MRI may be helpful for primary tumor staging and for detecting nodal and distant metastases.

In this regard, whole-body DW-MRI seems to be particularly promising.

Whole-body imaging: Whole-body DWI is performed using a STIR EPI diffusion-weighted technique, with a high 'b' value of 1,000 s/mm^2 for background suppression. By performing imaging at multiple stations in the body, a composite image of the whole body can be constructed. The images are processed using maximum intensity projection and are usually displayed using a reversed black-and-white gray scale. Signals from normal tissue such as blood vessels, fat, muscle, and bowel are suppressed. However, other normal structures, such as the spleen, prostate, testes, ovaries, endometrium, and spinal cord remain and visible areas showing restricted diffusion, for example, highly cellular lymph nodes, can be strikingly depicted.

Drug development/ clinical trials: As a pharmacodynamic indicator, DW-MRI may have a significant impact on pharmaceutical drug development by determining whether a drug produces a measurable effect, the magnitude of those effects and the potential biologic implications. In clinical trials, questions revolve around whether changes in individual patients can be measured reliably and reproducibly and whether they predict important clinical outcomes related to therapy.

Current Challenges and Future Development

The biggest challenge hindering its widespread adoption is the lack of a standardized technique which includes the varied choice of b-values which leads to considerable difference in the observed ADC values for normal and diseased organs using different techniques. The DWI is inherently very sensitive to susceptibility effects and motion and hence is noisy. Noise filtration and image registration may help improving the quality of acquisition and hence interpretation. Lack of reproducibility is another problem intriguing its use.

Summary

There is an extraordinary opportunity for DW-MRI to evolve as an unmatched noninvasive diagnostic tool which does not require any exogenous contrast agents, and does not use ionizing radiation yet can be quantitative and can be easily incorporated into routine patient evaluations. Potentially, DW-MRI could have clinical utility at all stages of a cancer patient's journey from detection to diagnosis, for staging and assessing therapy response, and finally, for assessing relapse.

(Dr A Jena, Director, Magnetic Resonance Imaging)

CLINICAL TRIALS

Breast Specific Gamma Imaging

A multicenter study conducted in New Britain, has shown that breast specific gamma imaging can detect malignant or high risk lesions in patients with negative or indeterminate mammographic findings. Molecular breast imaging techniques are increasingly being used for diagnosis of breast cancer in addition to mammography and ultrasound. Investigators assigned 1042 patients in the analysis, and breast specific gamma imaging was recommended if patient had at least two of the following indications: equivocal or negative mammogram or sonogram and an unresolved clinical concern, personal history of breast cancer or current cancer diagnosis, palpable masses negative on mammographic and sonogrphic examination, radiodense breast tissue or high risk for breast cancer. In 250 patients, lesions were classified as positive (malignant or high risk) and negative (beingn) in 792 cases. According to the results of breast specific gamma imaging, 408 patients were positive (227 malignant or high risk lesions requiring additional intervention), negative in 634 patients (23 with malignant or high risk lesion), and indeterminate in 69. patients. This technique had a overall sensitivity of 91% and specificity of 77% and the overall management provided is better than ultrasound.

(Am J Roentgenol, Jan 2012)

CT-MRI Co-Registration Techniques

Use of pre-operative radiation for patients with rectal cancer is significantly increased. Magnetic Resonance Imaging (MRI) provide increased soft tissue contrast compared to other radiographic imaging techniques, such as computed tomography (CT). Researcher from St James Institute of Oncology evaluated CT-MRI co-registration accuracy for patients treated in the prone position without using fiducial markers. Total 17 patients with biopsy-proven rectal carcinoma participated in the study, reference coregistration was done by radiologist and physicist. Accuracy and repuoducibility were analyzed using a measure of target registration error (TRE). Study has shown that MRI acquisition with the patient in prone treatment is well tolerated and is both practical and technically feasible. An automated technique achieved the greatest accuracy with TRE of 2.3 mm and it was also faster than their manual counterparts.

(Br J Radiol, Jan 2012)

Indian Initiative International Repute

CLINICAL SERVICES

• Surgical Oncology • Radiation Oncology • Medical Oncology • Paediatric & Hematology Oncology • Hemato Oncology
• Preventive Oncology • Nuclear Medicine • Anaesthesiology & Pain Management

OUR STRENGTHS

- Radiology • PET-CT Scan • MRI & PET-MRI Fusion
- Da Vinci Robotic System • Bone Marrow Transplant
- RF Ablation of Tumors • RT Treatment Planning System
- Brachytherapy • IMRT • IGRT • SRS • SRT • SBRT
- Pathology & Molecular Biology Lab • HIFU • Blood Bank
- Apheresis (Blood Component Separation)
- Image Guided Biopsies & Therapeutic Procedures
- Modular Operation Theatres with all monitoring facilities
- Home Cancer Care • Tumor Board & Multi Speciality Clinics

- World Class Cancer Care
- Dedicated Clinicians
- Evidence-based Decisions
- Cutting-edge Solutions
- State-of-the-art Equipments

Rajiv Gandhi Cancer Institute and Research Centre

A Unit of Indraprastha Cancer Society
Registered under "Societies Registration Act 1860"

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