EDITORIAL JIMSA January-March 2005 Vol. 18 No.1

Radiation Therapy - What is New?

Natural science may be defined as the search for "truth" about the natural world. In this definition, truth is characterized by principles derived from observations about the natural world that can be verified repeatedly through accepted norms of scientific experiments. As a branch of natural science, medical science is the quest for understanding one particular object, the human body, its structure and function under all conditions, from well-being to illness. This journey has yielded models of human health and illness that are useful in preventing disease and disability, diagnosing abnormal conditions and *designing therapies* to alleviate the abnormalities and restore the body to a state of relative, if not absolute wellness. Radiation therapy is a late enterant in the management of illness of human beings, X-rays having been discovered only about a hundred years ago. Though relatively a young branch of medicine, radiation therapy has evolved into a very important segment to provide care for cancer afflicted patients.

Radiation has been an ever present ingredient in the evolution of life on the planet earth. It is not something new created by human beings; it has always been there since the inception of Universe. What is new, what is man made, is the harnessing of this ever present radiation for cure of cancer in the last century. Amongst the peaceful uses of nucelar radiation, radiation Therapy stands high, offering a cure to early cases of cancer and palliation to the advanced malignancies. X-Rays were discovered in 1895 by the German physicist Wilhelm-Conrad Roentgen, and radioactivity in 1898 by Becquerel. In 1897, Professor Freund demonstrated before Vienna Medical Society the disappearance of a hairy mole by the use of x-rays and by the turn of century x-rays had been used in Europe and Amercia in primitive therapeutic applications using X-ray tubes and/or radium.

The last decade of the twentieth century saw radiation therapy come of age with significant changes in the technical aspects of radiation oncology. This has resulted largely from computer advances that have allowed the development of new technology related to diagnosis, planning and treatment in radiation oncology.

Image Processing and Integration : The currently available imaging techniques have provided an optimal tool for Radiation therapy planning and execution. The available spectrum of three dimensional anatomical studies project the detailed bony architecture and excellent soft tissue visualization to the oncologist. These anatomic imaging modalities can be complemented by functional imaging studies based on detection of radioactive pharmaceuticals or measurement of blood flow, as used in functional MRI. The relevant information extracted from multiple image data sets includes:

a) Accurate tumour delineation from complementary imaging modalities.

b) Localization of normal structures or functional areas to be avoided in therapy.

c) Estimation of the target volume changes after surgical or cyto reductive therapies.

d) Monitoring of response to therapy.

e) Quantifying target and normal organ motion caused by physiologic process.

Biological Process (Functional) Imaging

Angiogenesis is a fundamental aspect of tumour growth and subsequent metastases. Detection of angiogenic foci by current imaging techniques is dependent on alteration in both vacular architecture and physiology. The *angiographic tumour blush* is the most widely recognised phenomenon but is not quantitative. Dynamic MRI using gadolinium chelates is used clinically to detect and differentiate tumours.

Apoptosis is a universal cellular process that acts to balance cell division. Decreased apoptosis rather than increased cell-division may be the principal factor leading to growth in some tumour lines. Treatment induced apoptosis if quantified can serve as a surrogate marker of therapeutic response. *Phosphatidyl serine* is exposed on the cell's outer surface early in the course of apoptosis. *Annex in V,* an endogenous human protein, has a high affinity for this membrane-bound phospholipid. *Annex in V* has been labeled with technetium-99m and the proof of concept has been demonstrated in animal studies. The reported safety and relative ease of imaging with this compound suggest that it may reach clinical trials.

Three Dimensional Treatment Planning and Delivery : Three dimensional treatment planning refers to the use of the patients' three dimensional gemometry to select beam directions, design beam apertures, compute doses, evaluate plans and generate treatment verification images[1]. The primary goal of three-dimensional treatment planning is to improve the therapeutic ratio, either by increasing the tumour dose without increasing morbidity or by reducing complications without sacrificing tumour control. To achieve either aim requires sparing normal tissue by confining the high-dose region to the target volume. Treatment techniques that achieve this goal are generally called *conformal.* 3D CRT or 3 dimensional conformal radiation therapy can be delivered using (a) Gamma knife where gamma radiation is emitted from a fixed array of small Co^{60} (cobalt-60) sources located within a large hemisphere that surrounds the patients head (also named as Stereotatic surgery) (b) High energy x-ray radiation produced by medical linear-accelerator (LINAC) applying prefabricated circular collimators or miniature multileaf collimators to achieve conformation of radiation dose.

Intensity Modulated Radiation Therapy : Intensity modulated radiation therapy is an advanced form of three dimensional conformal radiation. Besides preparing a treatment plan with inverse planning, the delivery mode is different. Instead of uniformly homogenous dose intensity, each planned beam is segmented into small independent elements referred to as *beamlets.* Each beamlet carries a definitely assigned intensity of radiation depending upon the dose constraint having been given to the organ in which it will be delivered. Intensity modulated radiation is a very powerful tool to achieve the best target dose with minimal morbidity to the surrounding critical organs.

Gated Radiation Therapy : It may be possible to immobilize a patient to prevent changes in daily treatment set up using external restraints (head & body frames or casts), however internal organ motion between the treatments and within treatments is difficult to restrain. Inter treatment motion can be resolved through the use of repeated imaging, typically with CT-scan or sonography. Intra treatment organ motion results primarily from cardiac and respiratory motion in thoracic treatment; bowel movement and state of fullness of urinary bladder for intra abdominal malignancies. Radiographic, CT studies and MRI can reveal the extent of tumour motion resulting from respiration[2]. To account for the effect of respiratory motion the technique of *gating* is used, where in, the radiation is delivered only at specified times in the patient's respiratory cycle. There are two ways to achieve gating. (a) instructing the patient to hold breath in deep inspiration and match the accelerator output to the period of breath holding, (b) Active breathing control technique involves monitoring patients' respiratory cycle with a spirometer. At a specified point in the respiratory cycle, a valve closes the air supply to the patient and linear accelerator is turned on. After a pre determined period, the accelerator is turned off, the valve is opened and the patient can resume breathing. Both the deep-inspiration and active breathing control forms of gating require patient training and compliance to hold the breath. The help of a respiratory professional to monitor the spirometry and train patients in breath holding is required.

Molecular biology and Radiation Responses : The recent advances in the last two decades have highlighted the way cancer forms and progresses at the genetic level. The findings of Human Genome Project are postulated to be a boon to the understanding of this complex problem. The effect of radiation at the microcellular level can be enhanced with the addition of small molecule Tyrosine Kinase inhibitors or monoclonal antibodies against epidermal growth factor receptors.

Remote after loading brachytherapy : The first attempts at brachytherapy were with use of radium to be followed by artificially produced radioactive substances like Cobalt and Cesium in the early half of last century[3]. The development of Cathetron by Henschke[4], its fine tuning by Joslin[5] and the commercial unit made available by Nucletron (Holland) has made application of brachytherapy safer for the nursing staff, physicists, dosimetrists, radiation oncologists and the patients themselves. Applicators without a radioactive source are loaded into the patient under anaesthesia and after recovery the patient is wheeled into an isolated room for a short period of 15-30 minutes. The applicator is attached to a computer controlled, remote after loading, device and the medical staff leave the room after closing the door. The treatment delivery is automated from outside and after the treatment is over the patient may be discharged after applicator removal.

Endovascular brachytherapy : Percutaneous transluminal coronary angioplasty has been an attractive alternative to coronary bypass graft since the last two decades. Angioplasty has lower initial costs and produces fewer complications than bypass surgery, but the effectiveness of angioplsty is limited by restenosis, appearing within 3 to 36 months in 30% to 50% of patients after treatment[6]. Placement of coronary stents has been found to reduce the incidence of restenosis to 20%[7]. Recent studies have shown that radiation can further reduce the incidence of restenosis in such patients by means of intravascular brachytherapy.

Endovascular radiation can be delivered by means of catheters or radioactive stents. ^{192}Ir wire based array is attached to a guide wire, inserted into a balloon catheter and pushed into place in the stented vessel after angioplaty. A dose of 14Gy (1Gy=1 GRAY=100 rads) is delivered at 2mm from the centre of the source. Other catheter-based systems under development include several beta sources with ^{32}P (phosphorus), ^{90}Y (yttrium) and ^{90}Sr (strontium). ^{90}Y (yttrium) sources being given the most consideration at this time. Radioactive stents also under development have incorported ^{32}P (phosphorus), ^{103}Pd (palladium) and ^{51}V (vanadium). Intravascular radiation therapy is an emerging modality with potential applications for peripheral vessel angioplasty, bypass graft anastomosis, and arteriovenous dialysis grafts in addition to coronary vessels.

Heavy Particle Therapy : The physical distribution of dose delivery by heavy charged and uncharged particles at the end of their track 'Bragg Peak Effect' has a tantalizing property for their use in the clinical setting.

Permanent Seed Implants : Gold (^{198}Au) seeds for treatment of rectal carcinoma[8], ^{125}I (iodine) and ^{103}Pd (palladium) for the treatment of prostate cancer[9] have come a long way from empirical application to image guided brachytherapy using CT-imaging and real time sonographic assisted placement. Recently the 'real-time' treatment planning in the procedure room using a lap top-based planning computer has been introduced. This procedure allows radiation oncologists to view the dose as the seeds are implanted and to adjust the planned locations in light of this information. Future plans are to combine real-time treatment planning dosimetry with CT guidance and fluoroscopic verification of seed placement for permanent prostate implants. This procedure is currently limited by the size of current CT scanners and presence of bony structures in pelvis.

The exponential growth in information technology needs to be translated to benefit of health care and delivery of treatment for oncology. Teleradiation therapy is the new entrant on this horizon and once established will be able to provide optimized Oncology Care to the remotest corners of our country. The process of radiation therapy is guided by the application of multimodality imaging and, therefore, requires integration of images into the patient database. The demand for cost-effective patient information management with convenient and remote image accessibility increases as patient treatment becomes more complex in modern radiation therapy. The electronic management of patient information

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emerges as a promising approach for improving the operation procedures in a radiation oncology department. It is anticipated that it will (i) provide easier access to patient information and improve the effectiveness and timeliness of communications between staff involved in the treatment process; (ii) improve the accuracy and efficiency of treatment planning, delivery and verification; (iii) reduce the time spent managing films borrowed from other departments and reduce the number of lost or damged films; (iv) enable remote patient record access for consultration or collaboration and improve relationships with referring and primary care physicians by providing on-line access to patient information and treatment status; and (v) decrease the space required for archiving patient records. Collectively, these benefits translate into reduced costs and improved patient care.

A common solution to the management of patient information in radiation oncology department is a client-server configuration consisting of a dedicated server connected to generic client computer through World Wide Web (www). The WWW has already been adapted as a teaching tool, providing widespread access to case studies, patient records, and radiology images[10].

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