

The Emerging Role of Functional Imaging in Cancer Management

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Abstract: Functional Imaging offers great potential in investigative and therapeutic Oncology. Functional MRI (fMRI) is the current modality of choice for the demonstration of brain function in correlation with neuroanatomical localization using blood oxygenation level dependent (BOLD) contrast. Among scintigraphic functional imaging modalities, Positron Emission Tomography (PET) using 18F-2-deoxy-D-glucose (FDG PET) helps not only to highlight post-therapy residue not discernible by conventional imaging, it also distinguishes tumour recurrence from radiation necrosis. It also has found applications in the investigation of various other common cancers. Modern radiation treatment planning using computerized tomography (CT) or magnetic resonance images (MRI) can be incorporated with the relevant PET emission tomography images to provide detailed anatomic and physiologic correlation that would result in better target volume coverage leading to higher tumour control while minimizing radiotherapy sequelae. Commercially available software and hardware allows such integration with unprecedented user-friendliness in the application of state-of-the-art radiation therapy modalities like 3 dimensional conformal radiotherapy (3D-CRT), intensity modulated radio therapy (IMRT), brachytherapy etc. The future areas of basic research for functional imaging include use of such techniques for the localization, grading and differentiation of recurrence versus necrosis, prediction of chemo-radiotherapy resistance etc. exemplify the immense research potential available with functional imaging in the field of investigative oncology. Although these newer techniques are very exciting and hold a lot of promise for the future, but their cost of application at the moment is very high. The onus would therefore lie on the clinicians and researchers to explore their real worth and, until such time, to use these modalities extremely judiciously so as to make them cost-effective for the concerned patients.

Key Words : *Functional Imaging, magnetic resonance, positron emission tomography.*

The evolution of Modern Radiodiagnostics

The earliest application of Functional Imaging for medical purposes can be traced to the use of intravenous pyelography in radiodiagnosis and isotopic bone and visceral scans in nuclear medicine, that date back to the early part of the last century. Further progress in Diagnostic Radiology was rather slow, but the advent of a succession of newer modalities around the late 50's dramatically changed the course of medical diagnostics. Thus, regular clinical use of Ultrasonography during the 60's, CT scan from the 70's MR scans from the 80's along with contemporary advancements in nuclear scintigraphy, brought a veritable medical imaging revolution that has probably preserved more lives than can ever be imagined with any diagnostic modality. The major gainers of these spectacular developments were the specialties of Cardiology, Neurology, Neurosurgery etc., but the fruits of such research and developments have also passed on in substantial measure to cancer patients. The latest advancement in this field, Functional Imaging is poised to emerge as an indispensable tool in the Oncological armamentarium for purposes of investigation, planning and treatment of cancer patients.

Functional Imaging in the investigation of cancer patients

Brain tumours have remained in the focus of attention for clinical as well as research purposes since the development of computerized tomography and magnetic resonance imaging. Traditionally, MR Spectroscopy (MRS) has been used to identify specific areas of Motor function besides, at times to distinguish between benign and malignant lesions. The specificity and sensitivity of this study however has not been consistent for most sites and it also has had a limited utility for radiotherapy planning. Functional MRI (fMRI) undoubtedly has

emerged as the current modality of choice for pre-surgical mapping to define 'eloquent' areas of the cortex in order to prevent neurological morbidity during surgical tumour debulking. The underlying principle of fMRI is the demonstration of brain function in correlation with neuroanatomical localization on a real-time basis. The majority of such studies are performed with blood oxygenation level dependent (BOLD) contrast and, during the procedure, the patient performs a defined cognitive task that results in increased neuronal activity in the relevant area of the cortex. The latter induces local haemodynamic changes that are picked up as signal changes on the fMRI. Being of small dimensions, these require signal averaging and statistical processing to map the activation onto the topology of the brain. Future research would focus on microstructural imaging techniques to elaborate further linkage between microstructure and brain function with obvious clinical implications¹.

Isotopic scintigraphy has had a time honoured place in the investigation of cancer since 131-Iodine scans were in vogue for differentiated thyroid cancer many years back. Similarly 32-Phosphorus, 99-Technetium, 201-Thallium, 111-Indium, MIBG and a host of newer isotopes have been incorporated into the standard work-up of specific cancers, besides monitoring therapy response and follow-up evaluation. The most rapidly advancing scintigraphic functional imaging entity to make an impact on oncologic practice however is Positron Emission Tomography (PET). It is basically a diagnostic imaging technique that creates high-resolution tomographic images of the distribution and concentration of positron-emitting radionuclides e.g. 18F-2deoxy-D-glucose (FDG PET) after injection into the circulation. A similar scintigraphic study, the Single Photon Emission Computed Tomography (SPECT) does not match the sensitivity and specificity of the former and hence finds lesser clinical preference. Within a short period of about two decades, positron emission tomography has found extensive indications in the early diagnosis, staging, characterization, monitoring

of therapeutic efficacy and even for establishing recurrence of various cancers. In brain tumour management, positron emission tomography helps not only to highlight post-therapy residue that cannot be picked up by conventional imaging, but is also indispensable for distinguishing tumour recurrence from radiation necrosis. Positron Emission Tomography is increasingly featuring in the investigation and clinical management of various cancers e.g. of lung, breast, colon, gynaecological organs and the head and neck region. Wherever available, it is presently included in the routine pre-therapy work-up of lung cancers and in their post-therapy follow-up, because of its sensitivity for picking up sub-clinical primary as well as metastatic lesions.

Functional Imaging in the planning of radiotherapy

The benchmark for modern planning of cancer patients with radiotherapy is three-dimensional radiation treatment planning (3D RTP). This entails a dedicated, highly complex and advanced computerized system for the computation of patient and technical data, that is available as a computer-assisted graphic display of the target organ, in precise anatomic relationship with the surrounding organs. Such 'model' or 'virtual' image of the volume of interest represents for all practical purposes, the specific anatomic volume both, spatially as well as in the terms of the differential densities of the various constituent organs and tissues. Computerized tomography scans have formed the mainstay for acquiring and processing the relevant imaging information for 3D RTP. The quest for the ultimate precision in radiotherapy planning and delivery however, has led to attempts at incorporation of supplementary information available from allied imaging modalities like MRI, SPECT and PET scans to the relevant CT images. Whereas magnetic resonance imaging provides excellent soft tissue contrast allowing precise delineation of normal critical structures and treatment volumes, single photon emission computerized tomography and positron emission tomography imaging provide detailed functional information concerning tissue metabolism and radioisotope transport. These types of imaging data do not however provide the necessary geometric and physical information required in CT-based 3 dimensional radiotherapy planning⁽²⁾. The integration of such physiological image sets into the RT Planning process has the potential to provide the treatment planner with information about the morphology of a tumour including regions of hypoxia, increased cell proliferation, possible microscopic extensions and aerobic regions of tumour.

It thus appears quite logical that, the combined use of the metabolic information of a tumour derived from the positron emission tomography scans and the morphological image data acquired from computerized tomography scans, would lead to improved and efficient planning of the relevant radiotherapy technique. Facilitation of the integration of such physiological image data to the relevant computerized tomography images is done with the help of dedicated software and the integrated image is then transferred to the treatment planning system (TPS) for the necessary planning. The treatment planning system can then be interfaced with the radiotherapy unit and the target volume can be treated with extreme precision. An example of such a combined package of imaging and radiation therapy systems is the Millennium VG 'Hawkeye' integrated functional and anatomic imaging system (GE™) that is integrated with the Cadplan® and Helios® Treatment Planning Systems and the 2100EX linear accelerator (Varian™) that has recently been developed for delivering Intensity Modulated Radiation Therapy (IMRT). Thus, modern radiotherapy techniques like Stereotactic Radiation Therapy (SRT), Stereotactic Radiosurgery (SRS), 3-Dimensional Conformal Radiation Therapy (3D CRT) and IMRT, that today epitomize state-of-the-art radiation therapy, are all set

to cross unprecedented horizons of perfection in the conception and delivery of radiotherapy, due to the added information available from functional imaging. This holds great promise for tumours that are treated with a curative aim, in terms of both, higher percentage of long-term control and greater degree of freedom from distressing sequelae of radiotherapy.

The basic tenet of radiotherapy of administering maximal dose to the target volume that contains the tumour and minimum dose to the surrounding normal tissues, is fulfilled to a significant extent by brachytherapy. The traditional role of imaging for 'after-loading' brachytherapy techniques has centered on undertaking conventional roentgenograms for the verification of implant geometry and orthogonal radiographs for purposes of dose calculation. Computation of dosimetric data is now undertaken with the help of 3-dimensional dedicated brachytherapy planning systems and a great many of these use computerized tomography scan or Ultrasonographic images as the data source. With the advent of permanent brachytherapy implants for organs like the prostate, Ultrasonography guided techniques have been in vogue for more than 2 decades and have been proven user-friendly besides delivering the desired results. Current thrust is on the acquisition of biological imaging data and their integration with the relevant brachytherapy treatment planning systems to achieve much higher control rates by attempting tumour-targeted radiotherapy³.

Functional Imaging for the treatment of cancer

The final aim of the meticulous staging of cancer and optimized treatment planning and delivery is to enhance the possibility of long term disease control without inflicting unacceptable morbidity to host tissues. While three-dimensional treatment planning takes care of the latter by limiting the distribution of radiation to within the target organ as much as possible, susceptibility of the tumour cells to radiotherapy is often dictated by their innate biological behaviour. Molecular and functional imaging is expected to provide the 'fourth dimension' of the biologic and metabolic 'fingerprint' of the tumor cells so that the needful modification in therapeutic approach could be undertaken. This would include radiation dose escalation to selective sites and combination with other modalities like surgery or chemotherapy. Radiotherapy of malignant brain tumours like glioblastoma often fails to control the tumour both, by virtue of its radioresistant nature and due to the non-inclusion of its entire regional extensions within the high dose radiotherapy volume. The standard radiotherapy technique for high grade astrocytoma entails encompassment of the pre-surgical volume along with a 3 to 4 cm. margin of surrounding normal tissue. Despite the highest tolerable doses to this extended volume, 'geographic misses' are a common cause of treatment failure. The incorporation of positron emission tomography images to the magnetic resonance imaging or computerized tomography images acquired pre- and post-operatively and the composite images used for 3-dimensional planning are likely to throw light on its topographic profile and provide the desired breakthrough information for improving the clinical outcome of this formidable tumour. Similar hope can be nurtured for many other central nervous system neoplasia where limitations for treatment are imposed by virtue of highly radiosensitive organs in their vicinity and functional scans can help tailor individual radiotherapy volumes to offer a higher therapeutic radio.

Prostate cancer, that is fast emerging as the commonest cancer of the males in the West, has been the subject of much clinical research regarding the techniques for integration of functional imaging with the planned radiotherapy volume, with encouraging results. Mizowaki et. coll. have used magnetic resonance spectroscopy to outline intraprostatic deposits of cancer and attempted to customize dose delivery with

brachytherapy, thus paving the way for targeted radiation therapy³. Similarly, intensity modulated radio therapy, that today could be considered as the ultimate form of 'designer radiation therapy' would undergo further refinement with the incorporation of molecular inputs in its treatment planning.

Future research possibilities of functional imaging in oncology

While at the present time, functional imaging has made a limited though significant impact in the fields of diagnostic and therapeutic radiology, it has immense possibilities for future in areas of both, clinical as well as basic research. The integration of functional imaging with the modern diagnostic and therapeutic implements employed for the detection and treatment of cancers is bound to lead to a paradigm change in the outlook of most malignancies. Similarly, the use of coupled 201-Thallium and 99 Technetium-HM-PAO SPECT for the localization, grading and differentiation of recurrence versus necrosis in supratentorial brain tumours⁴ and Technetium-sestamibi to predict chemo-radiotherapy resistance for small cell lung cancer⁵ are some of the examples of the immense research potential available with functional imaging in the field of investigative oncology.

Conclusion

These recent and exciting developments in the realm of functional imaging and their link-up with various diagnostic and therapeutic modalities has opened a floodgate of new opportunities in areas of clinical as well as laboratory research. Integration of novel local and systemic disease markers would serve to redefine illness by indexing new reference standards for diagnosis of existing disease entities. Although Functional and Molecular Imaging have provided extremely beneficial inputs that are slowly but steadily being incorporated in

radiation therapy practice, their larger potential remains far from being fully tapped at present. These newer techniques are very exciting and hold a lot of promise for the future, but their cost of application at the moment is very high. The onus would therefore lie on the clinicians and researchers to explore their real worth and, until such time, to use these modalities extremely judiciously so as to make them cost-effective for the concerned patients.

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