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PRESIDENT WRITES

Dear Fellows and Members,

Explosive growth in knowledge and skills has made increasing specialisation essential. Fragmentation and narrowing of the field of vision follows increasing specialisation. The whole human being is more than the sum of his or her parts. When a feeling, thinking and apprehensive sick human being seeks help, modern medicine tends to channel this suffering individual into technology and procedures with narrow organ based thinking. We must strike a balance between technology and the human being. The role of a good family physician needs to be revived in the community. In the bewildering environment of the modern hospital the patients care must involve a broad speciality doctor who is to be the primary person to integrate and span the many specialised views on the best course possible, alongwith the patients wishes and ground realities. Organisations like ours can help to inculcate a holistic view grounded in facts and technology.

Continuing medical education needs to address not just single speciality needs but also how the medical community can ensure care for a sick human being, lest we forget our primary role as healers of sick human beings and promoters of health.

Dr. K. Jagadeesan,
President, IMSA



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FROM EDITOR'S DESK

Dear Colleagues

Radiation Therapy has evolved as a useful modality for providing care to the cancer-affected patients. This therapy not only offers almost complete cure in early stage of cancer but also a satisfactory palliation in advanced malignancy; this has largely been possible due to rapid advances in computer technology.

I take pride in presenting to you this special issue on '**Advances in Radiation Oncology**'. I am indeed grateful to **Dr. Tejinder Kataria**, a senior oncologist at the premier cancer Institute at New Delhi, for having personally seen that a high standard of the articles is maintained; the selection of the topics is well planned. Pains-taking effort put in by the team of experts must also be appreciated. The issue amply highlights the latest techniques and treatment advances in the field of radiation oncology; I am confident this publication will be of immense interest to those interested in this field.

I would like to take this opportunity to express my gratitude to all the members of editorial/advisory boards for their fruitful suggestions, cooperation and help rendered at various stages of the compilation of this issue. I am thankful to all the advertisers without whose help this publication would not have been possible.

P.D. Gulati

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Our Guest Editor

Dr. Tejinder Kataria is currently working as a senior consultant at Rajiv Gandhi Cancer Institute and Research Centre, New Delhi. She spent her undergraduate days at Indira Gandhi Medical College, Shimla till 1984 and is an alumunus of PGIMER, Chandigarh. She finished her M.D. Radiation Therapy training, in 1987 and moved to work as an Assistant Professor in a DST funded project at her parent department till 1992. She was selected as an



Assistant Professor under CHS and posted to Maulana Azad Medical College, New Delhi. She was awarded Leeds Fellowship under the aegis of Association of radiation Oncologists of India for the year 1993, the Commonwealth Scholarship in Cancer Research for the year 1994-95 and Clinical Research Fellowship for 3DCRT/IMRT at Toronto Sunnybrook Cancer Centre in 2001. She has published 23 scientific papers and 17 abstracts in academic journals, besides being a panelist and guest speaker at various conferences.

Dr. Kataria is interested in radiation treatment for different solid tumors with the aim of (a) functional/organ preservation, (b) reduction in acute and chronic radiation-induced morbidity; and (c) delivery of quality assured radiation therapy.

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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 nuclear 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 America 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:

- Accurate tumour delineation from complementary imaging modalities.
- Localization of normal structures or functional areas to be avoided in therapy.
- Estimation of the target volume changes after surgical or cyto reductive therapies.

- Monitoring of response to therapy.
- 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 vascular 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. *Annexin V*, an endogenous human protein, has a high affinity for this membrane-bound phospholipid. *Annexin 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 geometry to select beam directions, design beam apertures, compute doses, evaluate plans and generate treatment verification images¹. 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 Co⁶⁰ (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 respiration². 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 century³. The development of Cathetron by Henschke⁴, its fine tuning by Joslin⁵ 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 angioplasty is limited by restenosis, appearing within 3 to 36 months in 30% to 50% of patients after treatment⁶. 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. ¹⁹²Ir wire based array is attached to a guide wire, inserted into a balloon catheter and pushed into place in the stented vessel after angioplasty. 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 ³²P (phosphorus), ⁹⁰Y (yttrium) and ⁹⁰Sr (strontium). ⁹⁰Y (yttrium) sources being given the most consideration at this time. Radioactive stents also under development have incorporated ³²P (phosphorus), ¹⁰³Pd (palladium) and ⁵¹V (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 (¹⁹⁸Au) seeds for treatment of rectal carcinoma⁸, ¹²⁵I (iodine) and ¹⁰³Pd (palladium) for the treatment of prostate cancer⁹ 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

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 damaged films; (iv) enable remote patient record access for consultation 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 images¹⁰.

Dr. Tejinder Kataria

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The Emerging Role of Functional Imaging in Cancer Management

S.C. PANDE

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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 implications!

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 Technitium-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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Radiation Oncology and Molecular Biology - The Frontiers Ahead

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Abstract: Many randomized trials conducted over the last few decades show that combinations of radiation and chemotherapy given concurrently decrease the mortality rate of patients with locally advanced cancers of the head and neck, uterine cervix etc. However, as longer follow up data have become available it has become evident that the survival benefit has been achieved at the expense of increased toxicity and also that a substantial percentage of patients die of their index cancer progression. The identification of molecular prognostic markers that can predict the pattern of relapse and serve as a target for intervention to selectively sensitize tumours to radiation may help overcome this situation.

Key Words : *Signal transduction, epidermal growth factor, farnesyl transferase, Tyrosine kinase.*

Introduction

Radiation biology is dedicated to understand the effect of radiation on living beings. To many, the effects of radiation on living organisms are considered paradoxical; radiation is known to cause cancer, yet as administered in clinical radiotherapy, radiation represents the major anticancer modality in terms of successful tumour care and patient survival. Studies on the physical, biological and chemical changes which follow the interaction of radiation with living matter are of fundamental importance in understanding how radiation can be used to investigate normal and aberrant cell structure and function.

Basic Concept : Ionizing radiation are of two types-particle and electromagnetic. They cause ejection of electrons with release of energy. Electro-magnetic radiation are usually X-rays and gamma rays. Particle radiation are alpha, beta, proton, neutron and mesons. With a standard dose of radiation, its radiological effect depends on the type of radiation and type of tissue being irradiated. For example bone marrow and epithelium are highly sensitive where as brain is relatively resistant.

Radiation causes interruption of cell replication by causing damage to DNA, proteins and cell water. DNA damage causes single - or double - strands breaks, base alterations and cross linking of molecules. Proteins are denatured, cellular water undergoes radiolysis to make active peroxides, free hydroxyl radicals, electrons, hydrogen atoms and hydrogen peroxide molecules. Free radicals are atoms or molecules with at least one unpaired electron. 70-80% of the effect of radiation on cells is due to production of free radicals. The net result is necrosis and apoptosis with morphological changes like cellular swelling, cytoplasmic vacuolation, altered chromatin pattern, and nuclear vacuolation. The cells with a high mitotic rate are more sensitive than those with a low mitotic rate. Likewise cells with G2 and M cells are more sensitive to radiation than those cells in cycle G1 and G0. Cells are more resistant in the late S phase than other phases of the cell cycle. The cells with high oxygen content are more sensitive than those with low oxygen content. Poorly differentiated or anaplastic cells are more sensitive than well-differentiated tumour cells¹.

With the development of megavoltage treatment and computerized treatment planning, the quality and precision of radiation oncology has improved phenominally. It has contributed to better local

control for some cancers; however failed to control micrometastasis beyond the radiation treatment field, even with combination systemic treatment.

The discoveries that cancers result from genetic changes such as the activation of an oncogene or the loss of a tumour suppressor gene has offered new opportunities for targeting the tumour. Specifically, the finding that over expression of growth factor signal transduction pathways can drive uncontrolled tumour cell growth presents the opportunity to target specific genetic alterations that produced and support the growth of the cancer. The discovery has led to generation of antibodies and small molecules aimed at inhibiting aberrant growth factor receptor activation. This is a review of some of the basic biology and very early clinical results of combining these new "molecularly targeted" therapies with radiation.

Signal Transduction Pathways

The molecules responsible for transducing signals from receptors to downstream targets have been the subject of intensive investigation in recent years. Among the most well-studied signal transduction pathways are the mitogen-activated protein kinase pathway (MAP kinase) acting mainly at the genetic level in the nucleus; the phosphatidylinositol 3'-kinase pathway (PI3-kinase), the phospholipase 3-gamma pathway active mainly along the cell surface, and the Jun kinase/p38 MAP kinase pathways². Each of these pathways consists of a number of molecules, each of which is responsible for moving the signal from the molecule directly upstream to the one immediately downstream. In most cases, signals are propagated by progressive phosphorylation and dephosphorylation events, but other molecular methods can be operative as well. In addition, docking and scaffolding molecules are involved in placing signals in their appropriate subcellular locations.

There are three broad types of receivers that play important roles in mediating the mitogenic response to growth factors and matrix molecules (a) nucleus (b) cell-surface (c) mitochondria. Theoretically the monoclonal antibodies or small molecule inhibitors of growth factor receptors could have three distinct effects on the cancer cells expressing the target. These are (i) cytostatic activity (ii) cytotoxic activity (iii) potential radiation sensitizers.

There is a mechanistic basis for the ability of these compounds to sensitize cells to radiation because it has been shown that oxidative

stress resulting from radiation exposure can activate signaling pathways important for cell-survival³. Thus blockage of these radiation-activated signaling pathways can be expected to sensitize cells to radiation. Radiation is given as a multi fractionated treatment; the expected benefit of the presence of a signal targeting agent would be to block the proliferation of cells that survive each fraction of radiation; also tumour cell-specific cytostatic effects would prevent accelerated repopulation occurring late in the course of the treatment of aggressive tumours. The direct cytotoxic effects of the antibody molecule could have a synergistic effect on the potential gain due to radiation. Hence it is possible that future clinical trials are able to show a positive outcome of receptor targeted therapies along with radiation in tumours expressing, activated targets which act as a primary driving force for their malignant potential.

Epidermal Growth Factor Receptors and Radiation Response

The epidermal growth factor receptor (EGFR) represents the first member of the Erb B family of receptors. These receptors are transmembrane proteins from the family of type I receptor tyrosine kinases. On ligand binding, it initiates transduction signals that regulate cell division, proliferation, differentiation and death, all of which play an important role in cellular transformation and tumour response to therapy. In the clinical setting the Erb B₁ (EGFR) and Erb B₂ (HER2/neu) receptor are the most well-recognised and understood to date. Trastuzumab (Herceptin) has gained widespread use in the treatment of Erb B₂ over expressing breast cancer patients. The new Erb B₁ inhibitory agents are postulated to provide a clinical benefit to a broad spectrum of patients with epithelial malignancies expressing EGFR⁴. The interaction of EGFR inhibitory agents combined with radiation shows a highly favourable interaction profile in the preclinical studies. The EGFR inhibitory agents are often broadly classified as (a) large molecules including monoclonal antibodies, bi specific antibodies or immunotoxin conjugates. (b) small molecules most commonly include receptor tyrosine kinase inhibitors that are selective for the EGFR e.g. quina zolines.

A number of complementary mechanisms have been identified that may account for the favourable interaction profile observed regarding EGFR inhibitors combined with ionizing radiation. In general, signaling through the EGFR pathway is stimulatory to the cell cycle machinery that controls cells proliferation. Therefore, EGFR inhibitors provide an antiproliferative influence that has been studied in some detail from a mechanistic standpoint. The EGFR inhibitory agents primarily induce G1 cell cycle arrest. Epidermal growth factor receptor signal blockade precipitates a decrease in the activity of cyclin-dependent kinase (CDK2) via an increase in the expression of selected cyclin-dependent kinase inhibitors, such as p27, thereby preventing the transition of cells into S phase⁵. Radiation, on the other hand, most commonly induces G2 cell cycle arrest, which has been well documented in a number of model systems. In general terms, this radiation-induced G2 cell cycle arrest is thought to afford the opportunity for partial or complete repair of radiation damage before resumption of cell cycling. The fact that EGFR inhibitors induce G1 cell cycle arrest, whereas radiation induces a G2 cell cycle arrest, which may itself represent a key mechanistic contributor to the observed success of this combination therapy.

Epidermal growth factor receptor inhibitory agents have also been found to enhance radiation-induced apoptosis and to inhibit radiation-induced damage repair. These effects have been well established in human squamous cell carcinomas treated with the anti-EGFR monoclonal antibody IMC-C225 (Erbbitux, cetuximab: ImClone Systems Incorporated, New York, NY, and Bristol-Myers Squibb Company, Princeton, NJ)⁶. Similar results have recently been confirmed in this same squamous cell carcinoma model system using the EGFR tyrosine kinase inhibitor, ZD1839. A similar pattern of increased radiation effect has been documented in studies examining ErbB2 inhibition. Specifically, enhanced radiation response and diminished DNA repair capacity is observed in human MCF-7/HER2 breast cancer cells following monoclonal antibody blockade of the ErbB2 receptor. Quite distinct from the cell cycle checkpoint modulation described previously, the influence of EGFR blockade on apoptosis and damage repair may represent key contributors to the synergy observed with EGFR inhibition plus radiation in several model systems. It appears that downregulation of selected mitogenic signal transduction pathways can profoundly inhibit cellular recovery processes following radiation damage.

Finally, there is compelling preclinical data regarding the capacity of EGFR inhibition to modulate the processes of tumour invasion and angiogenesis. More specifically, downregulation of EGFR signaling can inhibit tumour angiogenesis via transcriptional downregulation of vascular endothelial growth factor mRNA and resultant protein expression. Several *in vitro* and *in vivo* model systems confirm these effects and may explain why the *in vivo* impact of EGFR inhibitory agents has often proved more potent than that observed in simple cell culture systems.

Farnesyl transferase inhibitors and radiation sensitization

Activation of Ras, by mutation, overexpression, or by signaling through tyrosine kinase receptors, is associated with radioresistance. Thus, therapies that inhibit Ras function could an effective means to radiosensitize selected types of solid tumours. Inhibition of Ras prenylation using a variety of farnesyltransferase inhibitors resulted in radiosensitization of tumour cells that expressed activated Ras, both *in vitro* and in xenograft models. Farnesyltransferase inhibitor treatment could also inhibit tumour regrowth following irradiation of mice bearing T24 tumour xenografts that express activated Ras. In a phase I trial of the farnesyl transferase inhibitor L-778-123 and radiotherapy in patients with locally advanced head and neck cancer and non-small cell lung cancer, a high response rate was observed coupled with a mild toxicity profile⁷. Additional clinical trials should shed light on the potential of this and other farnesyl transferase inhibitors to serve as radio-sensitizers and may identify molecular markers that could predict a response to these agents.

Benzotriazine di-N-oxide and hypoxia

Serendipity played a role in the discovery of a novel hypoxic cell toxin-benzotriazine di-N-oxide, known as TPZ⁸. The known fact that hypoxic cells were resistant to killing by X-ray is exploited for therapeutic benefits thus turning hypoxia from problem to advantage. It acts like a bioreductive drug. It is found that when TPZ is given in combination with radiation for head and neck cancers, TPZ potentiates cell kill by fractionated radiation⁹. Other approaches are being investigated for targeting hypoxia induced

proteins such as HIF-1 or using hypoxia to obtain tumour specific gene expression for gene therapy.

Tyrosine Kinase inhibitors as Radiation Sensitizers

The discovery of highly selective and potent compounds called the 4-anilinoquinazolines has led to the development of small molecule tyrosine kinase inhibitors as potential anti cancer agents. These agents inhibit essential cellular pathways in growth factor expression and can be administered as an oral formulation. Some of these agents, such as ZD 1839 and OSI-774, tend to bind in vitro only to the epidermal growth factor receptor tyrosine kinase while others, such as CI-1033, bind to multiple members of the ErbB family. The first clinical compounds that were developed such as ZD 1839 were reversible inhibitors. Recently developed irreversible compounds may be found to be more effective at producing long-term suppression.

These molecules have the ability to block cell growth, decrease the clonogenic potential of cells after chronic exposure, down regulate specific genes important for neoplastic potential and to sensitize cells to the lethal effects of ionizing radiation. In vitro studies have shown that combining multifraction radiation exposures (15Gy) with chronic administration of CI-1033, (an irreversible inhibitor of Erb B Kinases) can decrease the number of clonogens in a population of breast cancer cells by nearly a factor of 100 compared to that achieved with radiation alone¹⁰. Preliminary in vivo studies have shown that the combination of fractionated radiation and CI-1033 can produce a significant growth delay beyond that which occurs from either treatment alone. This occurs even when the cells have only moderate (i.e. clinically relevant) over expression of EGFR. Histopathologic evaluation of tumours treated with radiation and CI-1033 show central tumour and vascular necrosis, suggesting that the combination effect may depend on anti-angiogenic or other cytokine mediated factors.

Conclusion

The advances in molecular biology and the insight into the mechanisms of neoplastic transformation, progression and its response to radiation therapy is just beginning. A new frontier is being opened up, the vast vista of this knowledge is still in infancy and the next few years will help us unravel these mysteries.

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Literature Review

Compiled by Dr. P.D. Gulati

Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. Dellabella M, Milanese G, Muzzonigro G. J. Urol 2003Dec;170(6Pt1):2202-5.

The authors evaluated the efficacy of the alpha-adrenergic antagonist tamsulosin for conservative expulsive therapy in patients with ureteral colic due to juxtavesical stones. A total of 60 consecutive symptomatic patients with stones located in the juxtavesical tract of the ureter were randomly divided into group 1-30 who received oral floroglucine-trimetossibenzene 3 times daily and group 2-30 who received 0.4mg tamsulosin daily. The 2 groups received 30mg deflazacort daily for 10 days plus cotrimoxazole 2 times daily for 8 days and 75mg diclofenac injected intramuscularly on demand. Ultrasound followup and medical visits were performed weekly for 4 weeks. Stones passage rate and time, analgesic use, hospitalization and endoscopic intervention were evaluated. Statistical analysis was performed using the student test. The stone expulsion rate was 70% for group 1 and 100% for group 2. Mean stone size was 5.8 and 6.7mm, respectively (p=0.001). Mean expulsion time was 111.1 hours for group 1 and 65.7 hours for group 2 (p=0.020). The mean number of diclofenac injections was 2.83 for group 1 and 0.13 for group 2 (p<0.0001). Ten group 1 patients were hospitalized, of whom 9 underwent ureteroscopy, compared with none in group 2 (p<0.001, respectively). Tamsulosin used as a spasmolytic drug during renal colic due to juxtavesical calculi increased the stone expulsion rate and decreased expulsion time, the need for hospitalization and endoscopic procedures, and provided particularly good control of colic pain.

Association of Small Dense LDL with Coronary Artery Disease and Diabetes in Urban Asian Indians: Chennai Urban Rural Epidemiology Study. V Mohan, R Deepa, K Velmurugan, K Gokulakrishnan. JAPI 2005;53:95-99.

Earlier studies in Europeans have identified small dense LDL to be associated with coronary artery disease and diabetes. In this study we assessed the associated of small dense LDL with diabetes and CAD in Asian Indians. Study subjects were selected from the Chennai Urban Rural Epidemiology Study (CURES), a population based study on representative sample of Chennai City in Southern India. Group 1: non-diabetic subjects (n=30); Group 2: diabetic subjects without CAD (n=30); Group 3: diabetic subjects with CAD (n=30). LDL subfractions were estimated using LipoPrint LDL system. LDL subfractions 3 and above, defined as small dense LDL was summed up to determine the overall small LDL. 75th percentile of the overall small dense LDL in non-diabetic subjects was used as a cut-off for defining elevated levels of small dense LDL.

The mean age of the study subjects was not significantly different among groups. Overall small dense LDL was significantly higher in diabetic subjects with CAD (16.7 ± 11.1 mg/dl, p<0.05) and without CAD (11.1 ± 8.0 mg/dl, p<0.05) compared to non-diabetic subjects without CAD (7.2 ± 6.8 mg/dl). Small dense LDL showed a positive correlation with fasting plasma glucose (r=0.252, p=0.023), HbA1c (r=0.281, p=0.012), total cholesterol (r=0.443, p<0.001), triglycerides (r=0.685, p<0.001), LDL (r=0.342, p=0.002), total cholesterol/HDL ratio (r=0.660, p<0.001) and triglycerides/HDL ratio (r=0.728, p<0.001) and a negative correlation with HDL cholesterol (r=-0.341, p=0.002) and QUICKI values (r=-0.260, p=0.019). ROC curves constructed to predict elevated small dense LDL (9.0 mg/dl) revealed that triglycerides/HDL ratio and total cholesterol/HDL ratio had higher AUC values compared to other parameters. A triglycerides/HDL ratio of 3.0 had the optimum sensitivity (80.0%) and specificity (78.0%) for detecting elevated small dense LDL.

This data suggests that in Asian Indians, small dense LDL is associated with both diabetes and CAD and that a triglycerides/HDL ratio (3.0) could serve a surrogate marker of small dense LDL.

High Dose Rate Brachytherapy (HDR) - Its Role in Malignant Tumours

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Abstract: Introduction of remote control afterloading machines and production of high specific activity radioactive source of cobalt-60 and later on Iridium-192 led to introduction of high dose rate brachytherapy, which has advantages of short treatment time and therefore, comfortable to patient, maintenance of geometry, individualization of treatment and no radiation hazard. All the applicators used with low dose rate brachytherapy have been modified to be used with HDR. Calibration of sources is of utmost importance and computerized treatment planning should be carried out either in 2-D or 3-D format. Quality of high dose brachytherapy should be ensured. Linear quadratic model is useful for conversion of doses from low dose rate to high dose rate brachytherapy. HDR brachytherapy is to be used in fractionated manner to minimize late radiation morbidity with effective control of disease.

All types of brachytherapy can be practiced using high dose rate which includes intracavitary, interstitial, intraluminal and surface moulds. The treatment of each patient can be individualized and optimized which gives better control of disease with reduced morbidity. High dose rate brachytherapy is being commonly used in the treatment of carcinoma cervix and endometrium where it has been optimized and produces results which are similar to low dose rate brachytherapy and has additional advantage of reduced morbidity to rectum. HDR brachytherapy is being used with increased frequency in interstitial setting for treatment of head and neck and other carcinomas but still needs to be optimized. The introduction of HDR brachytherapy has made it simple and comfortable to the patient for treatment of carcinoma bronchus and esophagus in form of intraluminal brachytherapy due to short treatment time and gives best palliation. Surface moulds can also be practiced using high dose rate brachytherapy. Endovascular brachytherapy using HDR has made it possible to use it for preventing stenosis following angioplasty in coronary heart disease. Therefore in conclusion HDR brachytherapy is slowly replacing low dose rate brachytherapy and will be used with increasing frequency in future.

Key Words : *Brachytherapy, High Dose Rate, Individualization.*

Introduction

Radium was discovered in 1898 by Marie and Pierre Curie and was successfully used for brachytherapy treatment within five years of its discovery. Brachytherapy delivers very high dose of radiation in short time with sharp fall off of dose leading to best tumour control and minimum radiation morbidity. Manchester system of Paterson and Parker¹ was devised in 1930 and became most popular way of prescribing dose in brachytherapy for next 30-40 years. The technical advances in 60s and 70s led to introduction of Paris method of Ir-192 wire sources. All these methods of brachytherapy were practiced at low dose rate, (LDR) which gives better dose distribution, radiation is delivered continuously over a period of 7-10 days, helps in repair of sub-lethal damage thereby maximizing differential between early and late responding tissues and is considered to be treatment par excellence. However, limitation of this treatment include long treatment time and, therefore, discomfort to the patient, improper dosimetry due to haste in application being a loose system and radiation hazard as most of the low dose rate systems were pre-loaded.

The technological development in the form of remote control afterloading machines and production of high specific activity radiation sources of Cobalt-60 led to introduction of high dose rate (HDR) brachytherapy in 1965², which has advantage of short treatment time per application and, therefore, highly comfortable to patient, better maintenance of geometry leading to uniform dose distribution and this also made it possible to individualize the treatment. There is no radiation hazard associated with HDR brachytherapy as it is imparted through remote control afterloading machines and the treatment can also be done from out patient, thereby minimizing hospital stay and cost.

Physics of HDR Brachytherapy

HDR brachytherapy can only be practiced using remote control afterloading system, which should have shielding safe for sources, source position system, safety system to ensure operations, emergency system to withdraw sources and computerized control console to co-ordinate operations of the unit. High intensity radioactive sources of either Cobalt-60 in form of pellets in earlier days and now Iridium-192 is used, which is placed at the end of a drive cable and is transferred to applicator inside the patient through transfer catheters and the proposed unit should conform to international standards of safety and quality set forth by international standards organization-ISO-9000. Virtually all types of applicators used in low dose rate are modified for use with HDR brachytherapy of any type. The system should be closed so that there no possibility of any part of HDR sources getting dislodged in the patient³. Calibration of sources is of utmost importance. The dose calculation should be computer based in 2-D or 3-D format to get exact dose distribution. HDR gives the opportunity of optimization of dose distribution for an individual patient by manipulating the dose distribution by controlling the dwell times used at each dwell position. Quality control of HDR afterloading system, HDR brachytherapy planning computer and treatment planning as well as dose delivery should be ensured by the Medical Physicist.

Radiobiology of HDR Brachytherapy

HDR brachytherapy is a relatively new modality of radiation therapy, where documented expression or personal experience is lacking today. Radiation oncologist must commonly resist to use the bio-effect dose models to convert dose from LDR to HDR brachytherapy. Now-a-days linear quadratic model is used for

conversion of biological equivalent doses by calculating BED values commonly used for usch conversions⁴. High dose rates are high enough to delivered dose in the tissues which is less than the half time for repair for sub lethal radiobiological damage and the duration of treatment is less than few minutes. For long exposures, repair takes less time to occur and biological effects becomes less. Late responding tissue has great capability for repairing than the tumour or early responding tissue. But this repair does not take plaes as fully with HDR Large doses per fraction cause relatively more severe late damage then the tumour cell kill during HDR Brachytherapy and carries radiobiological risk of late complications for the same control rate. This risk can be minimized by altering the total HDR dose or distribution of dose. Therefore, it is necessary to use multiple HDR fractions and to decrease the dose to late responding tissue. If critical organs like rectum and bladder in carcinoma cervix treatment are kept at 80% of prescribed dose by displacing these structure away, 4-6 fractions of HDR can be given leading to minimum late radiation morbidity. Radiobiological consideration favour a large number of fractions which are not feasible in clinical practice⁵.

Clinical Application of HDR Brachytherapy

All forms of brachytherapy techniques are practised using high dose rate which include intracavitary, interstitial, intraluminal and surface mould brachytherapy and are discussed below :

Intracavitary HDR Brachytherapy

a) **Carcinoma Cervix** : Brachytherapy plays a sheet anchor role in the treatment of carcinoma cervix and is responsible for high degree of control rate and survival. Brachytherapy was practiced at low dose rate devised by Paterson and Parker at Machester, U.K. and is standard of care even today. Joslin et al in 1972 introduced high dose rate brachytherapy in the treatment of carcinoma cervix and is being practiced since then with increasing frequency⁶. He started with dose of 10 Gy.* per fraction weekly for 4 weeks but encountered high morbidity particularly to small bowel. But when the dose was reduced to 8 Gys. per fraction and a number of fraction increased to 5, this resulted in similar control rate and complications when compared with low dose rate brachytherapy^{7,8}. Since then dose ranging from 6-10 Gys. per fraction for a total of 3-7 fractions has been used by various workers. Early stage patitns are treated with 4-7 fractions of 7-9 Gys. per fraction on weekly basis with external supplement to parametrium only. Late stage patients are treated with external radiation to whole pelvis delivering a dose of 45-50 Gys. followed by 2-3 fractions of HDR brachytherapy. This produces the results which are comparable to LDR both for local control and late radiation morbidity. Meticulous treatment planning in 2-D or 3-D formatting is necessary and individualized optimization of dose distribution can be achieved particularly with Ir-192 source by altering the dwell time accordingly. Manchester or Fletcher Suite appliator used for LDR have been modified for use with HDR maintaining the same geometry.

*Gy=1 GRAY is a S.I. unit of radiation, named after a British scientist Dr. Hal Gray. 1 Gy = 100 cGy (centiGray)

Mostly non-randomized trial were carried out using HDR brachytherapy in cancer cervix which produced results similar to LDR brachytherapy^{6,7,8,9}. However, 3-4 randomized study have been carried out to assess and compare results of HDR with that of LDR brachytherapy^{10,11}. These studies have produced similar control rate of disease in the pelvis with similar or reduced morbidity with HDR. With increasing popularity of remote control after loading machines using high intensity Ir-192 source is likely

to become standard of care for treatment of carcinoma cervix due to its inherent advantages over LDR brachytherapy as discussed earlier.

b) **Carcinoma Endometrium** : Total abdominal hysterectomy with bilateral salpingoofrectomy is treatment of choice for endometrium carcinoma. There is 5-15% chances of recurrence at vault or in the vagina, therefore, surgery is followed by post-operative intravaginal irradiation, when there is invasion of myometrium more than 1/2 and tumour is of undifferentiated variety and reduces the chances of recurrence to 1-3%¹². The intravaginal radiation is delivered by a sorbo applicator using low dose rate. Introduction of HDR intravaginal brachytherapy has made it most suitable for these elderly patients because it prevents prolonged immobilization required for LDR and treatment is usually done on outdoor basis. HDR also provides opportunity for individualized treatment, which is necessary in this cancer. 3-4cm of upper part of vagina is treated and dose is prescribed at 0.5cm from mucosal surface. The vaginal applicator of diameter 2-3cm. can be used depending upon individual requirement. The fractionated dose ranging from 4.5 to 9.5 Gy per fraction has been used by different centers to a total dose of 21-36Gy. Dose of 5Gy per fraction daily for 5 days has been found to be most suitable, which gives good control with least morbidity. The 5 year survival rates have been reported to be more than 90% in most of the studies with late radiation morbidity of 3.7% to 11.2%^{12,13}. Higher dose of more than 6Gy per fraction increases the chances of late radiation morbidity¹². The Stage-II patient with involvement of cervix are best treated by whole pelvic external radiation of 45-50Gy to be followed by intravaginal application of 8Gy per fraction weekly for 2-3 treatment. HDR brachytherapy can also be used in pre-operative settings or in those patients, who are inoperable. The intracavitary application with vaginal sorbo is used and a dose of 8.5 Gy per fraction is delivered to a total fractions of 4-5 and gives good control of disease in such advanced disease. The intracavitary hgih dose brachytherapy can also be used for treatment of primary vaginal carcinoma, nasopharyngeal carcinoma or rarely in carcinoma of maxillary antrum but the experience in these areas is limited.

2. Interstitial HDR Brachytherapy

a) **Head & Neck Cancer** : Interstitial brachytherapy is often used in the treatment of early, locally advanced or recurrent carcinoma of head and neck more so in cancers arising from oral cavity and oropharynx. Low dose rate brachytherapy using radium was most successful and was governed by Manchester System devised by Paterson and Parker¹ and is standard of care. With introduction of remote control after loading machiens using high intensity iridium-192 sources is being used for high dose rate brachytherapy at present in all the above mentioned sites. It is used as the only curative treatment in early stage T1, T2 lesions or as boost treatment following external radiation in locally advanced disease. Plastic catheter are implanted in tumour area with adequate margin all around the tumour using single or double plane implants. These catheters are connected through transfer tube to the machine for treatment. The Treatment Planning should be done in 2-D or 3D format in treatment planning system and the machine is programmed accordingly to deliver the prescribed dose. The dose is usually delivered twice daily (6 hours apart) over a total period of 3-7 days depending upon intention of treatment whether radical or as boost. Dose of 3-6.5 Gys. per fraction has been used delivering total dose of 40-60 Gys. for curative therapy and 15-25 Gys. as boost treatment. However, the dose per fraction and the total dose needed for curative therapy still needs to be optimized. Higher the total dose and dose per fraction, more are the chances of late

radiation morbidity. It has been seen that dose of 3-4.5Gy per fraction gives similar control rate and radiation morbidity compared with low dose rate brachytherapy. Leung¹⁴ reported comparable and encouraging results using HDR brachytherapy in treatment of anterior 2/3rd of tongue. Quantitative assessment of HDR implant can be done using dosimetry procedure such as volumetric irradiation indices, dose non uniformity ratio and offer quantitative data on the extent to which the implant delivers the prescribed dose to the target volume and also determines the dose homogeneity within target volume and irradiation of tissue outside the target volume which helps in predicting the tumour control and late radiation morbidity¹⁵.

b) **Other Areas** : The HDR interstitial brachytherapy has also been extended to the treatment of parametrium in carcinoma cervix, prostate, soft tissue sarcomas, skin cancer and in carcinoma breast following conservative surgery and external radiation as boost treatment. Intraoperative implants are practiced in the treatment of carcinoma breast and soft tissue sarcomas using HDR brachytherapy.

3. Intraluminal HDR Brachytherapy

The intraluminal HDR brachytherapy is being used in the treatment of carcinoma bronchus, carcinoma esophagus, carcinoma bile duct and carcinoma of the nasopharynx as discussed below :-

a) **Endobronchial HDR Brachytherapy** : Surgery is the treatment of choice for carcinoma bronchus. However, only a small fraction of < 15% cases are suitable for surgery. Majority are treated with radiation using external radiation, rarely for cure being the intent in most patients. Patients with endobronchial disease are highly symptomatic and cough, dyspnoea and haemoptysis. External radiation provide slow relief of symptoms in a small number of cases. However, endobronchial brachytherapy in such patient usually produce quick and early control for symptoms and therefore, better quality of life. Endobronchial brachytherapy was started initially using low dose or intermediate dose rate brachytherapy which was not popular and uncomfortable to the patient due to long treatment time. Introduction of high dose brachytherapy by Spieser et al¹⁶ has made it easier to practice this form of treatment in carcinoma bronchus presenting with endobronchial obstruction

and is being used with great frequency. A 6F plastic catheter is introduced into the bronchus on bronchoscopy and is placed covering the growth with 2-3 cm margin on either side of the lesion. This catheter is directly connected to remote control after loading machine to deliver the treatment. A length of 6-10 cm can be treated effectively. The dose is prescribed at 1cm from central axis of the catheter. A dose of 5-20 Gy. per fraction has been in practiced. The endobronchial brachytherapy is used either alone or in combination with external radiation for palliative treatment of carcinoma bronchus¹⁶⁻²². The results of endobronchial brachytherapy are summarized in Table-1.

b) Intraluminal HDR Brachytherapy in Carcinoma Esophagus :

The rationale of using brachytherapy in carcinoma esophagus is that the dose of external radiation is limited by tolerance of perioesophageal tissue but with brachytherapy higher dose can be delivered to tumour and there is sparing of tissue outside the esophagus due to sharp fall off of dose. It was first practiced using low dose rate brachytherapy but did not become popular because of long treatment time and discomfort to the patient. Introduction of HDR has made it easier to deliver intraluminal brachytherapy in carcinoma esophagus. It is rarely being used with radical intention along-with external radiation in early stages; however is excellent for palliation in advanced carcinoma esophagus. HDR brachytherapy delivers high dose of radiation to the intraluminal tumour and produces extensive necrosis of tumour and therefore, quick relief of dysphagia. The plastic catheter is placed under endoscopy guidance in the esophagus covering the lesion with 2-3 cm margin on either side. A length of 6-10 cm can be treated effectively. A single dose of 15 Gys or 12-18 Gy. in 2-3 fractions is used commonly. External radiation dose of 30-40 Gys. is delivered in 2-3 weeks followed by intraluminal HDR brachytherapy delivering 12-15 Gys. in 2-3 fraction. More than 50% of cases achieve good relief of dysphagia with marginal increase in the median survival compared to external radiation alone²³⁻²⁶. The complications and radiation morbidity is within acceptable limits. 15% of patients developed stenosis, 5% fistulae and 10% ulceration of the wall of the esophagus²²⁻²⁵ Results reported in the literature are summarized in Table-2.

Table 1 : Relief of Symptoms following H.D.R. Endobronchial Brachytherapy.

Worker	Dose of I/L BRT	Improvement in Symptoms Disease (%age)				
		Overall	Cough	Dyspnoea	Haemoptysis	Pneumonia
1. Speiser,16 1993	30Gys.x3F	87	85	86	99	99
	22.5Gys.x3F	84	-	-	-	-
2. Chang,17 1994	27Gys.x3F	87	79	87	95	88
3. Gollin,18 1994	15-20 Gys.x1F	8	62	60	88	46
4. Taullette19 1998	24-40Gys.x3.4F	74	54	54	75	-
5. Kelly,20 2000	15Gysx5F	85	76	85	34	-
6. Gejerman212002	15Gysx3F	95	71	95	22	-
7. Sharma222002	-	-	50	66	81	57
	18Gysx2F	-	65	66	100	62
Dose of EXRT	37.5Gy/sx18F; 30Gys.x10F					

Table 2 : Relief of Dysphagia Following HDR Intraluminal Brachytherapy in Carcinoma Esophagus

Worker	Dose of EXRT	Dose of I/L BRT	Relief of Dysphagia (%age)	Dysphagia free Median Survival (Mos)
1. Sur,23 1992	35Gys.+25Ys.	-	37.5	
	35Gys.x15F	12Gys.x2F	70.6	
2. Jagar,24 1995	-	15Gys.	67.0	5.5
3. Sur,25 2002	-	18Gys.x3F	-	9.1
		16Gys.x2F	-	6.9
4. Vinay,26 2002	-	12Gys.x2F	48.0	10

4. H.D.R. Surface Mould Therapy

Surface mould therapy, which is used for the treatment of superficial surface tumour and has the advantage of control over depth of radiation and thereby sparing the tissue beyond certain depth. It did not become very popular at low dose rate because of associated radiation hazard. Introduction of HDR brachytherapy has renewed the interest of radiation oncologist in the application of surface mould therapy. It is delivered in a fractionated manner over a period of time using 5-8 Gys. per fraction for a total of 6-8 treatments given daily and gives excellent control. It is highly useful for treatment of superficial chest wall recurrences in post-mastectomy patients of carcinoma breast²⁷.

Conclusion

HDR brachytherapy is slowly replacing all forms of low dose rate brachytherapy due to its inherent advantages and will be standard of care for the treatment of various cancers.

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ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory *clinical trails* on new drugs, a number of *diagnostic procedures, therapeutic interventions and prevention measures* including the use of vaccines, are being introduced which involve human subjects. Further the advent of *new medical devices and radio-active materials* and therapeutic benefits of *recombinant DNA products* have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : i) **essentiality**, (ii) **voluntariness**, **informed consent**, (iii) **non exploitation**, (iv) **privacy and confidentiality**, (v) **precaution and risk minimisation**, (vi) **professional competence**, (vii) **accountability & transparency**, (viii) **maximisation of public interest** and **distributive justice** (ix) **institutional arrangements** (x) **public domain** (xi) **totality of responsibility** and (xii) **compliance**.

Recent advances in the field of **Assisted Reproductive technologies, organ transplantation, Human genome analysis, and gene therapy** promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)

An Overview of Prostate Brachytherapy

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Abstract: Prostate cancer is the most common male cancer in the European Union and United States of America. The incidence of prostate cancer had been rising before PSA screening and will continue to rise with PSA testing having become more widespread and an ageing population. Prostate brachytherapy is an effective treatment for early stage prostate cancer with some centres reporting 10 year biochemical control rates of up to 87% for low risk patients. However the outcome depends on the technical quality of the implant and careful patient selection i.e. a low prostate specific antigen (PSA) 10 or less, Gleason score of 6 or less and low International Prostate Symptom Score (IPSS)

Introduction

Prostate cancer is the most common male cancer in the European Union and United States of America. One in six new cases of male cancer are prostate, with a lifetime risk of one in fourteen in the U.K. The incidence of prostate cancer had been rising before PSA screening¹ and will continue to rise with PSA testing becoming more widespread and an ageing population.

The debate regarding prostate screening remains unresolved. At present the U.S. Preventive Services Task Force (USPSTF) does not recommend prostate screening for all men and it is not current U.K. practice. Currently there is no randomised clinical trial evidence that shows a difference between the number of prostate cancer related deaths in a screened and non-screened population. Hopefully the results from the Prostate, Lung, Colorectal and Ovary (PLCO) trial in the U.S.A., the Prostate testing for cancer and Treatment (ProtectT) trial in the U.K. and the European Randomized Screening for Prostate Cancer (ERSPC) trial in Europe will clarify the debate. However due to increased public awareness, despite the lack of evidence regarding any survival benefit from prostate cancer screening, the demand for PSA tests is increasing.

More early stage prostate cancers are being detected, often in asymptomatic patients, who are then presented with the dilemma regarding treatment options. Though active surveillance is an appropriate management for selected patients, patients with a projected life expectancy of greater than 10 years are usually offered radical treatment. The aim of a curative treatment for prostate cancer is to obtain local control with optimal preservation of bowel, bladder and sexual function².

In 1995, about 4 percent of men with localized disease received prostate brachytherapy and it is estimated in the U.S.A. that 40 to 50 percent of men will undergo this procedure by 2006 if current trends continue³.

History

Prostate brachytherapy was first described by Pasteau and Degrais in France in 1914 using radium needles⁴. In 1972 Hilaris and Whitmore at the Memorial Hospital, New York described their technique of iodine seed implantation using an open retro pubic approach⁵. Seeds were implanted manually according to a

nomogram and after dose finding studies a minimum peripheral dose of 160Gy# was decided upon. This technique was used in over 1000 patients and achieved good local control on digital rectal examination. However, once PSA testing became available it became clear that biochemical control was not often achieved, especially in those patients whose seed distribution was sub-optimal, and the technique was abandoned.

The technique of transrectal ultrasound (T.R.U.S.) and template guidance for prostate biopsies was developed in 1981 by Holm H. and in 1982 the same technique was used for percutaneous implantation of radioactive iodine seeds into the prostate under ultrasound control. From 1982-1987, 32 patients were treated using this technique⁶ but at ten years, 50% had died of metastatic disease and 14 patients had severe late complications and the technique was abandoned.

The T.R.U.S. and template technique was taken up in Seattle by Ragde and Blasko but modified so that a large number of low activity seeds were used. This modification obtained good results and the Seattle technique has been the basis for a number of other developments in trans-rectal ultrasound and template guided permanent seed implantation.

Remote afterloading brachytherapy became available in the early 1980's and was first used in Germany to treat prostate cancer with H.D.R. removable implants. The afterloading technique has been embraced by centres in the U.S.A. and elsewhere being further developed with the introduction of interactive real time dosimetry and optimisation of source position.

Image guided source placement with interactive real time dosimetry is now becoming possible for all techniques and allows consistent high quality implants to be performed in the vast majority of cases.

Patient Selection

The key to providing good outcomes from prostate brachytherapy is careful patient selection. One needs to identify those patients who are likely to have a good disease free survival and have a good functional outcome. The most significant prognostic factors for disease free survival are initial P.S.A. Gleason score and stage. Regarding functional outcome the initial prostate volume and lower urinary tract symptoms best characterised by the IPSS provide the best guide to outcome⁷.

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Gy-Grey (a unit of radiation)

Essential pre-treatment investigations include P.S.A., transrectal ultrasound and biopsy. the pre-treatment P.S.A. is an important screening test, which not only correlates with outcome but also predicts for the presence of extra-capsular spread of the tumour⁸. Those patients with pre-treatment P.S.A. of less than 10 have very good outcome with some centres quoting up to an 87% 10-year biochemical and clinical control⁹. In contrast those patients with a P.S.A. of greater than 20 have a high rate of relapse within the first 2 years though still 30-50% may remain biochemically controlled. Similarly the lower the Gleason score the better the outcome. Patients with a Gleason score of 6 or less have very good outcomes from brachytherapy¹⁰. Those patients with a Gleason score of 7 have about a 50% probability of relapse in the first 5 years and those with predominantly grade 4 have a worse prognosis than those with predominantly grade 3 (Gleason combined score 7). Patients with a Gleason score of above 7 should not be considered for brachytherapy.

A clinical history and patient IPSS score provides key information regarding flow and irritable urinary symptoms. Urodynamic studies should be considered in patients with significant symptoms. M.R.I. is the most sensitive radiological technique to predict whether the patient has T3 disease but in good prognosis patients (P.S.A. <10, Gleason 6) it's role is less clear. Surgical lymph node staging is not routinely used and therefore the lymph node status is assessed radiologically. Lymph nodes are judged significant if greater than 1cm and in an appropriate anatomical site.

Other radiological investigations are not routinely used. C.T. scan is of little value in assessing the local extent of the disease and bone scintigraphy is not recommended unless the pre-treatment P.S.A. is >10.

The stage of the tumour also predicts for clinical outcome. Patients with stage T1c to T2b disease i.e. with a low risk of extra-capsular spread have good outcomes from brachytherapy. Further information can be gained from the amount of tumour present in each biopsy, the total amount of biopsies that contain tumour cells and the presence of perineural invasion. For T3a disease brachytherapy alone should not be considered though combinations of external beam and brachytherapy are used.

The Partin tables that were derived from radical prostatectomy samples can be used to predict the chance of extra-capsular spread, seminal vesicle and lymph node involvement. The Partin tables, although a good predictive guide for the presence of extra-capsular disease, can not predict for those patients who have extra-capsular disease within 2-3 mms of the capsule, which would be encompassed in the PTV.*

Urinary outflow as measured by the IPSS score is a sensitive predictor of urinary morbidity. Prostate volume also influences the incidence of acute retention and urinary morbidity. Patients with a prostate volume of greater than 36 grams and higher IPSS/American Urologic Association (AUA) score (>10) appear to be at higher risk of acute retention¹¹.

Patients with a prostate volume of greater than 50 grams should have neo-adjuvant hormonal therapy to reduce the gland, but despite this the patient's risk of urinary morbidity remains higher.

Contra-indications to permanent seed implants⁷

1. Life expectancy less than 5 year.
2. The presence of metastatic disease.
3. Recent transurethral resection of prostate (TURP) with persisting large prostatic defect. It is often difficult to achieve a satisfactory seed distribution and these patients have a high risk of incontinence after brachytherapy. If TURP was performed several years ago and the prostate has largely regrown patients can be considered for brachytherapy but steps should be taken to optimize the dose distribution in order to reduce urethral dose and patients should still be counselled that the risk of incontinence is higher than for non-TURP patients.
4. There should be no bleeding disorder and patients on regular aspirin or anticoagulants should stop it at least seven days before implantation.
5. Patients with a prostate gland of greater than 50cm³ have a high probability to pubic arch interference, this means that part of the prostate is situated behind the bone and does not allow a geometrically satisfactory implant to be performed. These patients also need a large number of seeds and are at increased risk of morbidity. If otherwise suitable these patients can be treated after several months of hormone therapy. This usually produces a 30% reduction in volume which will often bring the gland down to 50cm³ or less.

Technique

Prior to the implantation the prostate volume must be measured to assess the amount and distribution of seeds. This has been traditionally done in our centre with a formal prostate volume study under general anaesthesia approximately 4 weeks prior to the procedure. The patient is aligned in the lithotomy treatment position using a grid system and moving stepwise every 5mm from base to the apex. a 3-Dimensional image is obtained. A target volume is defined. The urethra is avoided and careful margins around the rectum are defined. These images are then used for calculating the amount and distribution of the seed implants (according to TG-43#)²¹. In some centres this is performed under local anaesthesia¹⁶ but other centres including Cookridge find that a general anaesthesia provides better reproduction of the patient's position.

At Cookridge, to speed up the procedure, reduce waiting time and amount of general anaesthetics, suitable patients are assessed in the first clinic visit. A trans-rectal ultrasound is performed with no sedation or preparation. This gives an accurate prostate volume and an estimate of the number of seeds required can be obtained. The patient then returns for planning and brachytherapy as a "one-stop" procedure. This has many advantages:

Early assessment of the prostate volume identifies those patients who will require neo-adjuvant hormone therapy to reduce the prostate volume prior to implantation; reduces the amount of visits and in-patient stay; requires only one general anaesthesia.

The implantation procedure can be carried out under general or spinal anaesthesia. The patient is placed in the lithotomy position with a transrectal ultrasound and grid template in position. A perineal approach is used and the seeds, either single or in strands

*PTV - Planning target volume

are inserted using the co-ordinates on the grid and under direct ultrasound and fluoroscopy control.

Commonly used isotopes are iodine 125 and palladium 103. Iodine 125 has a half life of 60 days and an energy of 27KeV. In comparison, palladium has a half life of 17 days and an energy of 25KeV. Whilst iodine 125 is the most commonly used isotope, palladium, theoretically may have an advantage in more aggressive, rapidly dividing cancers due to its higher dose rate. However, there is no clinical evidence to suggest a difference between the two sources. The most commonly prescribed dose of Iodine 131 is 145Gy to the margin of the planned target volume according to the TG-43 guidelines. The total dose of Palladium 103 is reduced to 110Gy to account for the higher dose rate and give an equivalent biological dose.

High dose rate (HDR) brachytherapy is also used in some centres using afterloading techniques with iridium-192. HDR-brachytherapy has been used both as boost to external beam radiotherapy and alone in localised prostate cancer. HDR-brachytherapy alone has been given for good prognosis localised prostate cancer in phase II trials and have proved feasible and well tolerated¹⁴ though we await long term outcome data. HDR-brachytherapy has an advantage of being feasible in patients who have had a trans urethral resection of prostate and can treat extracapsular disease.

However, HDR-brachytherapy has to be given in multiple fractions, perineal catheters must remain in place during the treatment period and substantial movement of catheters between treatments means that verification films and adjustments are needed prior to each fraction¹³.

Side Effects and Follow Up

All patients are discharged from our centre with oral ciprofloxacin to prevent/treat infective prostatitis and alpha-blockers given to maximise urinary flow. Despite this all patients will develop a varying degree of urethritis. Anti-inflammatory drugs can be added if symptoms are severe. Approximately 15% of patients need a catheter due to temporary urinary retention. Altered bowel habit is relatively common and some patients can develop radiation proctitis. Most patients do not report deterioration in bowel function and symptoms improve with time¹⁵.

Symptoms of urethritis usually persist for the first 6 weeks and in the majority of patients settle by 3 months. However, a minority have ongoing symptoms for 6-12 months and in a series of 581 patients, although dysuria was a common event and peaked at 1 month (52%), at approximately 45 months all patients were free of dysuria¹⁸. Incontinence is very rare (<1%) following brachytherapy in comparison with radical prostatectomy. Impotence does occur after brachytherapy in 30-60% of patients and may be under-reported. Co-morbid factors such as hypertension, smoking, diabetes, hormonal manipulation and age are thought to reduce post-treatment potency. Multi-variate analysis has shown that only pre-treatment potency, diabetes mellitus and supplemental external beam radiotherapy have a statistical significant effect on potency. In a study of 425 patients 39% of patients (52% with brachytherapy alone) maintain potency at 6 years. Sildenafil is an effective treatment and 92% of patients maintained potency with

pharmalogical support¹⁷.

Patients are seen at 4-6 weeks post implant and then placed on 3 monthly follow-up. At this first visit a C.T. scan is performed to establish post-implant dosimetry. This is valuable for quality control as there is good evidence that the probability of achieving good biochemical control is related to the quality of the implant¹⁸.

Outcome

With improved patient selection and implantation techniques some centres report 10 year biochemical control rates of up to 87% for low risk patients i.e. pre-treatment P.S.A. < 10, Gleason 6 or less and T1-T2b disease⁹. In higher risk patients (Gleason 8-10) with T1-2a disease, external beam radiotherapy was associated with a significantly better 5-year biochemical relapse free rates (52%) vs. 28% for brachytherapy alone. However, in lower risk patients the 5-year rates were similar¹⁹. In a systematic overview of brachytherapy compared with radical prostatectomy in low risk patients (T1-2, Gleason 6 or less, pre-treatment P.S.A.<10) the outcome was comparable²⁰.

Salvage Therapy

To establish whether salvage therapy is indicated we need a definition of recurrence. The definition of a recurrence adopted by the ASTRO* after external beam radiotherapy is also applied to brachytherapy i.e. 3 consecutive rises in P.S.A. after the nadir level has been reached.

*ASTRO - American Society of Therapeutic Radiation Oncology.

The nadir P.S.A. is reached later in both forms of radiotherapy compared with radical prostatectomy and is further complicated by the P.S.A. "bounce" which can occur in approximately a third of patients in the first 2 years post-implant. If a *recurrence* is confirmed biochemically, treatment will depend on whether the recurrence is local or distant. local recurrence raises the possibility of salvage surgery, either radical prostatectomy or cryotherapy. There is very little published data, but both are feasible though a high complication rate has been reported. In post-brachytherapy radical prostatectomy the rate of positive margins is - 50%, incontinence 40-50%, and rectal injury 15%. Salvage cryotherapy after brachytherapy is feasible but also with significant morbidity with high risks of impotence and incontinence. Nodal or distant recurrence is managed with anti-androgen therapy.

Conclusion

Prostate brachytherapy is an effective treatment for early stage, T1-2, low pre-treatment P.S.A. and with low I.P.S.S. score. It has lower rates of impotence and incontinence compared with radical prostatectomy and much lower operative risk. In comparison with external beam radiotherapy it requires only one treatment, has less rectal morbidity but higher rates of short-term urethritis. The comparative rates of biochemical relapse free interval is similar for all three modalities in good prognosis patients though this is based on case-control and cohort studies. Randomised control trials allocating patients to either radical prostatectomy or brachytherapy would give clearer evidence but recruitment would be very difficult. Despite the lack of randomised trials there is abundant evidence that high quality brachytherapy with selected patients provides a safe, well tolerated and effective treatment for early prostate cancer.

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Drug Profile

TACROLIMUS

Tacrolimus is a macrolide lactone with potent immuno suppressive activity, isolated from streptomyces tsukubaensis. In contrast to all other US food & Drug Administration (FDA) approved immuno-suppressive agents developed to date, the clinical development of tacrolimus was conducted primarily in liver transplantation in 1994. It was used in Renal transplant recipients in 1996. It is viewed widely as preferable to cyclosporine for maintenance immuno suppression in high-immunological risk renal allograft recipients (Repeat renal transplant recipients, high panel reactive antibody renal transplant recipients, & combined kidney-pancreas transplant recipients). More recent experiences indicated that tacrolimus may have additional properties, including steroid-sparing properties, that may be superior to cyclosporine.

Mechanism of action : It exerts potent inhibitory effect on T-Lymphocyte activation. It binds to immunophilins FK 506 binding proteins (FKBP-12) and a complex of FKBP-12, Calcium, calmodulin & Calcineurin is formed, inhibiting phosphatase activity of calcineurin. This prevents dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT) and inhibits transcription of early T-cell activation gene, interleukin-2, Tumor necrosis factor (TNF- α) and proto-oncogenes; suppressing expression of IL-2 and IL-7 receptor. This results in inhibition of T-Lymphocyte activation. Tacrolimus also inhibits the mixed lymphocyte reaction, generation of cytotoxic T-cells dependent B-Cell activation.

Pharmacokinetics : Absorption of Tacrolimus after oral administration is incomplete & variable with oral bioavailability of 4-93% and mean bioavailability of 25%. Food appears to reduce the absorption & relative bioavailability of tacrolimus. In most cases, CMax is achieved after 0.5 to 1 hour. It is mainly metabolized (799%) in liver by a cytochrome isoenzyme (P450 CYP3A) to at least 15 compounds. The main route of elimination of tacrolimus metabolites is biliary & less than it is excreted unchanged in urine. Fecal elimination is around 92%.

Indication & Usage : It is used in liver & kidney transplant cases as immuno suppressive drug.

Warning: Administration of tacrolimus may cause diabetes mellitus. Neurotoxicity & nephrotoxicity. Mild to moderate hyper kalemia may occur with it. Patients receiving tacrolimus are at high risk of lymphomas, malignancies & infections due to oversuppression of immune system. Mild to moderate hyper-

tension is common with the drug.

Precautions : Patients with hepatic & renal impairment, lower dosage should be used.

Hypertrophic cardiomyopathy - It is observed in infant & children. Dosage reduction or discontinuation of therapy is required.

Pregnancy - No well controlled trials. It should be used only if the benefits outweigh potential risk to fetus.

Nursing mothers - Since it is excreted in human milk, should be avoided in nursing mothers.

Drug Interaction: As tacrolimus is metabolized by cytochrome P450 CYP3A enzyme, potential drug interactions are -

(a) increased tacrolimus blood concentration - Calcium channel blockers antifungal agents, macrolide antibiotics, corticosteroids, cyclosporine, prokinetic drugs, omeprazole & bromocriptine. (b) Decreased Tacrolimus blood concentration - Anticonvulsant, anticoagulants antacids & rifampicin. Vaccines - Drug may reduce the efficacy of vaccines & recipients of tacrolimus should not receive live attenuated vaccines.

Adverse Reactions : Tacrolimus shows adverse events common to other immuno suppressive therapies viz, neurotoxicity, nephrotoxicity, increased risk of infections & malignancy, diabetes mellitus & a lymphoproliferative disorder, related to Epstein Barr Virus common adverse events are - Nervous System - Tremor, headache, paresthesia, dizziness, insomnia, seizures, GI Tract - Diarrhoea, constipation, Nausea, vomiting, dyspepsia. CUS - hypertension chest pain.

Metabolic Disturbance - Hyperkalemia, hyper chloremic acidosis, hypomagnesemia - diabetes mellitus, hypercholesterolemia. Hypertension, Nephrotoxicity- Reduced Renal blood flow, glomerular perfusion, tubular & vascular toxicity.

Dosage & Administration - dosage 0.2mg/kg/day in 2 divided doses. The target trough blood levels of tacrolimus is 12-15 ng/ml in 1st month post transplant period, 1-3 months after transplant 10-12 ng/ml, 5-10ng/ml 3-6 month after transplant.

Emerging Role of Endovascular Brachytherapy in Arterial Restenosis

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Abstract: Angioplasty and stenting are highly effective modalities for the treatment of occlusive arterial disease yielding excellent immediate results. However, a restenosis rate of 20% to 40% remains a cause for dissatisfaction. In an attempt to bring down the restenosis rate, radiation has been tried in different ways using external as well as endovascular radiation. Various beta and gamma emitters such as ¹⁹²Ir, ³²P, ⁹⁹P and ¹⁸⁸Re have been tried using different techniques such as remote afterloading HDR, manual remote afterloading, radioactive stents and radioactive liquid Rhenium filled balloons. Results of historical trials such as the WRIST trial (Washington Radiation for In-Stent Restenosis Trial), the SCRIPPS trial (Scripps Coronary Radiation to Inhibit Proliferation Post Stenting), the BERT trial (beta emitter for intracoronary brachytherapy) etc. have been discussed. Although various mechanisms such as recoil, neo intimal proliferation and vascular contracture have been postulated to be involved in the process of restenosis, a better understanding of the molecular biology of restenosis and definitions of the actual targets, the timing of radiation, dose rate and fractionation etc. shall help us in achieving superior results.

Key words : *Endovascular Brachytherapy.*

Introduction

The treatment of occlusive arterial disease (coronary or peripheral) has undergone a slow evolution over past few decades. Various treatment techniques such as atherectomy, lasers, angioplasty and stent placements have been tried. Of these, angioplasties and stents have provided excellent immediate results but have been accompanied with a high rate of restenosis (30-40%) within 6-12 months. The incidence of post angioplasty restenosis varies with the anatomic site: 20% for aorto-iliac¹ and 40% for femoro-popliteal angioplasty. Similarly, the mesenteric and renal arteries have high restenosis rate.

Mechanism of Restenosis

The various mechanisms postulated to be involved in the process of restenosis are: recoil, neo intimal proliferation and vascular contracture². The causes of acute closure include spasm with or without thrombosis, dissection with complete closure and elastic recoil. Most common mechanism of delayed post angioplasty reconstruction is fibro cellular intimal hyperplasia (FIH). The major constituent of this is the smooth muscle cell (SMC). Bromo deoxy uridine labeling has shown that 10-20% of medial SMCs begin to proliferate within 24-48 hrs of balloon angioplasty. These SMCs then migrate to the intima at around 4 days, where some undergo further cycles of cell proliferation. The ongoing synthesis of connective tissue matrix and cellular hypertrophy causes progressive intimal thickening for up to 8 weeks.

The endotheloid denudation caused by balloon angioplasty results in loss of growth-inhibitory heparin-like glycosamine glycan³. Similarly, the platelets that adhere to the area of injury release anti heparin factors such as platelet factor 4 heparitinase. These reverse the effects of heparin sulphates produced normally by the smooth muscle cells. The heparin sulphates are believed to be responsible for maintaining the smooth muscle cells in a non-proliferating state⁴. This leads to actively proliferating SMCs that secrete extra cellular matrix. The endotheloid injury also results

in platelet adhesion. After adhesion, the platelets release all the contents of their alpha granules, including platelet derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor- β (TGF- β) and platelet factor EGF and TGF- β exert a synergistic effect on cellular proliferation. As a response to vascular injury and inflammation, the aggregated lymphocytes may play a role in intimal proliferation by release of their cytokines such as tumor necrosis factor, interleukins and TGF- β ⁵. It has also been seen that within hours of balloon induced injury, there is release of fibroblastic growth factor and angiotensin-II. These activate the proto-oncogene that is responsible for the transduction of mRNA in neo intimal and vascular smooth muscle cells.

Thus, a number of mechanisms collectively constitute the response to injury. When healing occurs in a controlled manner, the vessel wall is remodeled with an enlarged lumen. When the healing is uncontrolled, the hyperplastic lesion of restenosis results.

Exploring the role of vascular radiation

External Radiation : Radiation is known to be effective in the treatment of benign proliferative disorder such as keloids, heterotopic bone formation, pterygium of eye, graves exophthalmos⁶ and gynecomastia. This concept has been extended to the pathologic proliferative response after angioplasty. Various groups carried out treatment with external radiation to see the impact on restenosis. Schwartz et al⁷ tested a dose of 4 and 8Gy to stented pig coronary artery using Orthovoltage radiation and met with poor results. This was attributed to the use of Orthovoltage radiation, low dose of radiation and use of metallic stent. Styles et al⁸ used mega voltage x-rays (14Gy) immediately before, after or 2 days after the balloon injury. They found reduced neo intimal formation as compared with controls. They showed evidence of focal myocardial necrosis. To reduce the incidence of toxicity from even high doses sophisticated treatment techniques had to be evolved. The advantage of treatment with external radiation are that it can be done in a regular radiotherapy room, has the potential for fractioning the treatment course and time the treatment in

accordance with available information on growth kinetics of the medial smooth muscle cells. It provides more uniform dose distribution circumferentially around the vessel wall, which is good especially if the lumen wall is eccentric. Presently, external radiation with electrons is advisable only for arterio-venous fistulas. The location of most arteries precludes the use of external radiation owing to the high integral dose and attendant toxicity.

Endovascular Radiation : Following extensive research work in porcine & swine models, favorable results achieved in humans have led to ongoing randomized clinical trials of endovascular radiation for coronary and peripheral vessels using various types of radioactive isotope (gamma & beta emitters) using various techniques like catheters and stents. Wiedermann et al⁹ noted neo intimal suppression at 4 weeks after angioplasty by delivering 20 Gy at a radial depth of 1.5 mm just before arterial injury and persistence of this effect at 6 months. Waksman et al documented neo intimal suppression using ¹⁹²Ir with a dose response effect in vessels treated with 3.5, 7 and 14 Gy at a radial depth of 2mm and continued benefit at 6 months in arteries treated with 7 and 14 Gy. They have shown that radiation was just as valuable an adjunct to stenting as it was to angioplasty¹⁰. Figure 1 shows comparative neo intimal growth in irradiated versus non-irradiated pig coronary artery.

Fig.1: Substantial neo intimal growth in (a) non irradiated stented pig coronary artery versus minimal growth in (b) irradiated artery at 1 month as seen on light microscopy. L-Lumen; M-Media; N-Neo intimal; S-Stent wire

Endovascular Brachytherapy is ideally suited for delivery of moderately high doses of radiation to the vessel walls as it allows for a very rapid fall off of the dose beyond the target volume. The various approaches to endovascular brachytherapy are : (i) *HDR remote afterloading ¹⁹²Ir# (ii) HDR remote afterloading ³²P# (iii) Manual remote afterloading ⁹⁹Y^X (iv) Manual remote afterloading ¹⁹²Ir (v) Radioactive ³²P stents (vi) Radioactive liquid Rhenium filled balloons.

Treatment using HDR remote afterloading ¹⁹²Ir is possible only in a brachytherapy suite in a single fraction at the time of angioplasty and is therefore not suitable for coronary brachytherapy. The time required for the treatment is 2-4 minutes. Figure 2 shows a diagrammatic representation of ¹⁹²Ir afterloading irradiation technique within the stent of a superficial femoral artery.

Treatment using **manual afterloading ¹⁹²Ir** is applicable for all sites, feasible in catheter laboratories and has to be done at the time of angioplasty. However, special shields are required and the overall treatment time is 27 to 43 minutes. HDR Remote after

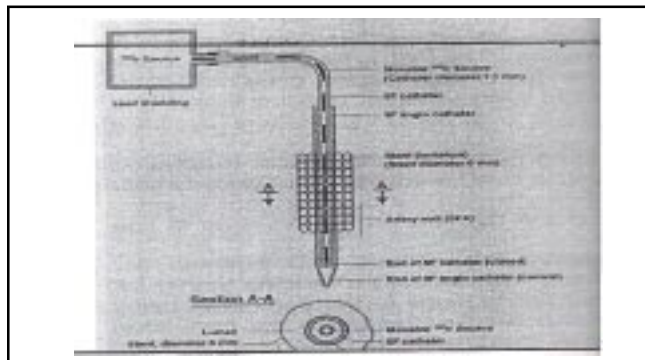
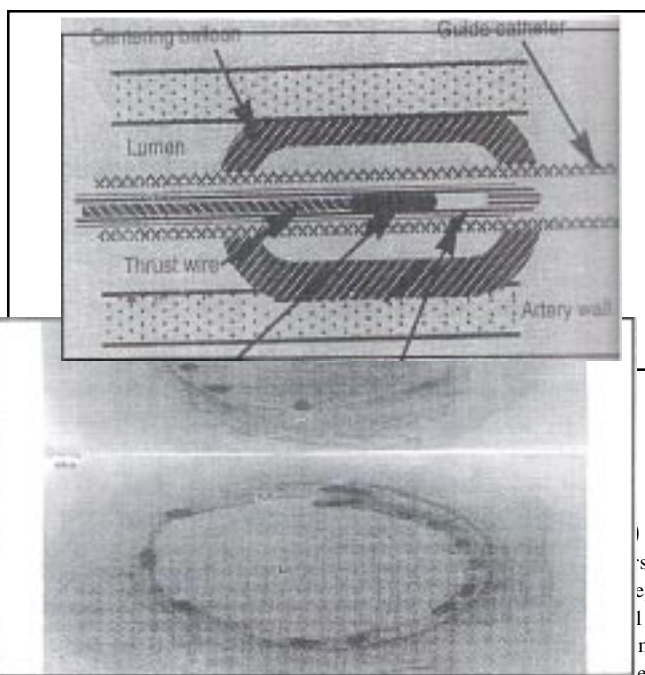


Fig.2: Catheter and loading system of Endovascular irradiation using ¹⁹²Ir afterloading technique within the stent.

loading ³²P permits treatment for all sites in a catheter lab in a single fraction at the time of angioplasty without any radiation protection issues. Fig. 3.



angioplasty of stenotic lesion in coronary vessels with poor results of 40% restenosis rate. Waksman et al¹³ has published results of 2-year follow up of the beta WRIST & gamma WRIST trials. 50 patients were enrolled in β WRIST, γ WRIST & placebo arms each in β WRIST arm. ⁹⁰Y pure β emitter with a maximum energy of 2.28 Mev (Million electron volts) and an initial activity of a 130m Curie was used. The source was a flexible 0.014-inch wire delivered into a centering balloon. The prescribed dose was 20.6 Gy (Gray) to a distance of 1mm from the surface of inflated balloon. In the γ WRIST study, a 5 French non-centered catheter was used. The prescribed dose was 15 Gy to 2mm from the surface of the source for vessels between 3-4 mm and 15 Gy to 2.4 mm for vessels more than 4 mm in diameter. Beta radiation showed a 36% relative reduction in target lesion revascularisation (42% vs. 66%, p=0.16), target vessel revascularisation (46% vs. 72%, p=0.08) compared with placebo at 2-year follow up. Most of these presented with an event within the first 6 months after the index procedure. All patients received post angioplasty clopidogrel 75mg or ticlopidine

*HDR=High dose rate; #¹⁹²Ir = Iridium 192; #³²P=Phosphorus32; ^{x99}Y=Yttrium99

500mg for one month. Late total occlusion of the culprit lesion occurred in 12% of beta WRIST and 8% of gamma WRIST patients.

WRIST trial (Scripps Coronary Radiation to Inhibit Proliferation Post Stenting) : Teirstein et al¹⁴ have reported 100% clinical follow up with ¹⁹²Ir treated patients and have shown reduction in total lesion revascularisation by 74% at 6 months and 68% at 3 years. They reported reduction in angiographic restenosis by 69% at 6 months and 48% at 3 years. No perforation, aneurysm or pseudoaneurysm was reported.

Leon et al¹⁵ have reported results of a multicentric double blind randomized clinical trial, the gamma one trial wherein they have shown statistically significant decrease in the rate of revascularisation of the target lesion in the ¹⁹²Ir group (24.4% vs. 42.1%) as compared to the placebo and also a decrease in the rate of progression to the prespecified composite primary end point of death, Myocardial infarct (MI), emergency bypass surgery and revascularisation of target lesion in the ¹⁹²Ir group (28.2% vs. 43.8%) in the placebo group. They however pointed out an increase in the late thrombosis (5.3% vs. 0.8%) in ¹⁹²Ir vs. placebo group resulting in more late MI (9.9% vs 4.5%). This occurred in patients only after discontinuation of antiplatelet therapy and who had received new stents at the time of radiation treatment. These findings are similar to those in earlier reports from several other trials of vascular irradiation using different isotopes in which therapy with anti platelet drugs was used for only 1 to 2 months following radiation¹⁶.

BERT Trial (Beta emitter for intracoronary brachytherapy) : Spencer King et al¹⁷ have used⁹⁰ Sr/Y for intracoronary brachytherapy and reported restenosis rate of 15%. This was the first trial of endovascular brachytherapy approved by the FDA and resulted in significant decrease in the treatment time and operator exposure.

RHENIUM - 188 Trials : Park et al¹⁸ have described treatment of diffuse in stent restenosis with rotational atherectomy followed by radiotherapy with Rhenium-188 Mercaptoacetyl triglycine-filled balloon. It can be applied to coronary arteries with a large diameter as well as angulated arterial segments without the aid of a centering device. ¹⁸⁸Re is a high energy beta emitter with a maximum energy of 2.12 Mev that is available as Rhenium perhenate solution from the 188W/188Re generator (Oak Ridge National laboratory, Tennessee) and has a half life of 17 hours. Restenosis rate of 10.4% has been reported at a follow up of 5.8+1.7 months of 50 treated patients. This is encouraging considering the long length of lesion (25.5 + -12.7mm). These results were superior to those by Hoher et al¹⁹. This may be attributed to inclusion of only restenosis patients, and use of atherectomy and optimal balloon angioplasty. The advantages of this form of treatment are that it can be used for treatment of vessels of various sizes, angulated segments, uniform dose distribution and no centering device issues. No late thrombosis has been reported so far and may also be attributed to the 6-month use of aspirin and cilostazol. Figure 4 illustrates the difference in dose distribution achieved by centering versus non-centering source of radiation. Two feasibility trials the CURE trial at Columbia University and the RADIANT trial are using radioactive liquid filled balloon.

Indian trial "INDIRA" of "Intracoronary irradiation in the prevention of coronary re stenosis" is a prospective randomized trial in collaboration with the Long Beach Memorial Medical center USA and involves four major medical centers in India i.e. MediCiti Hospital, Care Hospital, Apollo Hospital and Bibi Cancer center. 800 de novo patients are to be randomized to receive 11 Gy at 3mm radius. The study was approved by the Atomic Energy

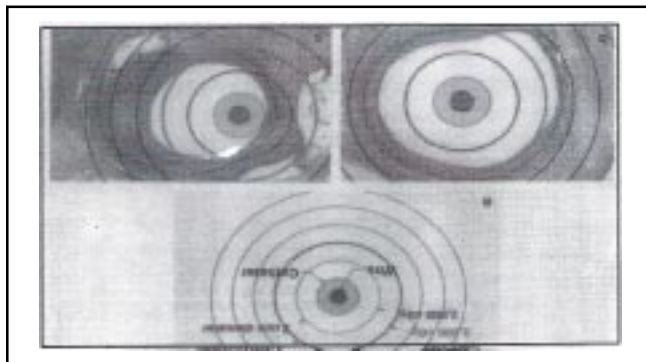


Fig.4: (a) Dose versus distance away from center of source. (b) Source centered in artery. (c) Source not centered in artery.

Regulatory Board and the trial was started in December 1998.

The European society for therapeutic radiology (ESTRO) and oncology working group²⁰ and the American association of Physicists in medicine task group on "Intravascular brachytherapy"²¹ have addressed general terms and concepts for target and dose specification as well as detailed recommendations for dose prescription, recording and reporting in Endovascular brachytherapy for both peripheral and coronary arteries. An example of prescribing, recording and reporting for a coronary artery with gamma radiation (¹⁹²Ir, non centered) as recommended by ESTRO is shown in Appendix A.

Conclusion

Endovascular Brachytherapy is still in its infancy. A better understanding of the molecular biology of restenosis and definitions of actual targets responsible for restenosis shall help us in achieving superior results with the same modality as well as help develop newer concepts in the treatment.

Issues such as the timing of radiation, length of the segment to be treated, dose, fractionation, dose rate and the point of prescription are still investigational and are being addressed to in various clinical trials. Prevention of late thrombosis following vascular brachytherapy needs to be looked at. A close collaboration between the interventional cardiologists, radiobiologists, radio oncologists, medical physicists and the industry is required.

Appendix A

Clinical Situation : 59-year-old female with a history of coronary disease for 2 years. Twenty-four months ago stenting of LAD was performed. Control angiography showed in-stent restenosis.

Aim of Therapy : Angioplasty of in-stent restenosis to establish normal arterial patency and endovascular brachytherapy to prevent restenosis.

Technique : Dilatation with 30mm/3.5mm diameter PTCA balloon and brachytherapy using 4F diameter non-centered radiation delivery catheter with ¹⁹²Ir ribbon source (14 seeds, 55mm). Following GRANITE, GAMMA 2 protocol with modifications.

Description of source, devices and technique

Isotope: ¹⁹²Ir, encapsulated in stainless steel. Source type : Source ribbon, 14 seeds (each seed 3x0.5mm, 1mm spacing), 55mm

length. Source strength: Reference air kerma rate of 0.133 cGy/h @ 1m, 854.4MBq (23.09mCi) per seed, 65.1cGy/min at 2mm from the source axis. Source movement: None Delivery device : Manual afterloader (Cordis Checkmate IRT (TM) System). Delivery catheter: 4F non-centered catheter.

Recording and reporting lengths, depths and dose

Lesion Length: 12mm; Interventional Length: 30mm; Clinical Target Length/Planning Target length: 40mm ASL:35mm; Reference Isodose Length: 46mm; Reference Lumen Diameter: 3.4mm; Reference Depth: 1.0mm

Dose prescription

Prercription point: 2mm from the source axis; Dose and dose rate: 14Gy, 0.65 Gy/min.

Dose recording and reporting

Reference Depth Dose (2.7mm) - 9.5Gy; Reference Lumen Dose (1.7mm) - 18.2 Gy; Minimum and maximum values for non-centered device: Reference Depth Dose min/max-6.4/19.5Gy; Reference Lumen Dose min/max-9.7/100Gy.

Time dose pattern

Total Treatment Time: 21.5 min

Total Reference Air Kerma: 0.048cGy@1m

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Evolution and Techniques of 3Dimensional Conformal/Stereotactic Radiation/Stereotactic Surgery for Brain Tumours : their impact on management of intracranial lesions

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Abstract: Radiotherapy is an important treatment modality in the management of several brain tumours, resulting in good to excellent long-term survival rates in a majority of childhood tumours and in adults with benign tumours. Conventional radiation therapy to a majority of brain tumours involves 2-3 static open beams with simple coplanar field arrangement, which may however lead to irradiation of significant volumes of normal brain and adjacent critical structures. Last few years have seen a tremendous refinement in the techniques of radiation planning and delivery. Three dimensional radiotherapy (CRT) is a technique in which radiation beams are conformed to the shape of the tumour with the help of multileaf collimators (MLC) or shielding blocks in multiple static beams while stereotactic radiosurgery (SRS) is a high precision technique in which multiple collimated beams of radiation are stereotactically aimed to a well defined target volume so as to deliver a single, high dose of radiation to a small volume of tissue. Stereotactic conformal radiation (SCRT) is a further advancement of CRT and SRS in which highly precise radiation can be delivered with firm immobilisation with relocatable frames, accurate target localisation, highly conformal shielding with micromultileaf collimators (mMLC) and focused radiation delivery in a fractionated manner. SRT/SCRT is particularly indicated in young patients with benign/low grade neoplasm where long-term survivals are expected and at risk to develop radiation induced morbidity.

Key words : *Stereotactic radiotherapy, radiosurgery, 3D conformal radiotherapy.*

Introduction

Brain tumours are relatively rare and account for 2-5% of all neoplasms. Advances in imaging and refinement in treatment modalities including surgery, radiotherapy and integration of chemotherapeutic schedules in the management paradigm of these tumours have generally led to some improvement in survival. From a prognostic view, these tumours seem to broadly divide themselves rather distinctly as seen in the adult and paediatric age groups. Malignant gliomas and metastases are commonly seen in adults and universally associated with dismal outcomes. On the other hand, paediatric brain tumours, the commonest solid tumours in this patient population, are potentially curable but can result in moderate to severe late disease and treatment related sequelae.

Radiotherapy is an important treatment modality in the management of several brain tumours, resulting in good to excellent long-term survival rates in a majority of childhood tumours and in adults with benign tumours, while the local control in these tumours has been reasonably effective, there have been concerns about treatment related morbidity, which includes neuropsychological impairment, endocrine dysfunction, growth retardation, risk of second malignancy and cerebrovascular events^{1,2}. Although the exact role of radiotherapy in the causation of these sequelae is not yet completely understood, it is fair to assume that radiotherapy is at least partly responsible. There have been attempts to modify the management in terms of avoiding, delaying radiotherapy or reducing the total radiation dose to the tumour with a view to reduce its impact on long term toxicity. However, reduction of radiotherapy

doses to the tumour has shown to result in poorer local control rates. Also, a majority of the patients in whom the radiation is delayed eventually do require radiation therapy at later stage. New techniques of radiotherapy are hence being explored since last few decades, to minimise the irradiation to the normal brain with critical structures without compromising radiotherapy doses essential for tumour control.

Conventional radiation therapy

Conventional radiation therapy to a majority of brain tumours involves 2-3 static open beams with simple coplanar field arrangement. The field dimensions are chosen to cover the tumour adequately as deemed appropriate on planning X-ray images (as on a simulator) with respect to the surface and bony anatomy. Typically, a generous margin of 2-3 cms (sometimes more) is given in order to overcome the possible errors in judging the coverage of the tumour, its microscopic extension and uncertainties in daily set up and treatment delivery. This may lead to irradiation of significant volumes of normal brain and adjacent critical structures. The three-dimensional picture of the tumour is difficult to appreciate in the conventional two-dimensional (2D) planning. Similarly organs at risk are also not visualised properly and it is very difficult to compute the dose received by various tissues. 2D planning also leads to restriction of the treatment using coplanar beams only. Three-dimensional (3D) planning evolved in an attempt to overcome these problems of 2D planning.

Last few years have seen a tremendous refinement in the techniques of radiation planning and delivery. This has been largely possible with major advances in integrating imaging such as CT and MRI

for better delineation of tumour volumes in treatment planning. There has been also a simultaneous technological revolution in radiotherapy planning with the emergence of dedicated computerised treatment planning workstations, which have helped in the evolution of newer high precision treatment techniques. Three dimensional CRT, SRS, and fractionated SRT or SCRT are such techniques that have the potential to minimise doses to the normal brain and critical structures as compared to conventional radiotherapy.

Conformal Radiation Therapy (CRT) : Conformal radio therapy is a technique in which radiation beams are conformed to the shape of the tumour with the help of MLC or customised shielding blocks in multiple static beams (Fig.1). The aim of CRT is to achieve a high dose differential between the tumour and the surrounding normal tissues, which may allow for either an increase in the tumour dose to improve local control or for a potential decrease in radiation damage to the normal brain. 3D conformal radio therapy is used in the treatment of various brain tumours like meningioma low-grade gliomas, pituitary adenoma, and craniopharyngioma.

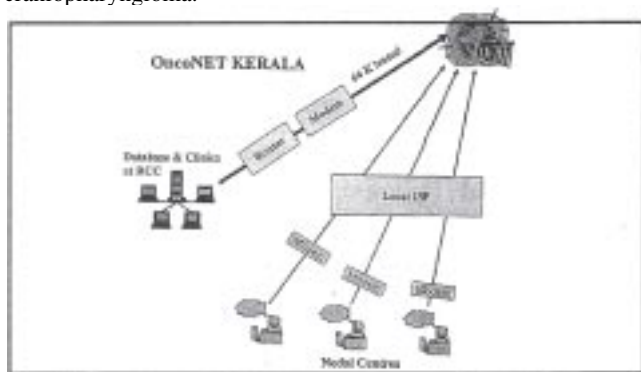


Fig.1: Schematic diagram of onconet kerala

Stereotactic Radio Surgery (SRS) : Stereotactic radiosurgery is a high precision technique of radiotherapy in which multiple collimated beams of radiation are stereotactically aimed to a well defined target volume so as to deliver a single, high dose of radiation to a small volume of tissue. The concept and initial implementation of radiosurgery was introduced by Lars Leksell in 1950s using initially orthovoltage and later multiheaded cobalt unit (described as gamma knife).

Gamma knife consists of 201 cobalt sources focused towards one isocentre, with the activity of the total cobalt ranging from 5500 to 6000 Curieci. SRS requires accurate immobilisation, precise definition of the volume to be irradiated, localisation of critical organs and ability to produce multiple plans. On a modified linear accelerator, SRS conventionally is delivered as an arc therapy. However, both gamma knife and arc therapy typically produce spherical dose distribution. Tumours being irregular are conformed only using multiple isocentres, which may lead to considerable dose inhomogeneity. The optimum manner to treat irregular shaped targets (frequently the case in clinical practice) is with multiple conformal static fields³. There is a large experience of stereotactic radio surgery in the treatment of artero venous malformations,

brain metastases and small tumours such as meningiomas and acoustic neuromas. Single fraction stereotactic radio surgery has however been sometimes shown to be associated with considerable neurological toxicity to the optic apparatus, the cranial nerves and normal brain^{4,5}. While stereotactic radio surgery may provide highly conformal doses around the tumours, its lack of superior local control in brain tumours to conventional management strategies and considerable risk of neurotoxicity has prompted to explore other means of irradiation to achieve less toxicity and maintain or improve local control rates. One of the ways is to deliver stereotactic radiotherapy in a fractionated manner, known as stereotactic radiotherapy.

Stereotactic Radio Therapy/Stereotactic Conformal radiotherapy (SRT/ SCRT) : stereotactic conformal radiotherapy is a further advancement of CRT and SRS in which highly precise radiation can be delivered with very firm immobilisation with relocatable frames, accurate target localisation, highly conformal shielding with micromultileaf collimators (mMLC) and focused radiation delivery in a fractionated manner. It also ensures homogeneous dose distribution with the irradiated volume, further reducing the risk of damage. Larger volumes therefore can be treated with multiple daily fractions like conventional radiation, to benefit from normal tissue sparing properties of fractionated radiation therapy. This has become possible with the utilisation of high precision relocatable non-invasive means of immobilisation. Initial experience with fractionated stereotactic radiotherapy involved varying dose schedules with relatively large dose per fraction. However, any part of the normal brain encompassed in high dose volume could result in significant radiation injury. On the other hand, fractionated stereotactic treatment with standard dose per fraction of less than 2 Gy has been shown to be safe without any increased toxicity.

Technical aspects

The treatment with 3conformal techniques involves few basic steps like accurate immobilisation, radiotherapy planning scans, target delineation, planning using multiple conformal beams, quality assurance and plan implementation. Few important steps in each are described below.

Immobilisation for radio surgery is done using the fixed frame. The frame is fixed to the patient's skull using four pins till they hit the periosteum. It affords excellent immobilisation and no margin is generally given for set up errors. For conformal radio therapy, the treatment lasts for 6-7 weeks and therefore the immobilisation device should be reproducible so as to maintain the accuracy of desired treatment delivery. An individual customised thermoplastic mould is used for patients planned for conformal radio therapy. The possible patient motion with this mould over a fractionated course of radiotherapy has been estimated to be between 5mm to 10mm. Patients considered for stereotactic conformal radiation are immobilised using the specialised relocatable mask based stereotactic frame. This provides even firmer immobilisation than the thermoplastic mould with possible patient movement estimated to around 1-2 mm (6) (Fig 2).

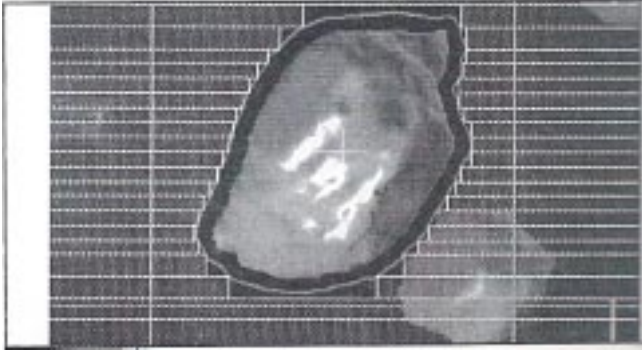


Fig. 2: Beam's Eye View of a conformal radiotherapy portal showing conformation achieved with the help of multileaf collimators.

Radiotherapy planning scans : Patients immobilised in their moulds or stereotactic frame undergo a contrast enhanced planning computerized tomography scans with 2-5 mm slice thickness at 2-5 mm separation. The computerized tomography data of patients is networked to the dedicated treatment planning system. Radio surgery/stereotactic radio therapy patients also undergo a planning magnetic resonance imaging scan which is also networked to the planning computer, where these images are fused with the planning CT scans images by an image fusion software. Integration of magnetic resonance imaging in planning has demonstrated to provide significant improvement in delineation of the tumours and normal structures facilitating the accuracy of localisation of the tumour and critical structures.

Contouring : Gross tumour volume (GTV) defined as the area of visible tumour or areas deemed to contain tumour is manually contoured by the clinician on each CT or CT-MRI fused slices. All pre-treatment imaging is generally reviewed to help in defining this volume. Critical structures such as the optic chiasm, pituitary hypothalamic axis, brain stem and the normal brain are also contoured. Target delineation remains one of the very important areas and recent advances in functional imaging such as magnetic resonance spectroscopy, positron emission tomography etc. are being currently explored to help in more accurate tumour visualisation.

Planning target volume (PTV) : A margin has to be defined around gross tumour to take into account the possible microscopic extension of the tumour not seen on the planning images and the spatial uncertainties in day to day set up. This margin depends upon the type of tumour, confidence in tumour volume definition, immobilisation device used and the set up uncertainty in daily treatment delivery. For patients treated with conformal radiation typically a margin of 10-20 mm is grown around the gross tumour to give the final planning target volume. SRS/SCRT involves firmer immobilisation, frequent use of MRI in tumour volume delineation and accurate treatment delivery. Hence the margin for stereotactic conformal radiation is 5 to 10mm while for stereotactic radio surgery, no margin is usually given (6).

Field arrangement and plan evaluation : Treatment planning is based on planning optimisation utilising beam energy, appropriate weighting, and wedges with different field arrangements. The

plans are finalised using International Commission on Radiological Units 50/62 recommendations ensuring PTV coverage by 95% isodose line and maintaining uniform dose homogeneity. CRT plans typically involve 3-4 conformal field arrangements. With the help of beam's eye view facility, conformation is achieved for all fields with either standard multileaf collimators having 1 cm leaf width at the isocentre or using conformal blocks. Analysis of rival plans is done by visual assessment and with the help of dose volume histograms (DVH) of the planning target volume and critical structures. Plan, which delivers uniform dose distribution in the planning target volume with adequate coverage and minimal possible doses to the normal brain and adjacent critical structures, is chosen as the final plan. Treatment parameters are then networked to the treatment machine where the treatment is delivered by 6MV photons.

Stereotactic Radio Surgery/Radio Therapy : Planning of Stereotactic Radio Surgery/Radio Therapy is more complex than conformal radiation. Every effort has to be made to achieve the best possible plan with respect to desired dose delivery to the target and minimal dose to the critical structures. The field arrangement typically used are 4-10 widely spaced non-coplanar beams using 6 MV photons. Uniform dose homogeneity as per standard ICRU criteria is necessary for all approved plans, particularly for stereotactic radiation. All radiation portals are individually conformed to the shape of the PTV with micromultileaf collimators.

Quality assurance and plan implementation : It is very important to have a good quality assurance program while implementing these relatively conformal techniques. The portal films for the isocentre check should be taken on the first day of treatment and compared with the digitally reconstructed radiograph, generated from the treatment planning system. Portal films should be repeated at least once weekly. For stereotactic treatments the isocentre of the linear accelerator is checked with Lutz test before the actual treatment is delivered. Care is taken to ensure isocentre accuracy and all fields checked before treatment, using the target positioner box.

Clinical experience

Low grade glioma (in adults) : The management options for low-grade gliomas are observation, surgery alone and surgery followed by radiation therapy. Surgery is indicated in symptomatic patients where surgical debulking is likely to reduce the symptoms. The European Organisation for Research and Treatment of Cancer prospective randomised trial has not shown any improvement in survival in early Vs delayed radiation therapy (7). In patients with progressive disease radiotherapy to a conventionally given dose of 50-54 Gy* stabilises or improves the neurological symptoms. The use of conformal radiation may be helpful to reduce the long-term toxicity due to the large volumes of brain irradiated.

High grade glioma : Surgery followed by radiation therapy is the standard treatment for high-grade gliomas. Radiation therapy involves radiation to the tumour as visualised on the contrast enhanced CT or MRI with a margin of 2-3 cm all around. The dose recommended is 60 Gy in conventional fractionation over a period of 6 weeks. As this may encompass large volume of

normal brain, conformal radiation can be used in dose escalation protocols, hyperfractionation and accelerated fractionation to decrease normal tissue toxicity. In recurrent gliomas radiation therapy can be delivered as stereotactic treatment with reasonable efficacy comparable to chemotherapy but may carry a relatively high risk of radiation necrosis necessitating re-operation⁸. Stereotactic Radiosurgery boost has been attempted in small malignant gliomas as a part of dose escalation but has failed to demonstrate any advantage. In fact, the recent randomised radiation therapy oncology group trial of Stereotactic Radiosurgery boost Vs no boost showed worse survival in the boost arm (unpublished data).

Optic chiasmal gliomas : Radiation therapy is the mainstay of treatment for optic chiasmal gliomas as surgical excision is not possible due to risk of damage to optic nerves. The recommended dose is 50-55 Gy in conventional fractionation to the tumour as seen on CT or MRI with 1-2 cm margin all around. conformal techniques may be helpful particularly as most of the patients are children and there are critical structures like pituitary and hypothalamus in the vicinity⁹.

Medulloblastoma : The standard treatment for medulloblastoma is surgery followed by radiation therapy with or without chemotherapy. Radiation therapy involves treatment of the whole craniospinal axis using a bilateral shaped cranial portals and single posterior spinal portal to the dose of 35 Gy/21 fractions over 4 weeks. This is then followed by tumour bed boost of around 20 Gy, delivered to the entire posterior fossa with bilateral portals. But as most of the recurrences are seen in the tumour bed itself, the need to irradiate the entire posterior fossa is questioned. Considerable activity is currently going on to evaluate the role of conformality in irradiation of the tumour bed as boost in order to minimise the treatment related toxicity¹⁰.

Meningioma : Radiation therapy for meningiomas is generally considered when the excision is partial or in cases of recurrence. The long-term tumour control rate using modern imaging and treatment delivery systems has been reported to be 80-90%. The recommended technique is to treat the residual tumour with 1cm margin to a dose of 54Gy in 30 fractions over 6 weeks. Stereotactic techniques allow smaller margin of the Planning target volume and hence better sparing of the normal tissues. radio surgery and conformal treatment have been explored in patients with cavernous sinus and parasellar meningiomas^{11,12}. Early results suggest good initial tumour control with less toxicity to the trigeminal and optic nerves. Both small and large tumours can be treated with Stereotaxy based treatments with potentially reduced complication rates¹².

Craniopharyngioma : Craniopharyngiomas are benign tumours in the suprasellar region arising from the Rathke's pouch, mainly seen in children. Conservative surgery followed by radiation therapy gives 5-year survival rates of 70-80%¹³. Radiation therapy is generally delivered with anterior and two lateral wedge pair portals encompassing the tumour with 1-2 cm margin. The use of Radiation Therapy Oncology Group with 4-6 fields may particularly be useful in children where it is important to spare the surrounding normal critical structures¹⁴. The recommended dose is 50-55Gy in conventional fractionation over 5-6 weeks. Radio surgery is associated with high morbidity and damage to optic nerve and is not advocated.

Pituitary adenomas : The initial management of these tumours is

surgical excision, which is generally done by transphenoidal approach. The timing of radiotherapy is a matter of debate and this issue is being addressed in an ongoing randomised trial at our centre. Radiotherapy achieves excellent long-term control to the order of >90% at 10-20 years¹⁵. The risks of optic nerve damage and second malignancies with conventional radiation is 1-2% at 10-20 years. Stereotactic conformal is the appropriate treatment for these tumours and should be preferred over Radio surgery, which has more risk of optic nerve and neurological damage^{5,16,17}.

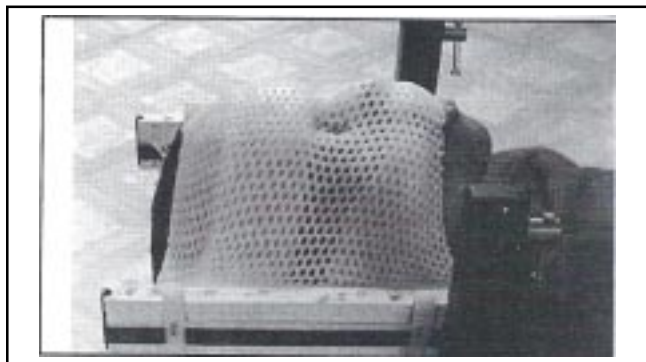


Fig.3: Patient immobilised in stereotactic relocatable mark for SCRT

Acoustic Neuroma : Various treatment options for acoustic neuroma include observation, surgery alone and radiation therapy. Radiosurgery is being done for acoustic neuromas with a 90-95% progression free survival at 5 years. But radio surgery may be associated with a relatively high risk of damage to VII and VIII nerve. Stereotactic conformal radiation is potentially a better option in which similar tumour control can be achieved with decreased neurotoxicity¹⁸.

Brain Metastasis : Conventional management of brain metastasis involves whole brain radiotherapy. However, surgical excision in solitary metastasis improves survival marginally. Radio surgery with or without whole brain radiation therapy have also shown encouraging results in solitary metastasis or upto 3 lesions. The maximum advantage is seen in patients with absent/controlled extracranial disease and with good performance status¹⁹.

There is increasing experience of utilisation of high precision techniques which have indeed become integrated in routine clinical practice in several centres of the world, including ours. Clinical experience in a range of tumours employing these techniques has shown comparable results to that of conventional radiotherapy. Because of their ability to conform radiation doses tightly around the target volume resulting in significantly less volumes of adjacent brain receiving high doses, they have the potential to minimise some of the radiation induced morbidity. However, most of the data addressing these issues is premature. Also, there has been some concern that these techniques typically employ tight margin and some concern, justifiably so, have been also raised to assess long term local control because of the real potential of geographical misses. These technologies, while existing are also expensive and their benefit needs to be validated in appropriately conducted clinical trials. In this regard, we are at present conducting a randomised trial comparing stereotactic conformal radiation and conventional radiotherapy in minimising late sequelae in children and young adults. The trial aiming to study 200 patients would provide very important longitudinal and reliable data regarding long-term sequelae in patients receiving focal brain radiation. More

*1GRAY = 100 Centi GRAY = 100 rads (unit of radiation prescription)

importantly, it will evaluate the efficacy of stereotactic conformal radiation with respect to conventional radiotherapy in terms of long-term local control and the incidence and magnitude of treatment related complications in the two arms.

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Intensity Modulated Radiation Therapy (MRT) : Its Scope in Radiation Oncology

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Abstract: Radiation therapy treatment has matured into an integral component in the management of cancer patients. The planning and delivery systems have evolved from superficial X-ray therapy to megavoltage therapy and highly precise deposition of radiation within the tumour and its margins has been made possible with the recent advent of intensity modulation of the radiation beams.

Key words : *Target volume, intensity modulation, Optimization*

Introduction

Radiation oncology is undergoing a technological revolution compared to that brought about with the introduction of medical megavoltage linear accelerators in the latter half of the twentieth century. Advances in medical imaging and computer hardware and software technologies have led to the development of image based three dimensional radiation therapy treatment planning systems and computer-controlled medical accelerators having advanced delivery and treatment verification features. These technologies have helped implement external beam radiation therapy techniques, in which the high-dose region is conformed much more closely to the cancer patient's target volume than previously possible, thereby, reducing the volume of normal tissue receiving a high dose. *In the late eighties*, articles began to appear in the literature suggesting methods to achieve a high degree of conformity of radiation dose to tumour volume from external beam sources¹. The major feature of this process was to divide the normal radiation port into a group of very small "beamlets" with weights that could be altered depending on the desirability of delivering radiation to the tumours through each beamlet. Such a system offers the advantage of reducing dose to normal tissues, boosting doses within the tumour volume concomitantly with standard doses to the remainder of the targets, and, if properly computerized, could perhaps be more effective than 3-dimensional conformal radiotherapy (3-D CRT). This computerization is the use of "inverse planning" to determine the best solutions to the many variables available (e.g. the position of the radiation ports, the weight of each beamlet etc.) and the use of computerized delivery systems which eliminate the need of fabrication and placement of beam modifiers for each treatment port.

The first clinical use occurred in 1994, within five years since the postulation of such a system². The term Intensity Modulated Radiation Therapy (IMRT) was applied to distinguish it from 3 dimensional conformal radio therapy (CRT), although it is an extension of the very same process. Since that time it has been impossible for the literature to keep pace with the rapidly expanding use of intensity modulated treatment.

Imaging in Intensity Modulated Conformal Radiation Therapy

The enabling technology for intensity modulated radiation therapy is geometrically correct computerized tomography (CT) image data sets of individual cancer patients, developed originally for the purpose of diagnosis. These data sets are accurate geometric

models of the individual patients if the image acquisition position is identical to the treatment position. CT data sets also encode information on electron density of the patient sufficient to compute accurate dose distributions. Magnetic resonance imaging (MRI), Positron Emission Tomography (PET), Single Photon emission computerized tomography (SPECT) and ultrasound studies may be fused to the treatment position study in order to obtain information on the target volume, as well as information on organs at risk. The soft tissue imaging provided by Magnetic resonance imaging augments CT reconstructions that approximate the electron density of the patients. In certain cases, the MRI images can resolve tumour volumes or normal tissues structures that are not visualized as clearly in the CT reconstructions. In order to use this information *fusion* imaging and DICOM-RT standards are used for image transfer and data exchange between various equipments. Integration of imaging and therapy has led to useful syntheses that have enabled the development of intensity modulated radiotherapy.

Patient specific target and normal tissue

Anatomy is identified with the acquired imaging data sets, with or without the use of contrast agents that can be used to select a Gross Tumour Volume (GTV) in three dimensions. The bounds of these volumes are geometrically accurate to within the resolution limits of the reconstructed data sets. Normally, the resolution will be about 1 mm in the transverse planes and will be set by the scan spacing (or spiral pitch) to about 2 mm to 10 mm in the superior/inferior direction. These data sets are processed for treatment planning using virtual simulation computer applications. The applications commonly provide for the determination of an origin and an orientation of a Cartesian coordinate system. Procedures have been developed to locate this coordinate system on the patient, using laser sidelight as the reference marks or alignment devices (fiducial markers) associated with the immobilization device and markings on the patient surface are employed.

The objective localization of the gross tumour volume (GTV) has been an area of active research. Determination of the bounds of gross tumour volume in three dimensions to within uncertainty of less than 5mm is rarely achieved because inter and intra-observer variations are considerable. However, this uncertainty, as well as occult tumour spread can be accounted for by expanding the gross tumour volume in three dimensions to define a Clinical Target Volume (CTV). To account for uncertainty in patient positioning and organ motion, a further expansion to a Planning Target Volume (PTV) is recommended. The selection of gross

tumour to planning volume expansion parameters provide the radiation oncologist with the opportunity to factor into the treatment plan the medical and technical issues specific to each patient.

Dose calculation algorithms in IMRT : Dose calculation algorithms can be broadly classified into correction-based and model-based approaches. Correction-based approaches correct the dose distribution in a homogenous water phantom for the presence of beam modifiers, contour corrections, and tissue heterogeneities encountered in treatment planning of real patients. The homogenous dose is obtained from broad field measurements obtained in a water phantom or reconstituted from a representative sample of such measurement. The *convolution/superposition method*³ is a model-based dose calculation method. Model-based methods directly compute the dose in a phantom or patient. the calculation takes into account the beam energy, geometry, beam modifiers, patient contour and electron density distribution. The Monte-Carlo method is another model-based method. Both convolution method and the Monte Carlo method compute dose per unit fluence (or energy fluence) which allows the beam monitor units (dose delivery units) to be expressed in a phantom in an independent manner as energy fluence per monitor unit.

In *intensity modulated radiation therapy* the beam is non-uniform in intensity (Fig. 1) The beam intensity pattern from one beam direction can be thought of as a two-dimensional map of energy fluence dependent on a patient. This map can be discretized into beam elements or "bixels". A bixel corresponds to a finite region of a compensator, a portion of the travel of a leaf of a conventional multileaf collimator or a leaf of a temporally-modulated (binary) collimator.

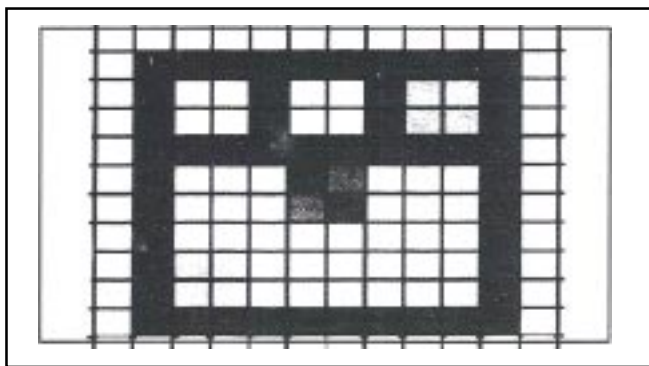


Fig.1: A test non uniform intensity pattern using a radiographic film.

The non-convolution dose model for high energy photon beams is the analytical method and is based on central-axis absorbed dose in a unit density material, including that under lateral and longitudinal electronic disequilibrium. The model is based on observations made by Nizin et al⁴ during the last ten years regarding the behaviour of the primary and scatter dose in photon beams. It is characteristic of the model that the knowledge of energy-fluence spectra is not required and majority of the necessary parameters can be derived from conventional beam data.

Computer Optimization and inverse planning

Computer optimization of radiation therapy treatment uses computer algorithms to find the best treatment plan for an individual patient or for a group of patients. A number of radiation optimization

techniques have been employed. Radiation therapy optimization is not new. Radiation oncologists, physicists and dosimetrists have employed trial-and-error optimization of radiation therapy dose distributions even when dose computations were not computerized. Computer-based radiation therapy optimization is often called the '*inverse method*' of dose calculation to distinguish it from the '*forward method*'. In the forward method the beam portals (beam orientation, shape and modifier) are first designed and then dose computation is performed. Forward optimization can be performed by then either changing the portal or adding another beam to make up for some dose that was missed in the target volume. The results of forward planning can produce radiation therapy plans with non-uniform beam intensities.

Treatment plan optimization, now referred to as "inverse planning", approaches the problem of designing a treatment from a more natural clinical perspective. The planning problems and constraints are defined in terms of clinical objectives and then the computer determines the best configuration of beams or beam intensities. If the results are not satisfactory, then there is no doubt that the required clinical objectives cannot be met within the range of available treatment configuration. Adding more treatment options, such as more beams, more energies, more modulation, etc., might produce a successful result. Otherwise, compromises must be made in the clinical goals, namely, tumor dose requirement must be relaxed or normal tissue doses increased. However, the planning focus is shifted away from the details of treatment delivery and onto the clinical consideration.

The most difficult task in optimization is mathematically defining the treatment goals. Increasing tumour dose, increasing tumour dose uniformity, and decreasing normal tissue doses are all incompatible goals yet, these conflicting goals for the target and normal tissues must be combined into a single figure of merit for each possible plan. This figure of merit is variously referred to as an *objective function*, *cost function*, or *score function*. It is used to compare alternative solutions and select the best one. A wide variety of objective functions have been developed and studied. Some use probability models for biological response, but most evaluate plans on the basis of dose alone. In general, dose-based objective functions are designed to favor uniform dose to the target and to apply penalties to plans that exceed tolerance doses of normal tissues. The relative merits of uniform tumour dose versus excessive normal tissue doses are controlled by the planner according to the judgement of the radiation oncologist. The mathematical methods and computer algorithms for optimization must be matched to the desired objective function.

To arrive at an optimal plan the radiation oncologist defines dose constraints to the normal tissues based upon the volume of tissue irradiated, critical tolerance of the specific normal tissues available from literature, his/her experience and the desired outcomes in a given case. Another example is prescribing the minimum dose to the target volume, but if the limit is too low the target coverage may be poor and if it is too high the normal tissue may get unnecessary dose. (Fig. 2) An alternative to use of constraints is to use *penalty functions* which are also called "soft constraints". Penalty functions are most often additional terms placed into the objective function. The penalty functions act to discourage, but not prevent, crossing the boundary out of a feasible solution had a constraint been used instead. Dose-volume-constraints are often

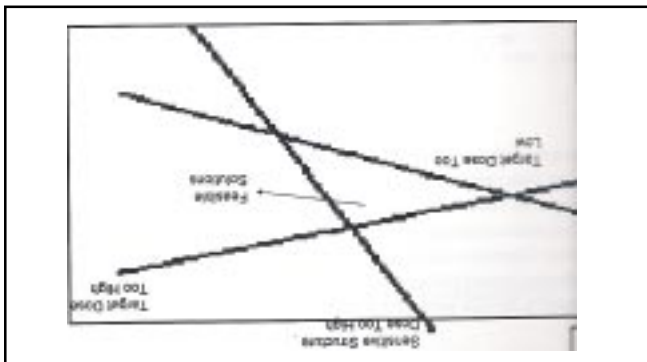


Fig.2: Dose constraints a feasible solutions.

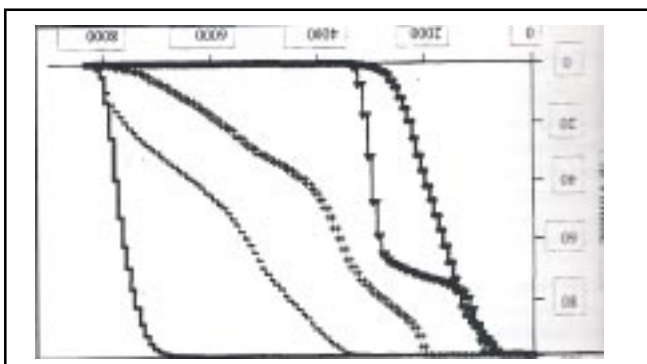


Fig.3: Shows the dose volume histograms for a seven field intensity modulated radiotherapy nasopharynx plan.

penalty functions⁵. Dose volume histograms are the pictorial representation of the dose delivered to percentage volume of the target and organs at risk (Fig.3).

Delivery systems for IMRT

There are various delivery systems available for delivery of intensity modulated radiation therapy and each has its own advantages. It is the comfort level and financial budgets of the treating team with each technology that has made departments equip themselves with different systems. Three important considerations to be given to the delivery process are (i) How accurately does the delivery system create the dose distribution created in the planner? (ii) How easily can we verify the safe operation of the delivery system? (iii) How long will it take to deliver the plan?

The commonly used delivery systems are :

A. Detachable tertiary collimating systems attached to the accessory tray holder of a linear accelerator e.g. physical intensity modulators and Peacock System® from NOMOS.

B. Inbuilt Multileaf Collimating systems (MLC): The multileaf collimator is primarily an efficiency device and makes the implementation of complex treatments involving many fields practical. The leaves are made of 5 to 6 cm thick tungsten and are typically 1 cm wide. More recently leaves of width as small as 1mm have been introduced.

i. **Dynamic mode** : The multileaf collimator (MLC) is primarily an efficiency device and makes the implementation of complex treatments involving many fields practical. The leaves are made of 5 to 6 cm thick tungsten and are typically 1 cm wide. More

recently, multileaf collimator with leaves of width as small as 1mm have been introduced. In the dynamic mode, leaves can be used to modulate intensities to produce two-dimensional non-uniform profiles of arbitrary shape. In a typical dynamic method, the gap formed by each pair of opposing leaves is swept across the target volume under computer control while the radiation is being delivered. The gap opening and its speed are continuously adjusted during motion, and the dose rate of the accelerator may be altered to achieve the desired result. Since the dose rate of the treatment machine might fluctuate slightly, the motion is indexed to monitor units (MUs) rather than time. The basic idea is that as the gap sweeps across a point, the radiation received by the point is proportional to the number of MUs delivered during the time the tip of the leading leaf goes past the point and exposes it until the tip of the trailing leaf moves in to block it again. Knowledge of the maximum leaf speed is taken advantage of to maximize the gap between the opposing pair of leaves and, therefore, to minimize the treatment time and the sequencing of leaf motions also can be optimized.

ii. **Step and Shoot** : In this delivery mode, the multileaf collimator is positioned into a predetermined configuration, a fraction of dose delivered, the dose turned off, the leaves moved to another position and verified, and another fraction of dose delivered. Enough "segments" are delivered until the desired intensity map is achieved. The gantry then moves under computer control to another position and the process repeated. The order of segments can be optimized to reduce delivery time.

(iii) **Tomotherapy and intensity modulation** has been introduced at Wisconsin University Madison and its clinical utility needs to be determined.

Verification of Incident Fluence and Patient positioning

The repetitive treatment delivery facilitated by the complex movements of leaves, placement of physical intensity modulators etc are verified on the therapy unit by either Radiochromic film exposure or by Electronic Portal Imaging Devices (EPID). At the first session of any radiotherapy treatment, it must be verified that the patient has been positioned such that the isocenter of the treatment has been placed at the correct anatomical location. Then the positioning of the patient must be correct on the day to day basis⁶. The isocenter locations can be verified by comparing portal films with Digitally Reconstructed Radiographs (DRRs) from the CT imaging data. The other parameter that can be matched is the superposition of the field boundaries of multileaf collimators on the DRRs using computerized virtual simulation programme. Acquisition of cranial photographs using optical images from a stereo camera system is a very useful method for patients undergoing brain irradiation.

Gated Breath Hold Devices and IMRT

Despite the external immobilization and laser localization on fiducial markers on surface of the patients it is not possible to bring to a stop all the internal organ motion. Intra treatment cardiac, respiratory and bowel motion can compromise the daily reproducibility of the complex intensity modulated beams. The patient can participate in Active Breath Hold Procedures or the

software can be tailored to deliver radiation dose during either inspiration or expiration as programmed. The CT imaging for planning also need to be taken with the help of similar programmes. Active research is ongoing to study and target radiation synchronized to internal organ motion in resting state.

Clinical considerations

Anatomical sites where IMRT has been extensively used are cancers of the head and neck^{7,8}, and cancer of the prostate⁸, cervical cancer⁹, breast cancer¹⁰, paediatric tumours¹¹, colorectal and intrathoracic malignancies are the areas being explored where the surrounding tissues have been a dose limiting factors. Intra-abdominal malignant conditions especially carcinoma pancreas and retroperitoneal tumours can benefit with this modality as the low tolerances of small bowel, kidneys, liver and spinal cord do not permit conventional radiation to delivery adequate tumoricidal doses.

Radiation therapy is essentially a physical solution to what is a biological problem; it will never be the entire answer to the problem of cancer therapy. Yet it remains an important component of the answers. A local treatment is best assessed for efficacy by probabilities of local control. Intensity modulated radiotherapy is an important tool in treatment delivery as it can provide us the corollary for dose-escalation to tumour, keeping the normal tissue morbidity levels at the lower end.

Cost considerations

The above discussion does lead to a few outstanding observations that intensity modulated radiotherapy is an expensive proposition in terms of (a) space, hardware and software that is required (b) the time involved in preparation of plans and execution of treatment (c) the manpower available to carry out such planning and treatment (d) the expenditures that go along with all these resources. The finite gain in terms of higher cure rates versus lowered morbidity however is the goal to be achieved and the economic considerations will appear miniscule if healthcare gains are kept in mind.

Conclusions

Intensity modulated radiation treatment (IMRT) has evolved from the three dimensional conformal radiation system over the last one decade. It has the promise of a new born technology that if used judiciously and with caution can lead to delivery of tumoricidal doses to control loco-regional malignant tumours with low distant

(haematogenous) metastatic potential e.g. head and neck cancers, early prostate cancer, anal canal, uterine cervical cancer; malignant astrocytomas and medulloblastomas. The latter especially amongst the paediatric age group patients to prevent neurocognitive and growth retardation sequelae. The studies in the next decade will hopefully show the mature results of the introduction of this technology and the improvements in tumour control/reduction in normal tissue morbidity.

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Telemedicine in Radiation Oncology: Challenges and Opportunities

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Abstract: Telemedicine is an emerging technology and Radiotherapy and cancer care are areas which can utilize these in appropriate application. Telemedicine can provide services in all aspects of cancer control from prevention to palliation. Radiotherapy planning, verification and treatment execution are components which have employed telemedicine. OncoNET Kerala is a telemedicine application in Kerala which has helped to provide cancer patient follow up at peripheral centres and in providing cancer related information to the community.

Introduction

Cancer is emerging as a major public health problem in India. Cancers of epithelial origin predominate and Radiation therapy as a single modality or as part of multidisciplinary management is essential in the treatment of these neoplasms. Radiation oncology needs a certain level of infrastructure, trained personnel and continuous quality assurance, all of which are not available uniformly. Health services at remote and geographically hostile locations can be augmented by providing more personnel or by transporting patients from the location to centres with all the facilities both of which are time consuming and expensive

Telemedicine which is defined by the American Telemedicine Association, as "the use of medical information exchanged from one site to another via electronic communication for the health and education of the patient or health care provider and for the purposes of improving patient care" is a technical advancement linking information technology and health care and can have a large number of applications in oncology and in radiotherapy. Telemedicine, or telehealth, involves the remote management of disease. When medical practitioners apply information and telecommunication technologies, together with robotics and such advances as lasers, they become capable of dispensing clinical care hundreds or even thousands of miles away from medical centres. Medical personnel in a small rural hospital faced with a difficult clinical problem are able to consult specialists at the foremost medical facilities in the country or in the world, and to even conduct operations under the remote guidance of these specialists - all in real - time. For less complicated procedures, robots may assist in operations, while guided from afar. Clinical tests, such as x-rays and biopsies, can be transmitted to tertiary centres, analyzed, and transferred back within short periods of time.

The first documented use of visual communication in health care was in 1959. Information Technology has become a major component of Health Care in the 21st Century. By combining images, text and data, doctors and technicians can help their patients and each other without the impediments of geography or time. The major limitations for telemedicine applications are in the areas of infrastructure, human resources, hospital systems, referral practices and illiteracy. However, the scenario is improving with fast connectivity becoming a reality. The scope and applications of Telemedicine in Radiotherapy can be considered under the

following areas :-

- (a) *Information Dissemination*
- (b) *Tele-consultation*
- (c) *Tele-Radiation Oncology and following up of cancer patients*
- (d) *Palliative care*

(a) *Information Dissemination* : An interactive web-portal in English and in regional languages can be a major avenue for providing information about risk factors for cancer, management of risk factors, early detection of cancer, cancer treatment strategies and palliative care. An interactive website can also provide information on various queries raised by the public and by cancer patients. Continuing medical education is an area that can benefit from telemedicine as it can provide live case demonstrations in addition to tele-teaching by experts.

(b) *Teleconsultation* : Teleconsultation is one of the main areas of telemedicine applications in cancer in which an expert at a specialty centre can be consulted from a remote site. Unlike communication over the telephone, tele-consultation makes available medical records, results of investigations and other medical details to the consultant first hand so that the consultations can be made more meaningful and effective. Cancer treatment is a field, which needs multiple specialties to interact and more than one specialist can log on to the network at the same time. A multi-disciplinary consultation can be provided which would be the optimal approach in cancer.

Interpretation of investigations including cytology smears, pathology slides and pictures of imageological investigations may require a specialist's opinion. This can be provided through teleradiology and telepathology.

(c) *Application to Telemedicine in Radiotherapy* : In addition to the above applications, radiotherapy is an area where telemedicine has many applications. In essence, Radiotherapy involves determination of the tumour volume, radiation portals, radiation planning and execution of radiation treatment. Most data required in the planning process can be transferred and stored digitally. New standards for data transfer such as 'Digital Imaging and Communications in Medicine' (DICOM), and its radiotherapy extension (DICOM-RT) and HL7 have substantially improved image and data flow management. Inoue et al suggest that image quality with a 640x 400 matrix transmitted via a 64 kbps ISDN though insufficient for radiodiagnosis is probably sufficient for radiotherapy treatment planning¹.

Telemedicine facilitates decentralized treatment planning. Olsen and colleagues define three levels of telemedicine support. A Level I facility features video conferencing and display of radiotherapy images and dose plans. Level I support is extensively used in telemedicine in general and is restricted by its functional limitations to chart rounds and video-conferencing about treatment plans and options. Remote online operations are not supported. Level II facilitates replication of selected plans from the remote data base and its manipulation thereof. However real time operation is not feasible. Image segmentation and planning is usually performed at the tertiary site and the final treatment plan transferred to the peripheral clinic with basic radiotherapy facilities. A Level III facility supports real-time remote operation. The manipulation of 3D-images cannot be performed using conventional telecommunication lines, since flow of large amounts of data need to be managed. Both level II and level III establishments therefore, require an interactive radiotherapy database, both at the tertiary and peripheral institutions. The required segments of the database alone are transferred between the clinics. Verification-and-record (V&R) system is currently the protocol that is used for data transfer. More advanced applications would require a larger data handling system analogous to PACS in digital radiology. Both level II and level III systems are cost-prohibitive at the moment. There are also legal issues to be resolved².

Advance radiotherapy facilities are usually located at tertiary referral centres and university hospitals. Hashimoto S. et al have developed a remote teletherapy planning system, THERAPIST (Telecommunication-Helped Radiotherapy Planning and Information System)³. The system consists of a planning computer, a digital scanner, and a video camera at the peripheral clinic linked via ISDN to the tertiary university hospital and is used to exchange the patient's image data, teleconferencing in real-time, and transfer of dose calculations and distributions, and treatment planning images including portal images. This arrangement has also been tested on the ground - radiation oncologists at the university hospital were able to suggest dose schedules and verify treatment plans in 12 patients with malignant spinal cord compression who required emergency spinal cord decompression⁴. Image quality and transmission time, according to the authors was "satisfactory". A cost benefit is also suggested though a comparison of the actual figures has not been mentioned. Most significantly, the mean time between onset of symptoms and start of radiotherapy was reduced from 7.1 days to 0.8 days. The quality of such digitally compressed images using a human thoracic phantom has been verified; there was no clinically significant loss of data⁵. Investigators at the IGD-Fraunhofer Institute of Computer Graphics, Darmstadt in Germany have evolved a virtual radiotherapy treatment planning Simulation protocol designated EU-VIRTUOSO⁶. The treatment planning is carried out on a virtual patient using the CT data of the actual patient. The physician is supplied with different volume rendering and volume interaction techniques such as digital reconstruction radiographs (DRR), mixed integer programs (MIP), gradient surfaces, and isosurfaces to simulate the actual treatment planning workstation environment. Radiation oncologists working at different locations can collaborate to plan and/or validate a treatment plan on-line in real time.

On a similar scale and allowing for interactive educational sessions, is the Internet-based 3D Radiotherapy planning and Information

System (IRIS) which was developed at the Department of Medical Physics, German Cancer Centre, Heidelberg⁷. IRIS is a client-server system which incorporates an atlas of preoptimised treatment planning dose distributions, a hypertext oriented multimedia tutorial about the basic methods in radiotherapy, teleconferencing software (e.g. Microsoft Netmeeting), and a discussion forum for radiation oncologists.

On a smaller scale, within the hospital itself, Santos et al. suggests the use of the local area network (LAN) to facilitate image segmentation of magnetic resonance images by the physician on his personal computer (PC) and fusion with CT images at the treatment planning workstation without the physical presence of the radiation oncologist⁸.

A secure framework is required for tele-cooperation in virtual simulation procedures⁹. There exists a potential role for telemedicine in oncology as an educational tool for learning advanced planning techniques as exemplified by IRIS. The advantages include interactivity, flexible learning schedules, saving in terms of cost of transport cost and cost effective access to learning material¹⁰. Multidisciplinary clinics networking experts in various disciplines in the multimodality management of cancer can also be established to evaluate treatment decisions and form consensus. A French group, which has established just such a multidisciplinary clinic in digestive tract cancer, feels that such a system is cost-effective¹¹.

d) Palliative care : Pain management and palliative care in advanced cancer is a major load on Radiotherapy clinics and clinicians. Patients who need pain relief and palliative care can be looked after in their homes with minimum technical support locally and with technical advice from a cancer centre. This application is relevant to India as majority of the cancer patients who attend the cancer treatment centers are in an advanced stage and will need palliative care, which is currently being provided at the tertiary care level. Through telemedicine network, patients can be provided the necessary care at their homes or nearby medical facilities. Sensitization and training of the local health providers are needed and this can be achieved. Telemedicine will help to optimize the resources for providing good quality palliative care in cancer.

Onconet - Kerala

The Regional Cancer Centre Trivandrum is a tertiary referral cancer hospital catering to South India. Approximately ten thousand new patients are registered and undergo treatment here annually. The number of patients on follow-up is approximately one hundred thousand per year. These patients have to travel great distances, at great expense for regular follow-up examinations. Regional Cancer Centre has six peripheral centres with essential infrastructure at Kollam, Kochi, Palakkad, Kodungalloor, Kannur and Kozhencherry. Monthly follow-up clinics have been established at these centres. Cancer patients in nearby areas presently attend these centres for follow up. A high speed ISDN-based data network was established connecting Regional Cancer Centre (RCC), Trivandrum with these centres. This telemedicine programme, dubbed Onconet Kerala was developed in collaboration with Electronic Research and Development Corporation of India located in Trivandrum with the support of the Ministry of Information Technology. This system serves to provide telemedicine services

in cancer detection, patient follow up, and palliative treatment and thereby continuity of care at these nodal centres (Fig.1). Case records are securely available over the internet at these centres and using the linkage identification number of each patient, the relevant information can be retrieved. The remote clinics are provided with text, video and audio chat facilities. Patients therefore communicate with their doctors in real time over the net. Regional Cancer Centre can thus use its resources optimally and concentrate on quality treatment for those who need active treatment. Teleclinics have proved to be a boon for those patients on chemotherapy who need regular check on their blood counts and frequent advice on side effects. The software also provides facilities for registration of new patients and for preparation of patient records. The recent introduction of Very Small Aperture Connectivity (VSAT) linking all the peripheral centres to Regional Cancer Centre will translate into better network performance, faster connectivity, and reduced operational costs.

Telemedicine offers several advantages in the practice of oncology. The number of emergency visits to the hospital can be reduced. Unnecessary admissions can be avoided. At the same time, early intervention is facilitated. Routine follow-up visits by the patient can be limited to the peripheral clinic. Physician visits from the tertiary hospital to the rural/peripheral centres can be cut down. However, there are disadvantages too. Telemedicine might disrupt the traditional physician-patient relationship. Patient privacy is an area of concern when information is exchanged over the internet; network and software security protocols consistent with national and state legal requirements should be provided. Some patients need to feel the "healing touch" to the care-giver. Prescriptions given over the internet can be misunderstood.

The primary aim of telemedicine in oncology as in any other field of telemedicine is deliver high quality health care in those areas where it is not easily available. Level I applications based on an ISDN backbone can readily be established in underdeveloped areas, where it has been provided to be cost-effective. Level II support which includes video conferencing and remote image viewing is more technology-intensive. The establishment of level III clinics is even more technology driven as it demands real time image manipulation. The cost-effectiveness of level II and level III support needs to be established. Experience with these clinics

is limited.

Telemedicine offers various avenues, which can find useful applications in cancer treatment and control and in radiotherapy in particular. The various infrastructure constraints are being addressed as part of the Information Technology advances and it is for the Radiation Oncologists and other professionals to come out with appropriate applications and content for use of technology for the benefit of the society.

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Heavy Particle Beams and Their Clinical Application

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Abstract: The heavy particle beam therapies deployed in radiotherapy have physical and radiobiological characteristics which differ from those of conventional photon beams and which offer a number of theoretical advantages over photon beams. This review briefly describes the properties and indications for heavy particle beam therapy and analyses various clinical studies conducted in this field. The analysis indicates that for select tumours (uveal melanomas and base skull/spinal chordomas and chondrosarcomas) heavy particle beam produces greater loco-regional control and disease free survival. The clinical gains in other tumours in terms of probability of higher tumour control, survivals and/or the reduced probability of normal tissue complications are however, not completely known. There is a considerable way to go yet, before any definite conclusions on the scope of heavy particle beam therapy can be arrived at.

Key words : *Neutrons, Protons, Heavy Particles, Bragg-Peak.*

Introduction

Radiation oncology has been driven till now by technological innovations for scientific disciplines more than any other medical specialty. The innovation of particle beam radiotherapy is a good example of this rule with work initially performed using particle accelerators built for physics research purposes. The first clinical use of particle radiotherapy with neutrons was by R. Stone and J. Lawrence in late 1930s¹. Studies of fractionated particle therapy in cancer were initiated using cyclotron produced fast neutrons at the Lawrence Berkeley Laboratory (LBL) in 1970s. Later synchrotrons were developed to generate higher energy charged particles. The particle beams of main interest are neutrons, protons, negative pi mesons and ions (helium, neon, carbon, silicon).

Two main factors motivated the work in particle radiotherapy. One is better depth dose distribution and lateral localization of the radiation dose, which allows a better expression of conformal radiotherapy, the second is presumably more favorable radiobiological properties of high linear energy transfer (LET) radiation. Linear energy transfer is the energy transferred per unit length of track of radiation. High-LET radiation offers the following advantages: (1) it is better able to kill hypoxic cells because it is less dependent on "indirect" (free radical mediated) form of cell killing; (2) cells are less able to repair damage induced by high-linear energy transfer radiation; (3) there is less variation in radiosensitivity across the cell cycle, and thus the therapeutic effect of high-LET radiation is not dependent on cells redistributing themselves in more sensitive phases of cell cycle during the course of therapy². The majority of studies done with high-LET radiation have been performed with fast neutrons, which test the potential radiobiological advantages. Heavy charged particles like silicon, argon or neon nuclei offer both the radiobiological properties of high-LET radiation and the conformal, dose localization characteristics of proton and α -particle beams. However, owing to the expenses and complexities involved in producing the heavy charged particles therapy beams, clinical studies have been fairly limited. Pi-Meson beams are "hybrid" in that during their entry into tissues they behave as low-LET type radiation, while at the end of their track they are captured by a

nucleus, causing a fragmentation event that consists of mainly high-LET particles.

All charged particles have the physical dose planning advantage and unique properties of minimal scatter as the particulate beams pass through the tissue, and deposition of the ionizing energy at a precise depth (i.e., the Bragg Peak) depending on their energy and mass. Tissues deeper to the tumour can be spared in contrast to the x-ray/telecobalt (photons) beams which are gradually attenuated and always deliver some radiation dose to the tissues beyond the tumour. The theoretical *advantages* provided by particle beams can be exploited for clinical gains when the following conditions apply:

1. Conventional treatment modalities do not provide adequate local tumour control.
2. The likelihood of metastasis prior to radiotherapy is small to nonexistent.
3. There is evidence that local tumour response depends on the dose of radiation delivered.
4. Delivery of an adequate radiation dose to the tumor is limited by the proximity of vital radiosensitive tissues or structures.

An effort has been made here to briefly summarize the various particle beams and their application in treatment of cancer.

Neutron Beam Radiotherapy

There are two kinds of neutron beams, slow and fast neutrons. Neutrons are neutral and do not carry any charge on them. Fast neutron beams are generated by cyclotrons, usually of 40-70million electron volts energy so as to give at least as good tissue penetration as cobalt or 4-6million volts photon beams. Protons are accelerated to a beryllium target, resulting in a forward-transmitted neutron beam, (Fig-1) which is attenuated exponentially in tissues like the x-rays because neutrons like photons are uncharged. The use of neutrons following World War II was based squarely on the premise that the presence of hypoxic cells limits the curability of human tumours by x-ray therapy. A lower oxygen enhancement ratio of neutrons was thought to be beneficial for tumour control. However, at a later date, it was theorized that the potential advantages of neutrons are purely radiobiological: Cells which are radioresistant due to very slow proliferation (long G1 phase) are

less radioresistant to neutrons than to photons, to the fact that neutrons are high-LET radiation and thus have high relative biological effectiveness (RBE) of 2-3. An RBE of 2 means that a given dose of high-LET radiation is twice as damaging as the same physical dose of photons. The disadvantage of neutrons causing a relatively high proportion of late complications for given tumour effect can be overcome by restriction of the total dose or by giving total dose in shorter overall treatment times, such as in 4 weeks instead of 6-7 weeks.

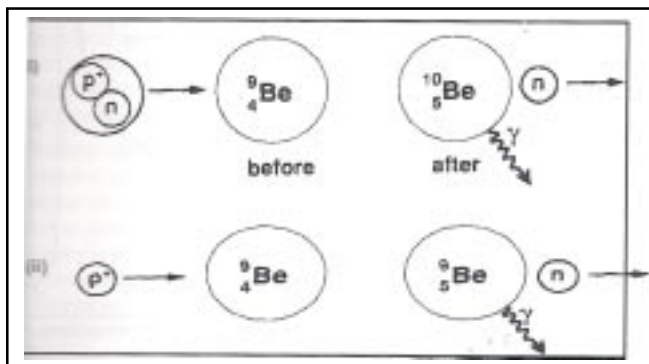


Fig.1: (i) The $d^+ - Be$ stripping process. Deuterons are accelerated to high energy in the cyclotron and are then made to impinge on a beryllium target. When incident on the target, the proton is "stripped" from the deuteron, leaving a neutron that retains part of the energy produced, on atom of beryllium is converted to boron. (ii) The $p^+ - Be$ process. Protons are accelerated to high energy in a cyclotron and made to impinge on a target of beryllium where they "knock out" neutrons.

Early Trials : Stone and co-workers¹ first tested fast neutron therapy clinically between 1938 and 1941 at Lawrence Berkeley Laboratory, California. About 240 patients, mostly with locally advanced tumours were selected for treatment. They reported that many advanced cancers had been successfully treated; especially cancers of salivary gland, prostate and secondary neck nodes, but late normal tissue complications were severe and common.

A re-evaluation of fast neutron therapy began in 1965 at Hammersmith Hospital, London where the first Medical Research Council (MRC) cyclotron unit was built. A prospective randomized clinical trial to compare neutrons with x-rays was started in 1971. Advanced head and neck cancers were treated because the available neutron beam could penetrate relatively superficial depths. The trial involved patients with tumours of the salivary glands, buccal mucosa, hypopharynx and larynx. The neutron treatments were delivered in only 12 fractions and were clearly superior to photons as judged by local control although there were higher complication rates³. In the following 30 years, about 30,000 patients have been treated with fast neutrons and only about 1000 of these have been recruited to randomized clinical trials.

The assessment of neutron beam therapy has also been difficult due to physical and technical limitations of the neutron generators used in early clinical trials. These limitations have included the unreliable performance or irregular availability of machines, poor penetrating power of neutron beams, low dose rates, fixed treatment heads and inadequate range of available field sizes. Another difficulty in evaluation of neutron therapy has been the different fractionation regimes used in the randomized treatment groups.

Clinical evaluation

Head and neck cancers : The study of neutron beam therapy has been mostly in head and neck cancers. There have been eight randomized

trials of head and neck cancers. Five trials have compared neutrons alone with standard photon irradiation^{3,6,7,8} while three have compared a combination of photon and neutron regimen with photons alone^{4,5,9}. In none of the eight randomized trials have neutrons been demonstrated to be superior to photons when the balance of local tumour control rates and incidence of late complications are taken into account. Megavoltage therapy is more efficacious than neutrons in the management of squamous cell carcinomas of head and neck.

Non-small cell lung cancer (NSCLC) : The results of first randomized trial of neutrons in patients of non-small cell lung cancer (NSCLC) were reported from Berlin-Buch in 1982¹⁰. In this study a total of 201 patients were randomized to receive either photons alone or a combination of photons and neutrons. The local control was significantly higher in the combined group (39%) than in the photon alone group (20%). No data were reported on the radiation morbidity rate. However, the mortality was significantly higher in the neutron treated group than in the photon treated group. Subsequently, two randomized trials compared neutron beam therapy alone with photon therapy alone in inoperable NSCLC. None of these two trials reported any advantage of neutrons in terms of local tumour control rate and survival rate over photons. Another randomized trial by radiation therapy oncology group on inoperable NSCLC cancer compared neutron therapy alone, combined neutrons and photons, and standard photon irradiation alone. In the final analysis of 102/113 patients the local tumour control rates were higher in patients treated with photons alone (44%) than in groups treated with neutrons (27%). The serious radiation related morbidity was significantly higher in the groups treated with neutrons (24%) than in the group treated with photons (5%). There was no difference in the survival rates in the three treatment groups.

The evidence from all these trials indicates that neutrons offer no significant advantage compared with photons in treating advanced inoperable lung cancers.

Prostate cancer : Two randomized trials of neutron therapy have been reported for inoperable prostate cancer. The first trial of radiation therapy oncology group 77-04¹¹ compared a combined schedule of neutrons plus photons (2 fractions neutrons and 3 fractions photons per week) with photons alone. Both regimens were given in 35 fractions over 7 weeks. Fifty-five patients were allocated in the combined group and 36 in the photon alone group. The overall survival (46% versus 29%) and cause specific survival rates (55% versus 43%) were significantly higher in the neutron treated group. The serious late radiation morbidity was similar in both the groups (13%).

The second trial by Russell et al¹² compared neutron therapy alone with standard photon therapy in 178 patients of inoperable prostate cancer. Neutron therapy was delivered in 12 fractions over 4 weeks (20.4 Gy) and photons in 35 fractions over 7 weeks (70Gy). The actuarial loco-regional control rates were 89% in neutron group and 68% in the photon group ($p=0.01$). The serious late radiation complications were significantly higher in the neutron treated group (24%) than in the photon group (8%). However, the overall and cause-specific mortality rates and distant failure rates were similar in the two groups. Improved loco-regional control and lack of serious treatment morbidity with use of multileaf collimator argues that fast neutron beam therapy is an acceptable form of treatment for prostate cancers. However, the superiority of fast neutrons alone in treating

inoperable prostate cancer still remains to be proven.

Bone and soft tissue sarcomas, malignant melanomas : No randomized clinical trials comparing neutrons and photons have been conducted so far for these tumours. However, these tumours are generally thought to be radioresistant and have many characteristics as being favorable for response to neutron radiotherapy. The comparative local control rates with neutron irradiation versus photon irradiation in patients with inoperable gross disease were 53% versus 38% for soft tissue sarcomas, 55% versus 21% for osteogenic sarcomas and 49% versus 33% for chondrosarcomas. Complication rates ranged between 7% and 29%¹³. At present it appears that a surgically based treatment regimen using adjuvant photon irradiation is the best approach to management of sarcomas, but neutron radiotherapy appears to be more effective than photon irradiation alone for those tumours in which a surgical resection is not an option.

Proton or Helium Ion Radiotherapy

Protons are of increasing interest in radiotherapy because of their advantage of good physical dose distribution and because the machines to accelerate them are smaller and cheaper than for the heavier nuclear particles. In the entrance plateau the average LET is about 0.5 KeV/mm rising to a theoretical maximum of 100 KeV/mm over a track. The dose deposited by a beam of monoenergetic protons increases slowly with depth but reaches a sharp maximum near the end of the particle's range in the Bragg peak (Fig.2). The beam has sharp edges, with little side scatter and the dose falls to zero after the Bragg peak, at the end of the particles range. The possibility of precisely confining the high-dose region to the tumour volume while minimizing the dose to surrounding normal tissues is the biggest advantage and attraction to the radiation oncologist.

The way in which the narrow Bragg peak can be spread out to encompass a tumour of realistic size is illustrated in fig. 3. In this figure curve-A shows the narrow Bragg peak of the primary beam of 160-MeV proton beam at Harvard cyclotron. Beams of lower intensity and shorter range, shown in curves B,C,D and E are obtained by passing through a rotating wheel with plastic sectors of varying thickness (filter). The composite curve S, which is the scan of individual peaks, results in a uniform dose over 2.8 cm. This figure shows the depth-dose curve for the 187-MeV proton beam from the synchrocyclotron from Uppsala, Sweden. The dose falls off laterally from 90 percent to 20 percent within a few millimeters.

The first clinical trials began in 1954 at Lawrence Berkeley Laboratory (LBL) where 30 patients were treated through 1957. In 1957 the LBL cyclotron was modified to produce a beam of helium ions, and 2054 patients were treated through 1991. The number of patients treated with proton beams exceeds 8500 in Boston (United States), 3000 in Moscow, and 5000 in Loma Linda, California (United States). Presently there are about 25 proton facilities operating throughout the world.

The use of proton or helium ion radiation therapy has been investigated in the following general categories of tumors/abnormalities :

1. Tumors located next to vital structures, such as *intracranial lesions* or lesions along the axial skeleton such that complete surgical excision or adequate doses of conventional radiation therapy are impossible. These tumors/lesions include uveal melanomas, chordomas, and chondrosarcomas at the base of the skull and along the

axial skeleton.

2. Primary therapy for *melanoma of the uveal tract* (iris, choroid, or ciliary body), with no evidence of metastasis or extrascleral extension, and with tumors up to 24mm in largest diameter and 14mm in height.

3. Tumors that are associated with a *high rate of local recurrence* despite maximal doses of conventional radiation therapy. The most common tumor in this group is advanced prostate cancer (i.e., T3 or

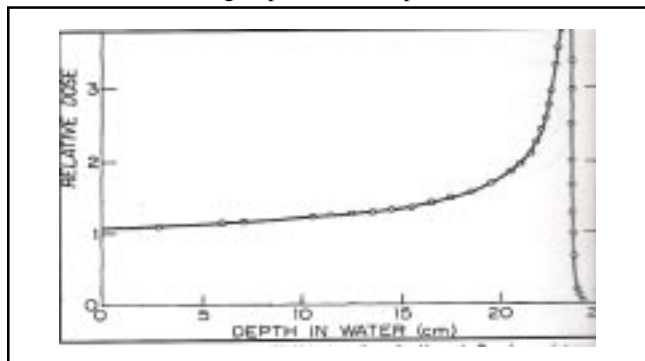


Fig.2: Depth-dose curve for 187-MeV protons from the Uppsala Synchrocyclotron. The dose reaches a sharp peak at a depth of about 23cm.

T4) without distant metastases. These patients are generally not candidates for surgical resection, however the 5- and 10 year local recurrence rate associated with conventional radiation are estimated at 24%-28% and 39%-42%, respectively.

Clinical evaluation

Uveal melanoma : The treatment of this tumour by protons or helium is now routinely used around the world, and is considered as treatment

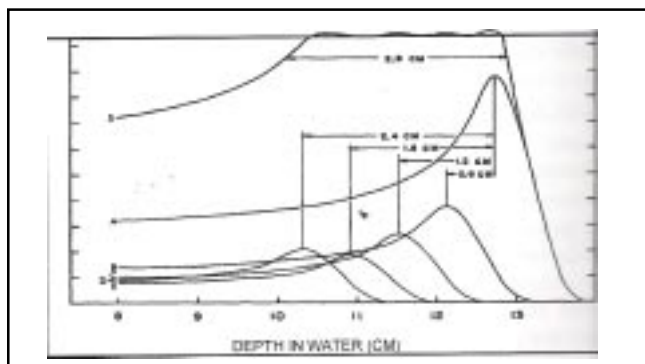


Fig.3: The way in which the Bragg peak for a proton beam can be spread out. Curve A is the depth-dose distribution for the primary beam of 160-MeV protons at the Harvard cyclotron, which has a half-width of only 0.6cm. Beams of lower intensity and shorter range, as illustrated by curves B,C,D, and E, can be added to give a composite curve S, which results in a uniform dose over 2.8 cm. The broadening of the peak is achieved by passing the beam through a rotating wheel with sectors of varying thickness.

of choice for many patients as an alternative to brachytherapy for small tumours located close to the optic disc or the macula and as an alternative to enucleation for large tumours. The rationale for preferring proton therapy to brachytherapy is that normal ocular structures receive the same dose as the tumour apex due to a homogenous dose distribution. With brachytherapy, however the structures located at the tumour base receive several times the dose delivered to the tumour apex. Also in proton therapy there is no exposure to the surgeon's hands as happens during fixation of episcleral plaques especially gamma rays emitting ⁶⁰Co applications. Patients are treated by focusing a pencil beam of radiation on to the precisely localized tumours by means of stereotactic beam direction techniques providing adequate local control while still preserving vision. Treatment is usually given in a smaller number of fractions (about 5) over 8 to 10 days. In a recent review¹⁴ 5 years

tumour control rate was 99% and a strong correlation was seen between local control rate and survival. Tumour related mortality was 27% for patients with locally controlled tumours and 53% for those with recurrent tumours.

Chordomas and chondrosarcoms : The available evidence suggests that proton or helium ion beams irradiation is superior to, conventional radiation or resection, as treatment for chordomas or chondrosarcomas of the skull base or cervical spine. High local control rates (70%) have been observed¹⁵. These excellent results have been obtained in treating carefully selected tumours, which have allowed complete sparing of the critical normal tissues. They therefore should be compared directly with historical series of photon therapy which often will have included large lesions for which the dose prescribed may have been greatly compromised by radiation tolerance of the central nervous system.

Prostate cancer : It is suggested, with some confidence, that the local control of prostate cancer may be greatly increased, without increasing normal tissue morbidity, by delivering higher doses of charged particles such as protons and helium ions to a well-circumscribed tumour volume. Shipley et al.¹⁶ have reported the results of one randomized trial of high dose radiotherapy using a proton therapy boost compared with conventional dose irradiation with mega-voltage photons. Two hundred two patients with locally advanced prostate cancer were recruited to this study. Patients first received 50.4 Gy photon therapy to the whole pelvis. They were then randomized to have either additional standard photon treatment of 16.8Gy or conformal proton therapy to a dose of 25.2 Gy (an increase of 12.5%). The local tumour control rates at 5 years were similar (about 86%) in the two treatment groups. However, the serious, late radiation-related complications were significantly higher in the group of patients who were given the high dose conformal proton therapy. In this study no significant differences were observed in overall or cause specific survival rates.

In 2000 Schulte and colleagues published 39 month outcomes in 911 patients with limited stage prostate cancer treated at Loma Linda University Medical Center¹⁷. Patients were treated with either protons alone or proton boost following standard external beam radiation therapy. The estimated 5-year outcomes of no biochemical evidence of disease were 82%. Actual long-term outcomes and survival are not included in the published report. In addition, new sophisticated treatment planning techniques referred to as conformal therapy and intensity modulated radiation therapy (IMRT), have permitted dose escalation of conventional radiation therapy to 80Gy, a dose higher than that achieved with proton therapy in the above study. There are currently no controlled clinical trials that have compared the outcomes of conformal photon beam therapy with that of proton beam radiotherapy.

Heavy Ion Beams

Heavy ions (heavier than protons) include helium, carbon, silicon, neon and argon beams. In comparison to photons, heavy charged particles such as protons or carbon ions provide a higher physical selectivity because of a finite range in tissue and in the case of carbon ions, biologic advantages such as an increased relative biologic effectiveness (RBE) in the Bragg peak region. These advantages lead to improved dose distributions, permitting a dose escalation within the tumour region and an optimal sparing of neighboring normal tissues. therefore, therapy with charged particles suggests a clinical gain in the treatment of non-radioresponsive tumours in critical locations that are rarely radiocurable with routine photon therapy. The experience in the treatment of chordomas and chondrosarcomas with heavily charged particles other than protons is limited. the results of RT with neon and helium ions at Lawrence Berkeley Laboratory (LBL), in Berkeley, California between 1977 and 1992 demonstrate the superiority of charged particles compared with photons in the management of these tumours. However, the advantages of particle therapy could not fully

be exploited because of passive beam delivery and the inability to achieve individual biologic plan optimization. Since August 1998, the irradiation of patients with chordomas and low-grade chondrosarcomas has been available within a clinical Phase I/II study at the heavy ion synchrotron schwerionensynchrotron (SIS) at Gesellschaft fur Schwerionenforschung mbH (GSI) in Darmstadt, Germany. Treatments are carried out within three beam time blocks of one month each year using carbon ions¹⁸.

Negative Pi-Mesons : In the 1960s, negative pi mesons appeared to be promising in radiotherapy. They have a mass equal to 230 electrons, which is about 1/8 of that of a proton. They traverse tissues depositing ionization at low linear energy transfer but at the end of their range they are captured into a nucleus, which then disintegrates ejecting several alpha particles, neutrons, or protons and a beryllium nucleus in the form of a 'star' of partly high-linear energy transfer radiation locally in the tumour. Pion therapy requires extremely large, complex and expensive beam generation and delivery systems. They are produced in a low yield by very high-energy proton beams, 600-800 MeV, and are therefore very expensive to produce. Three pion facilities were developed in 1970s, in Los Alamos, United States, in Vancouver, Canada, and in Villigen, Switzerland but none of them is now being used to produce pions.

About 1200 patients were recruited to clinical studies of pion therapy between 1974 and 1996, of whom only about 160 have been included in randomized trials. Two randomized studies at Vancouver comparing pions with photons in supratentorial astrocytomas and inoperable prostate cancers did not show any enhanced therapeutic benefit in terms of survival and morbidity with pions compared to photons^{19,20}.

Conclusions

Amongst the range of the charged particles, protons, helium and heavy ions that have been evaluated only protons appear to show continuing promise in radiotherapy. Their physical advantages are clear, and have shown important advantages in treating a number of selected, rather uncommon tumours. There is good evidence, although not conclusive, that protons are more effective than photons in treating chordomas and other tumours of the base of skull and upper cervical spine. Protons have an established role in treating choroidal melanomas and are considered to be the treatment of choice for many of these lesions. The clinical indications for proton therapy and highly sophisticated techniques employed must continue to be developed and evaluated. There is need for much more evidence from phase III randomized trials about the possible advantages of protons compared with the best conformal photon radiotherapy.

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IMSA News

IMSA Chapter Activities Jan.-March 2005

Tamil Nadu Chapter

- 9.1.2005 : Prof. G. Krishnamoorthy, "Consciousness"
 13.2.2005 : Dr. P. Venugopal, S. Menon, "Novel Thiozole Compound with Antioxidant Property and its role in Diabetes"
 13.3.2005 : Dr. A.r. Chandrasekaran, "Emerging Trends in Primary Health Care".

Delhi Chapter

- 8.1.2005 : Dr. A.P. Arora, Dr. V.K. Gujaral, "Acute Coronary Syndrome in Diabetics. Pitfalls & Precautions in Diabetics Management in cardiac patient." Venue: Seminar Hall, National Heart Institute.
 20.1.2005 : Dr. G. Kapur, "An Overview of Paediatric malignancies & their chemotherapy".
 : Dr. A. Saharia, "Organ preservations in paediatric tumours: surgical aspect".

: Dr. A.K. Anand, "Targeted radiotherapy - reducing late radiation morbidity in paediatric solid tumours".

12.2.2005 : Dr. A.K. Jhingan, "The diabetes is a vascular disease".

: Dr. (Prof.) S.K. Agarwal, "Diabetic Dyslipidemia".

22.2.2005 : Dr. Lt. Col. S.K. Malau, "Acute Myocardial Infarction".

: Dr. Col. K.K. Singh, "Seizures".

24.2.2005 : Dr. L.M. Prasher, "ENT today; What all possibilities are".

: Dr. Kapil Kochhar, "Incisional Hernia - Revisited".

12-3-2005 : Dr. Vinod Sharma, "Percutaneous Interventions in 21st century: controversies, the challenges and follow-up guidelines".

: Dr. O.P. Yadav, "CABG in diabetics; challenges & follow-up guideline".

15-3-2005 : Dr. Raghugaind (UK), "Care of Elders".

30-3-2005 : Dr. Col. D.P. Vats, "Cataract".

: Dr. Col. Rajal Kumar, "Approach to Care of Anaemia".

Election of Fellows/Members 25.2.2005

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 Dr. Sreeramadasu Ramaiah
 Dr. (Mrs.) Chrusheela Satishchandra Gaikwad
 Dr. Deepak Singhal
 Dr. C.R. Sundararajan
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HONOUR Dr. Mohsin Wali, Fellow of International Medical Sciences Academy has been elected as a Fellow of the American College of Cardiology on 1.2.2005. IMSA is proud to have him on its roll and congratulates him on this achievement. *President, BOT and CEC members and all the fellows and Members of IMSA.*

Announcement

IMSACON 2005 International Medical Sciences Academy is holding its annual meeting 'IMSACON 2005' at Jaipur (Rajasthan) on 22,23,24 Oct. 2005 at Rajputana Palace Sheraton Hotel, Jaipur. *Theme of the Conference is 'Emerging Health Challenges'.* **Dr. S. Panickker** is the **organising secretary**; his address is *Sanjevani Hospital & Diabetes Centre, F-58, Kalidas Marg, Bani Park, Jaipur-302016.*

All fellows and members are welcome to attend the conference with their spouses and accompanying persons. In case they intend to present paper in the scientific sessions of the conference, they may send abstract of their papers to the organising secretary (Jaipur) at the address given above with a copy to the secretary general IMSA at Headquarter.

IMSACON 2006 International Medical Sciences Academy will be holding its annual conference 'IMSACON 2006' at Lahore (Pakistan) on 3,4,5 November 2006 at 'Lahore Medical and Dental College'. *Theme of the conference is 'Update in Medical and Dental Sciences.'*

Role of Sonography in Ocular Disease

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Abstract: A prospective study was conducted to assess the role of sonography in ocular diagnosis. Thirty six (36) patients with suspected ocular disease were examined using non-dedicated ultrasound scanners by small part probe. Sonographic (US) findings were correlated with clinical course of disease, surgical or histopathological findings. Amongst 29 patients with opaque media, US diagnosis was correct in 27 and partially correct in 2 patients. In 7 patients with clear media, US diagnosis was correct in 6, partially correct in one patient, and gave additional information in 2 patients. It is concluded that ocular contact B-scan sonography is a simple, safe, inexpensive, and accurate procedure and can be used as the diagnostic method of choice in ocular lesions.

Key words : Sonography, ocular

Introduction

The spectrum of lesions that can occur in the eye and orbit is vast and complex¹. Advances in radiologic imaging in the past 20 yrs. have played an important role in practice of ophthalmology. Ultrasonography was first introduced as a diagnostic tool in the field of ophthalmology in the 1950s². In spite of this, most radiologists are unfamiliar with the anatomy of the eye as depicted sonographically, largely because ophthalmic sonography has principally been the domain of ophthalmologists³. Due to its superficial location and cystic nature, the globe is an ideal structure for examination by US⁴. The study was undertaken to assess the role of sonography in the diagnosis of ocular disease.

Material and Methods

The study was conducted in all inpatients and outpatients with suspected ocular lesions, referred by the Ophthalmology Department; a total of thirty six cases were examined.

Ultrasound scanning was done using a non dedicated Philips P 700/Esaoe Biomedica scanner with a small parts high frequency 7.5-10.0 MHZ linear array transducer. Scanning was done with the patient lying supine, when the pull of gravity is exerted in the direction of the optic axis. Procedure of scanning was explained to the patient in detail. The patient was instructed to close the eyelids throughout the examination. Both eyes were examined in all patients. The entire eye was scanned in both transaxial and longitudinal planes. In some cases, oblique scanning was used to avoid artifacts from a dense cataract. Gain settings were adjusted to increase near field amplification of echoes for the assessment of vitreous and then to decrease near-field amplification for evaluation of the retina. The eye was observed as its moved from side to side and up and down to identify membranous structures. The site, nature, echotexture and size/extent of the lesion were studied. Attempt was made to evaluate the optic nerve head. Patients with open globe injury were not taken up for ultrasonography. In case of ocular trauma or recent ocular surgery, care was taken that pressure is not applied to the globe, as it may come expulsion of intraocular contents from an occult ruptured globe. Sonographic findings were confirmed by clinical course, surgical findings, or histopathological results.

Results

A total of 36 patients with ocular lesions with age range from

newborn to 75 years equal male:female distribution were examined. Most common symptom was diminution of vision; common indication for US examination was posterior segment evaluation for opaque media. Amongst 36 patients' media was opaque in 29(80.5%) and clear in 7 patients (19.4%). Most common cause of opacity of media was vitreous haze in 21 patients, (58.3%), followed by cataract in 15 (41.6%); other causes were corneal opacity, anterior segment exudates or hyphema, and leucocoria; many patients had multiple causes for opacity of media. The most common abnormality in patients with vitreous haze was hemorrhage, present in 13 cases; abnormalities like retinal detachment, vitreous detachment, vitreous hemorrhage, and choroidal detachment were detected in 15 patients with cataract; these abnormalities were not suspected clinically. Retinal detachment was seen in 15 cases, partial in 2 cases, total in 10 cases, and was associated with ocular mass in 3 cases; intraocular foreign body was detected in 3 cases. US was able to make a correct diagnosis of ocular mass in 4 cases, i.e. retinoblastoma in 3 and choroidal mass in one case.

In 7 cases with clear media, ultrasound was done to confirm the clinical diagnosis and to detect any associated abnormality. US diagnosed total retinal detachment in 3 cases, partial in 2 cases, 1 case each of bilateral fundal coloboma and choroidal hemangioma.

In 29 cases with opaque media, US diagnosis was correct in 27 cases, and partially correct in 2 cases. In 7 cases with clear media, US diagnosis was correct in 6 partially correct in one case, and gave additional information in 2 cases (Table 1).

Discussion

Congenital Lesions :

Three (3) cases with congenital ocular lesions were diagnosed. One case of congenital cataract was seen. Normal lens appears as a linear echogenic structure; echoes being caused by the posterior capsule. Cataractous lens appears as an oval hyperechoic structure⁵. Increased anteroposterior diameter of eyeball was noted in a case of buphthalmos. A case of bilateral fundal coloboma was diagnosed (Fig.1 (a) & (b)). Coloboma is a condition resulting from incomplete closure of the fetal fissure. It may involve the lens, iris, chorioretina or optic disc. US shows a funnel shaped excavation⁵.

Status of the Vitreous (Table 2)

Vitreous hemorrhage : Most common abnormality seen in patients

Table 1 : comparison of us and final diagnosis.

S. No.		No. of Case3	%	US Diagnosis	No. of Cases	%	Final Diagnosis	No. of Cases	%
1.	Ocular Lesions								
	Opaque Media								
	i) Cataract	15	41.6	a) At. with total R.D. b) Cat. with V.H. c) Cat. with C.D. d) Cat with VH & RD e) Cat. with V. Membrances f) Cat. with PVD g) Congenital Cataract	6 2 2 1 1 1 1	16.6 5.5 5.5 2.8 2.8 2.8 2.8	a) Cat. with total R.D. b) Cat with V.H. c) Cat. with C.D. d) Cat. with VH & RD e) Cat. with V. Membrances f) Cat. with PVD g) Congenital Cataract	6 2 2 1 1 1 1	16.6 5.5 5.5 2.8 2.8 2.8 2.8
	ii) AC haze	2	5.5	a) V exudates b) Thick eyeball coats (Uveitis)	1 1	2.8 2.8	a) Endophthalmitis b) Uveitis	1 1	2.8 2.8
	iii) Corneal Opacity	3	8.3	a) PVD with VH b) V. exudates c) Buphthalmos	1 1 1	2.8 2.8 2.8	a) PVD with VH b) Endophthalmitis c) Buphthalmos	1 1 1	2.8 2.8 2.8
	iv) Vitreous haze	21	58.3	a) V.H. b) V.H. with R.D. c) V. exudates d) Phthisis bulbi e) VH with PVD f) V. membranes g) i) V.H. with FB vitreous ii) V.H. with FB chorioretina h) V.H. with scleral tear	5 1 5 1 3 3 2 1	13.9 2.8 13.9 2.8 8.3 8.3 5.5 2.8	a) V.H. b) V.H. with R.D. c) Endophthalmitis d) Phthisisbulbi e) VH with PVD f) V. membranes g) V.H. with FB chorioretina extending into vitreous h) V.H. with Scleral tear with # med.	5 1 5 1 3 3 3 1	13.9 2.8 13.9 2.8 8.3 8.3 8.3 2.8

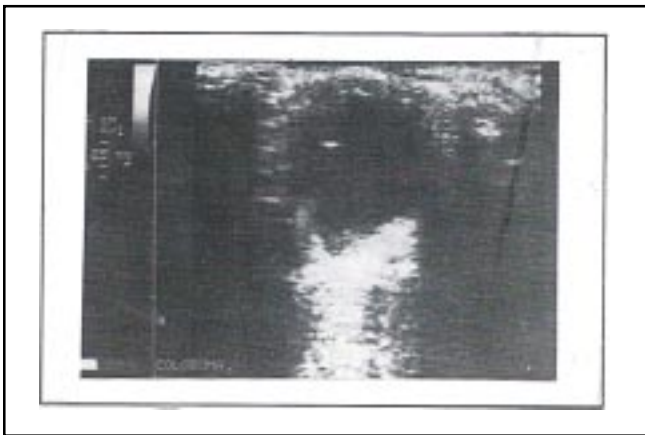


Fig. 1 Coloboma. US shows a funnel shaped depression in the fundus of both eyes.

Table 2 : Status of Vitreous.

Status of Vitreous	No.	(%)
Vitreous Hemorrhage	13	36.1
Vitreous Exudates	5	13.9
Vitreous Membranes	4	11.1
Intra-Vitreous foreign body	3	8.3
Intra-Vitreous Mass	3	8.3
Vitreous Detachment	4	11.1

with vitreous haze was hemorrhage, which was seen in thirteencases. Most common cause or hemorrhage in this study was trauma, present in 9 cases. A fresh vitreous hemorrhage is

completely dispersed throughout the vitreous gel and gives little or no echoes, because there are no acoustic interfaces between hemorrhage and vitreous⁶. Hemorrhage may get organized to form fibrous bands, indicating long standing hemorrhage. Such fibrous bands may mimic retinal detachment. However, membranes cannot be traced to optic nerve head and reducing the gain of ultrasound can eliminate its echoes⁷.

Vitreous exudates : Out of 21 cases of vitreous haze, 7 were due to inflammation. In 3 cases, exudates were organized and did not show any movement on dynamic scanning. In 4 cases, low level internal echoes were seen which showed movement on dynamic scanning and were indistinguishable from vitreous hemorrhage. Clinical correlation was required to make accurate diagnosis. Dacey et al⁸ studied 136 patients with infectious endophthalmitis; eye findings were associated with poor final vision; these were dense vitreous opacities, vitreous membranes, presence of retinal or choroid detachment and extent of retinal detachment.

Posterior vitreous detachment : This may be focal or extensive. The posterior hyaloid may separate completely from the posterior pole or it may remain attached to the optic disc. A posterior vitreous detachment is usually smooth and it may be thick especially posteriorly and inferiorly, when blood is layered along its surface⁹. The reflectivity of a posterior vitreous detachment can vary from extremely low, as in a normal eye to extremely high, as in dense hemorrhage⁵. Posterior vitreous detachment was seen as an undulating membrane, which showed considerable aftermovement on dynamic scanning and was not attached to the optic nerve head vitreous detachment is frequently accompanied by a partial ciliary body detachment. This event reduces aqueous production and tends to perpetuate the hypotonous condition¹¹.

Choroidal detachment is generally seen in the postoperative period following vitreous loss. It is classically seen on US as a dome shaped membrane not attached to the optic disc. When it progresses, both membranes may touch each other, producing the

classical 'kissing choroid' sign⁵. Three cases with choroidal detachment were diagnosed in the present study. It was seen as a biconvex echogenic membrane in the posterior segment, which was not attached to the optic nerve head and showed minimal to no movement on dynamic scanning. Suprachoroidal echoes suggestive of hemorrhage were seen as a cause of detachment (Fig. 2).

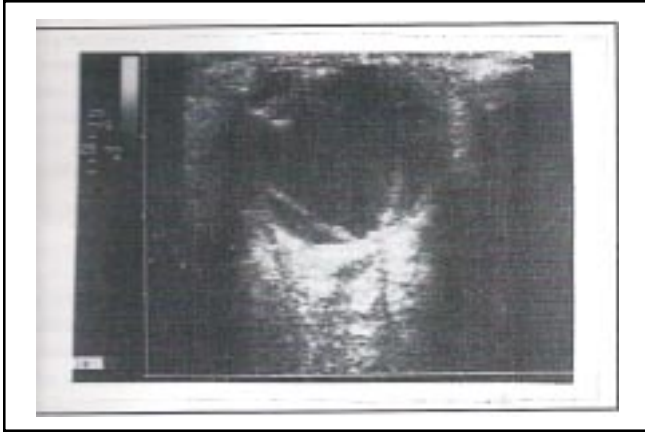


Fig. 2 Choroidal detachment with suprachoroidal hemorrhage. Biconvex membrane is seen in the posterior segment with echoes deep to it. No attachment to the optic nerve head is present. Blood-fluid level is also observed.

Intraocular foreign body : Intraocular foreign body was detected in three cases. The echographic findings for most metallic bodies are generally similar. They are irregular in shape and produce bright signal that persists at low gain settings⁵. Nicholas et al¹² examined the value of real time sonography and CT in evaluation of intra-ocular foreign body. They concluded that ultrasonography is superior to plain radiography in demonstration of intra-ocular foreign bodies including non-opaque foreign bodies. CT was, however, superior to ultrasound in demonstration or precise location and its relation to sclera and lens. However, resolution of intra-ocular structures and their damage was much more detailed on US. All 3 foreign bodies identified in our study were metallic and were seen on plain X-rays. On US, they appeared as high amplitude signals with distal acoustic shadowing, which persisted on reduced gain settings. However, accurate location of foreign body was correctly diagnosed only in two cases. Associated ocular damage was well depicted on US in the form of location and extent of vitreous hemorrhage.

Ocular mass : (4) cases of ocular mass were examined. Clinical presentation was leucocoria in one case, proptosis in 2 cases, and gradual loss of vision in one case. On US, a diagnosis of *retinoblastoma* was made in three cases. Retinoblastoma is the most common malignant intra-ocular tumor in childhood¹³. The common growth patterns are endophytic, exophytic and diffuse type. The spread occurs along the optic nerve with subarachnoid extension or choroidal invasion. Distant secondary deposits of bone marrow, liver and lymph nodes may be present⁵. Small tumors are smooth and dome shaped. However large tumors are highly irregular and heterogenous in texture. Usually, it comes out from one side or retina and fills the posterior segment. Calcification is a typical feature of retinoblastoma and is accompanied with acoustic shadowing¹⁴. In our study, retinoblastoma appeared as an irregular, heterogeneous mass arising from the retina and growing into the posterior segment. Calcification was observed

in 2 cases. US also excluded extraocular extension of mass into the retrobulbar space. US findings were confirmed on surgery.

One case was diagnosed as *choroidal hemangioma*. It appeared as a uniformly echogenic dome-shaped mass in the macular region. Associated serous retinal detachment was also observed (Fig.3). Choroidal hemangiomas are characteristically singular masses found at the posterior pole of the globe.

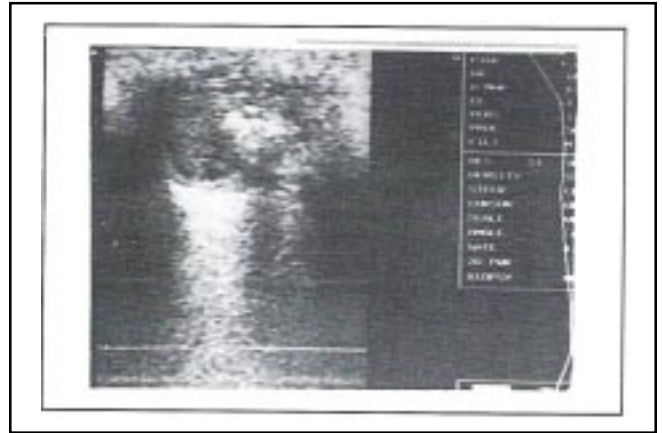


Fig.3 Choroidal hemangioma. US shows a uniformly hyperechoic dome shaped well defined mass in the macular region. Associated partial retinal detachment is observed.

Status of Retina and Choroid : (Table 3)

Retinal detachment : In 36 cases with ocular disease, retinal detachment was seen in 15 cases. Retinal detachment may also be classified according to the pathogenetic mechanism responsible. The most common form is *rhegmatogenous retinal detachment*, which occurs as the result of a full thickness retinal break. The second category, *tractional retinal detachment*, occurs when vitreoretinal adhesions mechanically pull the retina off the underlying retinal pigment epithelium. The third type of detachment involves a *combined rhegmatogenous and tractional mechanism*. A fourth category, *exudative (serous) retinal detachment*, is secondary to an associated process, such as a tumor or inflammation, which results in accumulation of subretinal fluid¹⁰.

Table 3 : Status of Retina and Choroid

Chorioretinal Status	No.	(%)
Total R.D.	5	13.9
Partial R.D.	2	5.5
R.D. with Ocular Mass	3	8.3
R.D. with Retinal Cysts	3	8.3
R.D. with Sub-Retinal Echoes	2	5.5
Choroidal Detachment	3	8.3
Thick Chorio-retinal Layers	3	8.3
FB Embedded in Chorio-retinal Layers	2	5.5
Not Visualized Adequately	2	5.5
Coloboma	2	5.5
Disrupted	1	2.8

In our study, total retinal detachment was seen in 7 cases which appeared as a uniform echogenic membrane extending from the optic nerve head to the ora serrata, taking a V or funnel shape (Fig.4). Long standing retinal detachment was seen a Y or closed funnel shaped membrane due to formation of adhesions between the opposing retinal layers (Fig.5). Degenerative retinal cysts

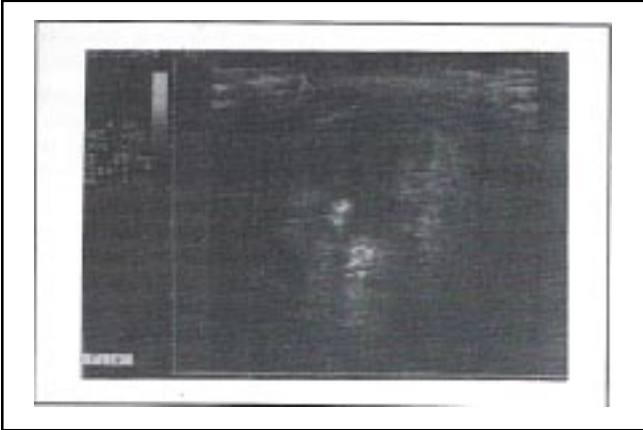


Fig. 4 Total retinal detachment. US shows an echogenic membrane attached to the optic nerve head and extending anteriorly till the ora serrata.

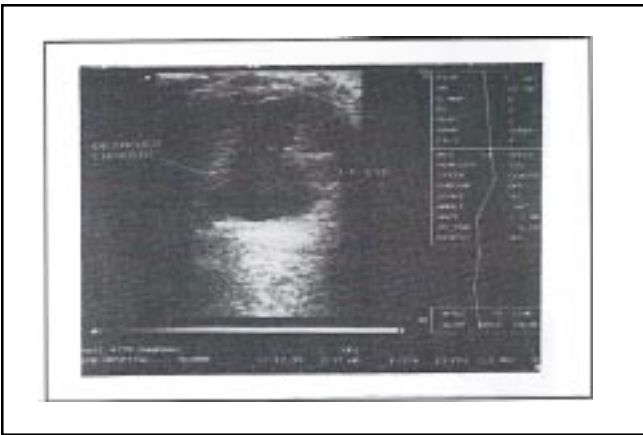


Fig. 5 Old retinal detachment is seen as a Y shaped membrane attached to the optic nerve head.

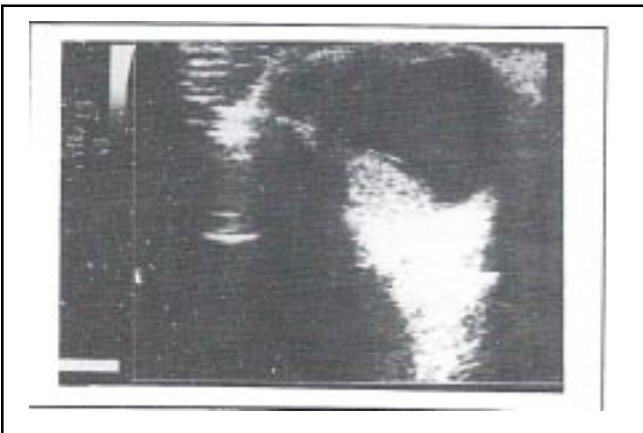


Fig. 6 Long standing retinal detachment with complete apposition of retinal leaves and degenerative retinal cysts.

were also seen three of the old detachments (Fig.6). In two cases, retinal detachment was associated with retinoblastoma.

Choroidal detachment : Choroidal detachment is caused by hypotony. Low intra-ocular pressure favours transudation from the blood vessels into the potential space between the choroid and sclera, which results in choroidal detachment. Choroidal secondary

changes include exudative, retinal detachment, cystic degeneration and pigment epithelial mottling of the overlying retina. A useful clinical sign is blanching of the lesion with pressure on the globe¹⁵.

Ocular lesions with clear media :

Out of 7 patients with clear media in our study, clinical diagnosis of retinal detachment was made in 6 cases by fundus examination. On sonography, 6 cases were found to have retinal detachment. Three had total detachment, 2 had partial detachment, while one case had partial retinal detachment with choroidal hemangioma. Clinical examination failed to detect subretinal pathology, i.e. subretinal hemorrhage in one case and subretinal mass in another.

Conclusion

Ultrasonography is quick, safe, non-invasive method of imaging the eye, especially when light conducting media is opaque, rendering ophthalmoscopy difficult. US is the only diagnostic tool that may be applied in preoperative evaluation of posterior segment in patients of cataract. In clear media, it provides supplementary information to that obtained by optical and clinical methods. An accuracy of 85% to 95% correct diagnosis is expected in ophthalmic sonography and the results in the above study are well within this range^{16,17}. It can be concluded that ultrasound is an ideal diagnostic modality for the diagnosis of ocular lesions.

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Spinal Neurenteric Cyst and Hydrosyringomyelia with Vertebral Anomalies in an infant

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Abstract: Spinal neurenteric cysts are rare intradural development lesions, usually composed of a thin walled cyst whose lining mimicks gastro-intestinal or respiratory epithelium: A3 months old baby presented with backward deviation of neck since birth along with scoliosis of spine. MRI revealed multiple vertebral anomalies along with hydrosyringomyelia and spinal neurenteric cyst. The case reported being submitted on the account of rarity of anomalies of these cysts with hydrosyringomyelia.

Introduction

Spinal neurenteric cysts are rare intradural developmental lesions, usually composed of a thin walled cyst whose lining mimicks gastro-intestinal or respiratory epithelium. Older age and cervical location are found to be statistically characteristic of solitary cysts in contrast to younger age and lumbo-sacral location for dysraphic cases (1). Association of these cysts with hydrosyringomyelia has not been reported. We report a case of spinal neurenteric cyst and hydrosyringomyelia with multiple vertebral anomalies.

Case Report

A 3 month old male baby born to non consanguineous parents was brought with history of fever for 15 days, cough and nasal discharge for 12 days. There was history of backward deviation of neck since birth. There was history of drug intake antenatally for a male baby. The exact nature of the drug was not known. Baby was 6th in birth order. Two elder siblings were females. There was history of death of two elder female siblings at the age of 1 and 2 yrs due to pneumonia. Developmental history was normal.

On examination weight was 3.3 kg, length was 53cms and head circumference was 39cms. Vitals were stable. Anterior fontanella was 1x1cms and was at level. There was a bulge on right side of chest. Scoliosis of spine towards right side was present. Examination of chest revealed bilateral vesicular breathing with crepitations on back on right side. Cardiac and central nervous system were

normal. Liver was palpable by 3.5cm below right costal margin and span was 5cms. Rest of abdominal examination was normal. On investigations haemoglobin was 10gm%, TLC 16000/mm³ with polymorphs 51%, lymphocytes 37%, monocytes 3%, eosinophils 3% and band cells 6%. Blood culture showed no growth of pyogenic organisms. CSF examination was normal. X-ray chest showed kyphotic deformity towards right along with vertebral anomalies in upper thoracic region. MRI of spine showed scoliosis of cervico-dorsal spine along with multiple vertebral anomalies with fused block vertebrae, hemivertebrae and butterfly vertebrae. Spinal cord showed hydrosyringomyelia at two levels cervico-dorsal and lower-dorsal. Dural ectasia was also present (Fig.2). A posterior mediastinal mass was also seen. It was well define and hyperintense on T2 weighted images and hypointense on T1 weighted images with internal separations. The mass extended caudally till D10 (Fig.2). It was spinal neurenteric cyst in the thoracic spine. Patient was diagnosed as a case of pneumonia with spino-vertebral anomalies. Treatment in the form of I/V fluid, oxygen inhalation, inj. Ceftriaxone 100mg/kg per day in divided doses I/V and inj. Vit. K 2mg I/M OD was given. Patient responded to the treatment.

Discussion

Neurenteric cysts are rare congenital lesions of spine and are lined with endodermal epithelium. They result from anomalous endodermal-neuroectodermal adhesion in the 3rd week of embryonic life with persistence of canal of Kovalevsky. The most common location is cervico-dorsal region and usually lie ventral to spinal cord². A detailed review of literature revealed 80 cases of solitary spinal neurenteric cysts which were analysed and compared regarding clinical and pathological aspects with 56 such cases of those with concomitant evidence of dysraphism. Older age and cervical location are found to be statistically characteristic of solitary cysts in contrast to younger age and lumbo-sacral location for dysraphic cases, magnetic resonance imaging is the diagnostic modality of choice¹. A definite diagnosis can only be made by biopsy and histological examination³. Solitary cyst are mainly composed by endodermal derivatives while dysraphic cases also have mesenchymal and ectodermal elements indicating an earlier area in development¹. Therapy of choice is complete resection⁴.

Associated vertebral anomalies, scoliosis, hemivertebrae and anterior spina bifida⁵ gut cysts, bowel duplication, the presence of keratin markers and mucin secreting cuboidal or columnar intestinal

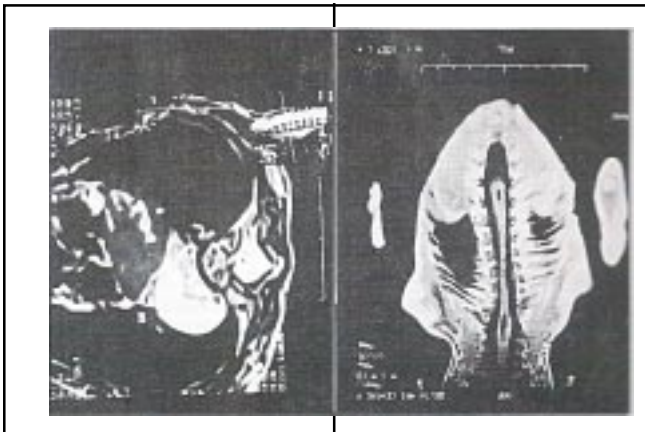


Fig.1: MRI showing hydrosyriago myelia at cervieu dorsal and lower dorsal region. Fig.2: MRI showing spinal neuro enteric cyst.

epithelium in their walls confirm their endodermal region².

In our case neurenteric cyst was present in thoracic region. It was associated with multiple vertebral anomalies and hydrosyringomyelia.

Syringomyelia is a cystic cavity within the spinal cord that may communicate with the CSF pathways or remain localised and non-communicating⁶. It is associated with congenital malformations as well as trauma and tumours⁷. Incidence of scoliosis with syringomyelia has been found to vary from 4% to 20%^{8,9}. In one series, it was 18.4% in boys and 2.6% in girls⁸. Scoliosis develops in children as a result of damage done to the anterior horn which innervates the muscles of trunk by an asymmetrically expanded syrinx¹⁰. Absent superficial abdominal reflexes in patients with scoliosis is an indication for investigations for underlying syringomyelia. Patients with thoracic curves are generally asymptomatic. Their neurological signs are subtle. Patients with thoracolumbar curves have neurological signs¹¹. Spontaneous shrinkage of syringomyelia in children is not unusual and is associated with improvement in tonsillar herniation, scoliosis and the neurological deficit¹².

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Recent Advances in the Management of Alzheimer's Disease

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Abstract: Alzheimer disease is the most common cause of dementia and contests closely stroke as 4th leading cause of death in developed world. Fortunately, the scale of the problem in India is not as big as of now; but it is likely to grow substantially in the time to come due to the presence of rapidly ageing population in India. The cause of this dementing illness has however remained elusive. Most important hypothesis hovers around the ill effects of beta-amyloid. Myriads of other hypotheses have also been proposed; the latest one is that it may be a disease caused by endothelial dysfunction. Before the development of anticholinesterases, the treatment was non-specific enhancement of cognition with the help of nootropics. Now over half a dozen such drugs are available. They are given with the notion of correcting defective or deficient transmission of acetylcholine. Tacrine is not favored now because of its hepatotoxicity and availability of safer alternatives such as donepezil, matrifonate, and rivastigmine. Some clinical trials have shown that the incidence of gastrointestinal side effects with donepezil are less than rivastigmine. Because of this reason, and the fact that it needs to be taken once daily; it is favored drug now. Some studies are underway to explore the disease modifying or their potential to slow neurodegeneration. Preventive strategies such as NSAIDs, estrogens or statins need to be evaluated further before they can be recommended for mass usage. Vaccine development has suffered a setback due to failure of the maiden clinical trial.

Introduction

Alzheimer's disease (AD) is characterized by progressive loss of memory and cognitive functions¹. The disease affects 10% of the world population. The incidence increases with increasing age steadily from 0.5% after the age of 65 to 8% after 85 years. It is most common cause of dementia and is already a major public health problem in the industrialized countries. Although the incidence and prevalence according to Indian studies has been low; but this can have a devastating influence on the developing countries. This is because according to a World Health Organization projection by the year 2020; approximately 70% of the ageing population will be in developing countries like India, which will account for 14.2% of this number². This simply means that every 7th elderly will be an Indian. This would then impose strains on already thin resources to manage problems related to aging in India.

At present, the disorder afflicts approximately 5 million people in the United States and more than 30 million people worldwide. A larger number of individuals have lesser levels of cognitive impairment, which frequently evolve into a full-blown dementia, thereby increasing the number of affected persons. This disorder is a major public health problem when looked at from the economic perspective. In fact, the cost of caring for patients with AD was over \$ 110 billion per year in the early 1990s in the United States, and the average yearly cost per patient is about \$ 45,000³.

What causes Alzheimer's disease?

Despite the publication of a large number of case control studies about the risk factors of AD over the last decade; our current knowledge of the risk factors is quite limited. Of the some putative 20 risk factors for AD, only advanced age, Down syndrome, and history of dementia in first-degree relatives have

consistently been associated with AD³. Myriads of hypothesis have been proposed; reflecting the uncertainty about its causation. Leading hypothesis are summarized below :

a) *Is Alzheimer a result of exaggerated ageing?* It should be appreciated that many of the changes encountered in Alzheimer's disease are also seen in ageing brain⁴. This had led to the speculation that AD may represent one end of the spectrum of ageing changes. Neuron loss is a feature of normal ageing. It is calculated that after the age of 30 years, all of us lose about 100,000 neurons on daily basis. By the age of 85 years, it translates into loss of 31% neurons in hippocampus (the site where normally neuron loss is marked), and 52% in subiculum. In addition to this, deposition of pigments, formation of plaques, vacuoles, and intracellular inclusion bodies also occurs⁵. These changes are mostly non-specific and indicate degeneration of nervous system, which can also be a manifestation of Alzheimer's disease and other dementias⁶.

b) *Deposition of beta-amyloid causative?* AD is the most common and important degenerative disease of the brain characterized by severe degrees of diffuse cerebral atrophy that evolves over a few years and is invariably associated with dementia⁷. The earliest change is degenerated neuronal processes having degenerated clusters of mitochondria, large number of lysosomal bodies and PHF. Amyloid is a 4 KD beta A4 protein derived by proteolysis of larger amyloid precursor protein (APP). Polyclonal and monoclonal antibodies raised against synthetic peptides of different segments of BA4 are a very sensitive marker for plaque as well as vessel amyloid. There is some evidence that this abnormal amyloid is neurotoxic. Amyloid deposition occurs in meningeal and parenchymal vessels leading to ischaemic damage. They stain with Congo red and give greenish yellow birefringence on polarized microscopy. The anatomic pathology of AD includes cerebrocortical atrophy (predominantly at the expense of association

regions), neurofibrillary tangles (NFTs) and senile plaques (SPs) at the microscopic level; accepted now universally as a hallmark of the disease. Note that while these lesions are characteristic of AD, they are not pathognomonic of the condition⁴. In fact, numerous other neurodegenerative conditions that are distinct from AD are characterized by NFTs (eg, progressive supranuclear palsy, dementia pugilistica, sabacute sclerosing panencephalitis, Nieman's Pick disease, Pick's disease, Parkinson-Dementia complex of Guam, post encephalitis Parkinson's myotonic dystrophy) or SPs (eg, normal aging), indicating that the mere presence of these lesions is not sufficient to make a diagnosis of AD. In addition to NFTs and SPs, many other lesions of AD have been recognized since Alzheimer's original papers. These include the granulovacuolar degeneration of Shimkowitz, the neuropil threads of Braak et al, and both neuronal loss and synaptic degeneration that are thought to ultimately mediate the cognitive and behavioral manifestations of the disorder⁵. A recent Indian study by Shanker et al observed NFTs in 14 out of 42 cases, the frequency increasing with advanced age, whereas in his early study on 10 brains above the age of 50 he did not find NFTs⁶. NFTs consist of dense bundles of long branching filaments called paired helices filaments (PHF) which measures 20 micron across with regular constriction of 10 nm occurring at every 80 nm interval. Tau, a microtubule associated protein having abnormal phosphorylation of six isomers is the major component of PHF. Normally, tau protein functions to stabilize the microtubules for rapid axonal transport. Other component of PHF is ubiquitin, a 76 amino acid polypeptide involved in non-lysosomal ATP dependent degradation of intracellular proteins.

c) Defective genes are the key? Substantial progress has been made in last few years in developing the tools to study the molecular genetics of disease. These have shown that there are four genetic loci that contributes to the etiology and pathogenesis of the disease. These include APP, APO E, presenilin 1 and presenilin 2 genes. Whereas APO E gene is a risk factor for late onset (> 60 years), other three genes are responsible for early onset (<60 years) AD⁶. In addition, mutations in alpha-2 macroglobulin have also been identified. These mutant gene products cause dysfunction/death of vulnerable population of neurons important for memory, higher cognitive functions and behavior. Several gene based therapies such as inhibitors of amyloid production, fibrillary plaques, immunization, antioxidants and free radical scavengers, and gene therapy are on horizon.

d) Is AD a neuroinflammatory disease of brain? There is evidence that inflammation may an important mechanism of neuronal death in AD⁷. World over, this hypothesis has become major focus of attention. In post mortem specimens of cases with AD activated inflammatory cells secreting mediators of inflammation have been found. Use of Non-steroidal drugs has been associated with the decreased incidence of AD⁸.

e) Estrogen deficiency plays a role?? It seems that estrogens play an important role in keeping the neurons healthy. Direct stimulation of cholinergic neuron is a characteristic feature of estrogens¹⁰. Therefore, their deficiency increases the risk of AD and reverse is also true i.e. prophylactic administration reduces the risk¹¹. Other mechanisms by which estrogens might be useful in

keeping the brain neurons functional are; stimulation of development of gliocytes, scavenging of free radicals, down regulation of amyloid beta-proteins and a decrease in excitotoxicity.

f) Latest hypothesis-is AD a vascular disease? It has been proposed that the neuronal damage occurring in AD may at least partly be due to overgrowth of capillary endothelium¹². The endothelium gets damaged by the deposition of beta-amyloid, which then leads to hypoxic damage to neurons.

Diagnosing a case of Alzheimer's disease^{5,13,14,15}

Ever since Dr. Alois Alzheimer diagnosed a case of 51-year-old woman with progressive dementia, he reported a wide range of symptoms. The disease is characterized clinically by prominent impairments in cognition and is often accompanied by neuropsychiatric behavioral disturbances in the face of an otherwise bland elementary neurological examination. Clinical criteria for its diagnosis (DSM-4, ICD-10 & NIH-National Institutes of Health-Alzheimer's Disease and Related Disorders Association-ADRDA) include onset between ages 40 and 90 years, progressive dementia as defined by prominent memory loss plus impairment in at least one other cognitive domain such as language or praxis sufficiently severe to impair social and occupational function; no disturbance of consciousness and absence of other brain and systemic diseases that can cause dementia.

Dementia of AD starts as benign forgetfulness in elderly thus making the early diagnosis difficult. This is because it can easily be mistaken as benign forgetfulness of senescence. It typically begins with gradual onset of amnesia with most prominent early deficit being impairment of explicit memory for recent events, misplacement of objects, and repetitive questions, even though patients themselves may be unaware of the problem (anosognosia). Word finding difficulty (anomia) is the next common manifestation. Over a period of several years, cognitive problems start interfering with daily life of the patient. The problems vary considerably from patient to patient, ranging from complete unawareness of considerable insight resulting in frustration and anxiety in middle stages. Patient gets easily confused and is unable to work except under close supervision. Clinician with appropriate training and expertise can diagnose 85-90% cases with AD.

Though generally considered to be the disease of old age, it has been described at almost all ages of adulthood. Increasing age is in fact the most important risk factor for the development of Alzheimer disease. Majority of the clinically diagnosed cases are in their 60s or are older. Only about 5% patients in whom Alzheimer's disease develops are younger than age 60 at onset (early-onset Alzheimer's disease). In these patients, autosomal dominant inheritance is often involved. Three genetic defects are known to cause early-onset Alzheimer's disease in families. The only well-established genetic risk factor is the 4-allele apolipoprotein E gene (APOE-4) on chromosome 19.

The onset of mental changes is usually insidious and gradual development of forgetfulness is the major symptoms. There is difficulty in remembering small day-to-day happenings; seldom or uncommonly used names and appointments. Some degree of memory loss; the hallmark of a case with AD extends to all decades of life-its establishment heralds the onset of other

abnormalities like halting speech, interrupted writing, restricted vocabulary, stereotyped and inflexible expressive language. Difficulty in calculation, defective visuospatial orientation and difficulty in locomotion becomes increasingly apparent. Later, there is echolalia, acalculia, anomia, aphasia, ideational and ideomotor apraxia. Social graces are retained in the initial phases of illness but troublesome alterations gradually appear in this sphere reflecting in imprudent business deals, restless and agitation, inertia and placidity, personal neglect, anxiety and phobias and disturbances in the normal circadian rhythm. Ultimately, the patient is left a mute, rigid, bedridden state requiring complete care.

A number of other severe psychiatric abnormalities manifest like poorly organized paranoid delusional state (with or without hallucinations), suspiciousness, sexual disinhibitions, egocentricity, and indifference with coarsened affect. Later on primitive reflexes also appear like grasping and sucking reflex. Sphincter continence fails and the patient sinks into a state of akinesia and mutism. The symptomatic course of this illness usually extends over a period of 5 or more years and a lengthy preclinical period (7 years or more) of stepwise decline in memory and attention span precedes the clinical diagnosis. Eventually, the patient is in a bedfast state and intercurrent infection such as aspiration pneumonia or some other disease terminates life.

Pharmacological Management of a case with AD^{16,17,18,19,20}

Available pharmacological therapies for AD are symptomatic in nature and are aimed at ameliorating the cognitive and neuropsychiatric impairments without affecting the cause of the disease¹⁶. The mainstay of the treatment; the anticholinesterases are based upon the rationale that cognitive dysfunction in AD are caused at least in part of cholinergic dysfunction¹⁷. Treatment options attempt to relieve behavioral symptoms associated with dementia, including depression, agitation, and psychosis, relieve cognitive dysfunction to improve memory, language praxis, attention, and orientation, slow the rate of illness progression, thereby preserving quality of life and independence, and delay the time of onset of illness. The first two comprise the most important from clinical standpoint. The Treatment can broadly be divided into five types: supportive, specific, preventive, non-specific and educational.

The behavioral complications of the disorder can be responsive to a variety of medications, and increasing evidence has mounted to guide specific therapy. This is important for two reasons because firstly they are present in large number of patients; secondly, they are often the cause of distress in the caregivers.

Supportive treatments : Relieving the behavioral symptoms associated with Alzheimer's disease is an important goal¹⁹, since the lifetime risk of such symptoms in the patient with dementia approaches 90%. Behavioral manifestations of dementia include agitation, psychosis, depressive features, anxious features, apathy, and disturbances in sleep and appetite. In most patients, some or all of these manifestations may be amenable to treatment with safe psychotropic medications, including antipsychotics, antidepressants, and anticonvulsants.

Antidepressants : Depression syndrome of AD exacerbates and produces distress in both patients and caregivers. Amelioration of mood disturbances can bring about rapid symptomatic improvements. Selective serotonin reuptake inhibitors (SSRIs) have fewer side effects than tricyclic antidepressants. Therefore these agents are the treatment of choice for patients who are clinically depressed. Citalopram, sertraline, fluoxetine and fluoxetine can be used. If patient fails to respond to SSRI, the treatment with tricyclic agent with fewer anticholinergic side effects such as protriptyline, nortriptyline or desipramine can be used. Agents with dual mechanism of action such as venlafaxine can also be used.

Antipsychotic agents : Patients with AD who exhibit psychotic features should be treated with antipsychotic medications. The preferred drugs include, clozapine, olanzapine, risperidone, quetiapine. These are preferred due to their fewer propensities to cause extrapyramidal symptoms. Mood stabilizers such as lithium, carbamazepine or valproic acid are increasingly being used to reduce daytime agitation in AD. Carbamazepine has been reported to cause fewer side effects than other agents used for this purpose. Agitation can also be reduced with benzodiazepines such as temazepam or non-benzodiazepine sedative hypnotic named zolpidem.

Anxiolytics : Benzodiazepines are generally avoided in patients with AD because they can cause confusion and can aggravate the cognitive dysfunction. However, when needed, these should be used in low doses¹⁷. Patients with frequent episodes respond to single doses of oxazepam or lorazepam. These are safer in elderly because they have less tendency to accumulate and are not toxic to liver. This is because they are well metabolized in elderly. For patients requiring the long-term administration of anxiolytics; buspirone, an azapirone derivative may be an attractive option. In some cases, treatment with propranolol may be beneficial.

Sedative hypnotics : Sleep abnormalities are common in AD and disturb caregivers and patients alike. Sedative hypnotics may aid in sleep and provide sleep maintenance. Agents include trazodone, zolpidem and temazepam. Longer acting benzodiazepines such as diazepam or barbiturates such as phenobarbitone should be avoided.

Specific Treatment

The most successful therapeutic approach of AD has been based upon aiming improvement in cholinergic transmission²⁰. Mounting evidence indicates that central cholinergic dysfunction is an early and prominent feature of Alzheimer's disease. The primary implication of the "cholinergic hypothesis" is that potentiation of central cholinergic function should improve the cognitive, and perhaps even the behavioral, manifestations of Alzheimer's disease. The search for the specific treatment has been elusive until the synthesis of tacrine (tetraaminohydroquinoline). This was the first drug approved by US FDA in the treatment of dementia. The efficacy of this agent has extensively been studied and documented. Several other cholinesterase inhibitors are either available or nearing the end of clinical trials since the arrival of this agent. It is however only infrequently used and is not available in USA due to its hepatotoxicity and availability of safer agents. Donepezil hydrochloride, a piperidine derivative, the first second

generation cholinesterase inhibitor to be approved by the most widely used agent now a days²⁰. Improvement in cognitive functions often occurs when the drugs is used in single doses of 5-10mg. It needs to be given once daily as opposed to four times daily administration with tacrine. Some clinical trials have suggested that incidence of gastrointestinal side effects like nausea and diarrhoea are greater with galantamine and rivastigmine. Rivastigmine is available in twice-daily doses and has similar efficacy. Galantamine is unique in that it is an allosteric modulator of nicotine receptors. However all of these drugs result in modest improvements in memory and other cognitive functions in the short term. Recent laboratory (and quite unexpectedly) and clinical evidence suggests that they might also have disease-modifying effects. These drugs reduce the neuropsychiatric manifestations such as apathy and visual hallucinations. The major effect of anticholinesterases which remains to be confirmed their ability to slow the progression of disease. So far, only high dose of Vitamin C has been shown to have this effect. Numerous other agents such as acetylcholine precursor (in attempt to boost synthesis of deficient neurotransmitter), direct acting agonists or receptor stimulants (e.g. areocholine), antioxidants, nootropics, hormone replacement therapy, and cerebral vasodilators have been used with little or no success. the existing treatments are summarized in table-1. Before initiating cholinesterase inhibitor therapy, patients should be thoroughly assessed, and the diagnosis confirmed, preferably by a specialist. Compliance with cholinesterase inhibitor therapy should be monitored and the response (in global, cognitive, functional and behavioural domains) reassessed after 2-3 months of treatment.

Acetylcholine precursors such as choline and phosphatidylcholine (lecithin) have been used in an attempt to augment acetylcholine synthesis, analogous to the use of a dopamine precursor in Parkinson's disease. Numerous trials, however, have generally yielded negative results. Small but reliable improvement in memory performance has been found after administration of physostigmine salicylate, although individualized dosing appeared to be necessary to optimize this effect. Short duration of action and a high rate of cholinergic side effects (nausea, vomiting, diarrhea, flushing, sweating, bradycardia) are among the limitations of physostigmine. A sustained-release formulation is being developed. There is evidence that long-term administration of physostigmine retards deterioration in cognitive function over time even in patients who fail to improve with short-term administration. Cholinergic receptor agents: The rationale for the use of direct cholinergic agonists rests on the facts that postsynaptic muscarinic (m1) cholinergic receptors are relatively intact in Alzheimer's disease and that presynaptic m2 receptors, which are decreased in Alzheimer's patients, regulate acetylcholine release. Although past trials of muscarinic cholinergic agents showed them to be minimally efficacious and to cause substantial side effects, newer agents now under development are expected to produce fewer toxic effects and to have greater affinity for the m1 and m2 receptors.

Tacrine

It is a centrally active, reversible, nonspecific cholinesterase inhibitor. An early case series claimed "dramatic" improvements with tacrine

Table 1: Major treatment options for patients with AD

<i>Precursors</i>	<i>Cerebral vasodilator</i>
Phosphatidylcholine (lecithin)	Calcium channel blocker e.g. nimodipine
Choline	
<i>Cholinesterase inhibitors</i>	
Tacrine	<i>Ergot alkaloids</i>
Donepezil	Ergoloid mesylates
Metrifonate	
Eptastigmine	<i>Neuroprotective</i>
Memantine	Nerve growth factor
Long acting physostigmine salicylate	
Galantamine hydrobromide	<i>Neuron regenerators</i>
<i>Cholinergic receptor agents</i>	Estrogens
Arecoline,	
Pilocarpine HCL,	<i>Anti-inflammatory agents</i>
bethanechol chloride	<i>Non-steroidal anti-inflammatory agents (NSAIDS)</i>
oxotremorine, nicotine	<i>Corticosteroids</i>
Milameline	
Xanomeline	<i>Antioxidants</i>
<i>Gangliosides</i>	Vitamin E
Phosphatidylserine	
Nootropics	
<i>Piracetam</i>	

in patients with Alzheimer's disease. Since then, well-designed multicentric trials have shown improvement with tacrine versus placebo in cognitive function and on global clinical scales and indices of daily functioning, leading to marketing approval in the United States and other countries. Fewer than a third of patients originally assigned randomly to receive tacrine showed modest, although meaningful, improvement in comparison with those who received placebo. Up to 20% of patients were unable to tolerate tacrine because of cholinergic side effects, generally gastrointestinal distress. Asymptomatic, reversible elevations of serum transaminase levels caused by direct hepatotoxicity occurred in about 50% of patients.

Tacrine's development and approval process helped set standards for antidementia drug trials and focused attention on proper evaluation for dementia. It afforded hope to patients who had given up on the possibility of an effective therapy. The tacrine experience proved that despite the potential for cholinergic and hepatic toxic effects, nonselective cholinergic therapies can be safe when used properly. Some patients who showed only mild improvement with tacrine therapy nonetheless viewed this as important, as did their caregivers. The tacrine experience also facilitated the development of a host of other cholinesterase inhibitors. Further, recent evidence suggests that prolonged treatment with tacrine, in patients able to tolerate it, results in significant delay until nursing home placement. These data are generally in agreement with early long-term experience with other cholinesterase inhibitors. Finally, preliminary evidence suggests that tacrine, as well as other cholinergic agents, can produce positive behavioral effects.

Donepezil

It is a reversible acetylcholinesterase inhibitor^{20,21} that has dose-dependent activity showing greater selectivity for

acetylcholinesterase and a longer duration ($t_{1/2}$ 70 hours) of inhibitory action than tacrine or physostigmine, as well as greater specificity for brain tissue than peripheral tissue. Encouraging preliminary studies led to the completion of multicenter, placebo-controlled studies examining donepezil at doses of 5 and 10mg/day versus placebo for 15 and 30 weeks, respectively, as well as another 30-week trial conducted in Europe. Results of these studies showed statistically significant benefit in both of the primary outcome measures (cognitive function and global clinical impressions), which was somewhat greater at 10mg/day. Donepezil has been reported to be safer and more tolerable (especially in terms of gastrointestinal distress) than tacrine. Donepezil was approved by the Food and Drug Administration (FDA) in November 1996 for a number of reasons: Its efficacy is generally equivalent to that of tacrine, it is not associated with hepatotoxicity or elevated transaminase levels, and it is thought to have fewer cholinergic side effects than tacrine. The ease of its once-daily dosing may result in improved patient compliance. It also has reduced potential for drug-drug interactions and may be taken with food. Because of donepezil's improved tolerability and because therapeutic doses are achieved quickly, rather than taking months, substantially more patients are expected to experience benefit with donepezil than with tacrine. A study exploring the long-term effects of the drug in slowing the progression is underway. If the results are positive, then the drug may be recommended in patients not yet exhibiting clinically recognizable cognitive decline. It is used in dose of 5mg daily, and it can be increased to 10mg after one week. Further information about donepezil also suggests that, as with some other cholinergic agents, improvement gained with early treatment is sustained with ongoing therapy. Studies are under way to assess donepezil's effectiveness over the long term as well as in patients with more severe dementia or comorbid medical conditions; results should help illuminate its usefulness in a broader patient population.

Metrifonate : This organophosphate was originally developed as an insecticide²². This agent that does not inhibit the enzyme cholinesterase but acts as prodrug^{22,23} for the long-acting cholinesterase inhibitor dichlorvos. The cholinesterase inhibition half-life is nearly 2 months, meaning that its effects are long lasting. Early studies have shown significant improvements on both cognitive function and global clinical scales, accompanied by typical cholinergic side effects. It has a low incidence of extraintestinal side effects and is not associated with hepatotoxicity^{20,23}. Common side effects are cholinergic, as expected, such as abdominal pain, cramps, diarrhoea, flatulence, and bradycardia etc²⁴.

Rivastigmine : It is a reversible inhibitor of acetylcholinesterase and butyrylcholinesterase and was approved in April 2000 for the treatment of mild to moderate AD²¹. It is shown to have significant benefits in the areas of cognition, global functioning and activities of daily living. In controlled studies, the dosages of rivastigmine are found to be 6-12 mg/day, given as twice-daily doses²⁵. It is well absorbed from gastrointestinal tract with half-life of 1.5 hours. Metabolites are excreted mainly through urine. It is widely distributed throughout the body. And is 40% bound to plasma proteins²⁴.

Galantamine : It is also a reversible inhibitor of AchE, and is modulator of nicotinic receptors²⁶. Several double-blind placebo controlled clinical trials have shown its efficacy in the treatment of AD in dosages of 16,24 and 32 mg per day. The adverse effects occur less commonly if the increment in doses is done slowly (e.g. 8mg every 4 weeks). Recommended dose is between 16-24 mg daily.

Memantine : There is evidence that the excitatory activity of L-glutamate plays a role in the pathogenesis of Alzheimer's disease and in the damage from an ischaemic stroke. A low affinity antagonist to N-Methyl-D-aspartate (NMDA) type receptors, such as memantine, may prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate required for memory and learning. Memantine, an uncompetitive antagonist with moderate affinity for NMDA receptors, demonstrates voltage-dependency and relatively fast on/off receptor kinetics. Black triangle Memantine 20mg/day significantly slowed the rate of deterioration in outpatients with moderate to severe Alzheimer's disease in a 28-week US randomised, double-blind, placebo-controlled, multicentre study. Memantine 10mg/day improved measures of dementia in care-dependent inpatients with Alzheimer's disease or vascular dementia in a 12-week randomised, double-blind study. Significantly more memantine than placebo recipients were responders according to Clinical Global Impression of Change scores and the Behavioural Rating Scale for Geriatric Patients Care Dependence subscale.

Physostigmine : It is a potent inhibitor of ChE with an efficacy similar to others in this group²¹. A sustained release formulation is available now a days. It is better tolerated than the original formulation but is not free from cholinergic side effects.

Eptastigmine : Eptastigmine²⁷ is a ChE inhibitor that has been shown to be an effective enhancer of cognition in patients with AD. As compared to AChE, the cholinergic side effects of this drug are low. Occurrence of dose dependent neutropenia in 6% patients and rarely other hematological side effects (e.g. aplastic anemia) is a concern.

Preventive Treatments

Alzheimer disease ties closely with cerebrovascular disease and is 4th most common cause of death. Therefore, its epidemiological importance needs no emphasis. Prevention of the disease (both primary and secondary) remains to be a dream of most scientists working in this area. A number of preventive strategies have been explored in last few years; however, at the moment none is sufficiently efficacious to be recommended at mass scale. These are summarized below.

Vaccination for Alzheimer's disease: hope or hype? Vaccination against Alzheimer disease has been an area mixed with enthusiasm and frustration. This is because; following the demonstration that A beta (42) competent of amyloid precursor protein is neurotoxic and is responsible for most manifestations of AD: the efficacy of vaccine was demonstrated in transgenic mice. It was believed that the vaccine would be able to destroy this peptide selectively by inducing antibody formation²⁸. This fueled interest among the scientists that vaccine is a reality. However, recent fiasco of the

first ever trial in humans has lessened the enthusiasm of vaccine development. Trial of A beta (42) peptide (AN-1792) vaccine has been abandoned due to development of meningoencephalitis in many patients²⁹.

Non-steroidal anti-inflammatory drugs : Epidemiological evidence has shown that use of NSAIDs for indications like joint diseases is associated with lower incidence of AD compared to the placebo takers³⁰. More than 20 studies conducted in 9 different^{7,8} countries have shown that the risk reduction (50-70%) is clinically significant. However, the side effects of long-term administration force us to take into consideration the risk versus benefit ratio³¹. Even in initial secondary prevention trial with indomethacin, the drug was discontinued due to gastrointestinal side effects^{31,32}.

Hormone replacement therapy : The fact that the risk of developing AD increases steeply after the age of 65; and more so in women led researchers to investigate the effects of sex steroids in prevention or secondary prevention of AD. Two large, prospective, longitudinal studies have shown the risk reduction of 50-70% in elderly women²¹. However, many studies have yielded negative³³ or inconsistent³⁴ results also. However, it continues to be explored³⁵.

Statins : The reputation of statins as remedies of prevention has grown substantially in last decade. Now they are the primary line of treatment in a variety of dyslipidemias (e.g. diabetes, postmenopausal) and prevention of complications in those with high risk for cardiovascular diseases. Pathophysiology of AD appears to be related to AD. Patients carrying an APO E 4 have cardiovascular disease and are also at increased risk of AD^{33,36}. Cholesterol is also involved in deposition of plaques of amyloid. Therefore reduction of cholesterol brings about beneficial effects.

Care giving for the cases with Alzheimer's disease

Increasing attention is being given in developed countries as to how the families of the caregivers should cope up with the stress of caring for a case with Alzheimer's disease. While in west, there are counseling centers and training schools for teaching the relatives and caregivers; in India, the issue is a new one. Caregivers are given training with regard to anatomy of brain, drugs, their side effects, patients disease, and how to cope up with newly arisen stress from care of the patients. Specialists should make sure that they educate the relatives of the patients regarding these issues²⁰. Caregivers suffer a number of adverse health consequences such as anxiety, depression, frustration, poorer immune functions, more respiratory infections, slower wound healing and are at risk for alcoholism, and drug abuse etc. They sleep poorly, less likely to exercise and more likely to have disruption in their lives. Studies in India have shown that the family disruptions are severe enough to cause breakdown of marriages and careers. Possible mechanisms to reduce stress may include counseling to the vulnerable persons who are involved in care giving. In India, there are few institutions or non-governmental organizations that can provide information, support, and appropriate activity for both patients and caregiver easing the burden on the long journey of care. The caregiver should be told to try to develop a new and warm relationship with the impaired person. They should be cordial, kind and helpful without being negative. They should avoid arguing with the patients. Some caregivers benefit

from adopting spiritual means. It seems that if the lost abilities of the person with AD are compensated and remaining abilities are promoted; then rate of decline of disabilities may get decreased.

Conclusion

Due to the advent of numerous anticholinesterase drugs; the most common degenerative disorder of brain is no longer treatable now. Though they cause modest improvement in the symptomatology but still improvement in memory and cognitive decline can help the patients and relatives cope up with the stress. A real test of these drugs would be whether they modify the course of the disease or retard the course of illness; if its confirmed by ongoing studies then they may also be recommended for primary prevention of patients at risk for the development of AD. Many preventive treatments are also on horizon now; these include, NSAIDs, estrogens, antioxidants such as vitamin E etc. To what extent do these agents lead to prevention of the disease remains to be seen in long-term studies; they appear to attractive options for prevention. Vaccine trial started with great easing the burden on the long journey of care. The caregiver should be told to try to develop a new and warm relationship with the impaired person. They should be cordial, kind and helpful without being negative. They should avoid arguing with the patients. Some caregivers benefit from adopting spiritual means. It seems that if the lost abilities of the person with AD are compensated and remaining abilities are promoted; then rate of decline of disabilities may get decreased.

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BOOK REVIEW

Principles & Practice of Emergency Medicine *Praveen Aggarwal, LR Hurmu, C.S. Yadav, BI Publication Pvt. Ltd., New Delhi 2005*

In the last three decades, medical science has advanced so rapidly that it is difficult to keep pace with the newer knowledge. With the availability of newer diagnostic tool and intervention technique, management of medical disorders has revolutionized and it is extremely difficult for medical practitioners to keep abreast with the advancement.

Medical emergencies constitute an important part of medical practice. Correct diagnosis, prompt and appropriate treatment are essential and life saving. One not only requires the presence of mind but also the speed and confidence to tackle the medical emergencies.

Management of emergencies is the most demanding and stressful aspect of medical training. Very few books on emergencies are available written by Indian authors and they mostly cover only one type of emergency.

This book written by Dr. Praveen Agarwal additional Prof. of Medicine, Dr. L.R. Murmur additional Prof. of Surgery and Dr. C.S. Yadav, associate Prof. of Orthopaedics, includes the general medical, surgical and orthopaedics emergencies. The authors being on the faculty of All India Institute of Medical Sciences, new Delhi have extensive experience in managing the emergencies in their respective fields. They have designed the book in such a way that the doctor can manage the patients in a much more effective manner.

The pathophysiology has been discussed in brief while more emphasis has been laid on clinical features, differential diagnosis and management of the clinical problems. Each chapter starts with an initial approach to a patient presenting with an emergency. The diagnostic and therapeutic aspects are dealt with in a stepwise manner. A large number of tables and flow diagrams are provided for quick reference. In view of the above, this book will help the doctors immensely in rendering effective and safe care to acutely sick or injured patients. This book will be an asset to medical students, residents and practitioners in managing their emergency cases.

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Drug Abuse Among Physicians - Specific Concerns in Anaesthesiologists

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Abstract: The drug abuse by physicians in general and anaesthesiologists in particular is a significant societal problem that affects all aspects of medical care. Earlier studies have revealed that 10-14% of physicians become addicted to drugs or alcohol at some point in their careers. Amongst all subspecialties, incidence of chemical dependency is most frequent amongst anaesthesiologists. Of all physicians treated for drug abuse, 13% are anaesthesiologists. Special risk factors for drug abuse amongst anaesthesiologists are complex. Stress is probably an important factor. Chronic fatigue due to long working hours is another factor that leads to consumption of alcohol or drugs to 'relex', when off duty. Access to opioids and occupational exposure to other psychotropic drugs play an important role in the onset of drug abuse. Early diagnosis and treatment of drug abuse can be remarkably effective but must be done by experts in the field. Tighter regulation of controlled drugs and education have been tried to reduce this menace. Most important factor in successful rehabilitation of such anaesthetists is individual's own will. Enthusiastic, supportive and compassionate colleagues will be the vital factor in satisfactory outcome.

Key Words : *Drug abuse, Physicians, Anaesthesiologists.*

Among the physicians, self-administration of drugs is far more common than other potential threats. No occupational hazard in the practice of anaesthesiology has more devastating consequences than the abuse of drugs¹. For example, no serious effects from waste gases have been reported except occasional hepatitis while administering halothane, but the suicide rate in anaesthesiologists is three times higher than an appropriate control group². Drug abuse may play a role in this figure. Otherwise, also four to eight deaths of residents by overdose are reported each year (Arnold WP: Personal observation). The signs and symptoms of drug abuse or chemical dependence or are so subtle that the disease is not detected until it has reached its last stages. It is hard to imagine that a friend in this profession may be addicted to drugs and may feel powerless when it occurs.

The experts in the field of drug abuse have provided the terminology³. 'Addiction' is the compulsive continued use of a drug in spite of adverse consequences. 'Drug dependence' is either physical or psychological dependence on a drug. It is the result of an inability to control drug use. 'Drug abuse' or 'drug abuse' is use of drugs in a detrimental way, but not to the point of addiction. Simply speaking, drug abuser can quit without help; the addict cannot. 'Recovery' is the process of conquering the disease. The individuals who have previously been drug dependent are referred to as 'recovering', rather than as recovered. It has been emphasized that drug dependence is an incurable disease, like other chronic diseases, such as, diabetes and hypertension. It can be controlled but not cured.

Drug abuse as an illness

It has been proved that addiction is a chronic, relapsing disease resulting from long-term effects of drugs on the brain⁴. By considering an affected colleague to be ill rather than an object of disdain, one may provide better initial guidance that the impaired colleague needs. Genetics also plays the role in addiction. For example, alcoholism is four times more common in the offspring

of alcoholics and is related more to genetic than to environmental influences⁵. Most of the addicted persons are male. All the drugs of abuse work through a single pathway in the brain. The mesolimbic reward system is not only activated by drugs of abuse, but is also altered beyond repair following chronic exposure to these drugs. The molecular, structural, cellular and functional changes are responsible for relapses that follow periods of abstinence. At the outset, drug abuse is a voluntary event. However, once these neural changes develop, it becomes an addiction that is characterised by compulsive, irrational, drug-seeking behaviour.

Concerns in Anaesthesiologists

The exact incidence of drug abuse and drug dependence in physicians is unknown⁶. However, a survey estimates a 2.1 percent annual and a 7.9 percent life-time prevalence among physicians while it is 16 percent in general population⁷. In medical field, it is more common in anaesthesiologists⁸. Through questionnaires and treatment centres, it has been observed that prevalence in anaesthesiologists ranges from 1-2 percent^{9,10}. However, how many drug abusers become actually addict, is not known. Treatment programmes also provide the data. Twelve to 14 percent of physicians treated were anaesthesiologists, although only 4 percent of USA physicians are anaesthesiologists¹¹. Out of 1225 physicians treated in one centre, 146 were anaesthesiologists. Nearly 50% of them were younger than 35 years of age and one-third were residents. Fifty percent of anaesthesiologists used both drug and alcohol, 40 percent used drugs alone and 10 percent used only alcohol. Younger anaesthesiologists more frequently prefer narcotics. Fentanyl was the most commonly abused narcotic followed by sufentanil, meperidine, morphine and oral agents. Some use of benzodiazepines, cocaine and marijuana was also reported. Some believe that this apparently high incidence is indicative of the diligence of anaesthesiologists in recognising the disease in colleagues.

Causative Factors

Drug dependence is a complex disease with multiple factors

modifying the genetic predisposition. There are various factors prevalent among the anaesthesiologists, as listed below :

Availability of drugs : Among physicians, anaesthesiologists are unique, as they administer drugs directly rather than order their administration by others. Therefore, drugs are immediately available. This is the most important cause of addiction in the speciality. Some recovering anaesthesiologists said "we work in the candy store". In one report, 85 percent anaesthesia residents treated in a programme stated that having drugs within reach influenced their career choice¹¹. Some hospitals have developed strict control measures to combat drug pilferage. However, an addict, who is desperate for drugs, can make all such measures inadequate.

Exposure to Stress: In the practice of medicine, exposure to stress is a universal feature. Most physicians manage these stresses through acceptable outlets, such as exercise programmes, social interactions and occasional drinking in moderation. A few do not have these abilities and withdraw from others. About one-half of residents need counselling¹². Residency is particularly difficult for some. The working environment is highly competitive. True relaxation is not available and some patients may evoke negative emotions. Some non-professional pressures, such as, marriage, bringing up of children, separation from parents and financial matters also play a role. A sense of professional inadequacy is quite universal¹³. Death of a patient after a resident has provided high-quality care may result in such feelings. Residency may lead to social isolation i.e. withdrawal from friends and family. It causes further stress because physician senses social failure. There is self-imposed isolation that may extend well beyond the resident years. All these elements lead to drug abuse and excessive use of alcohol, which are unhealthy escapes.

Potency of drug : Drug abuse is much more prevalent than addiction. Some physicians abuse drugs for 'recreation' to get high; others 'self-medicate' to treat stress. Causal abuse of alcohol does not always lead to addiction. Though very risky, abuse of morphine, meperidine or codeine also may not lead to addiction¹⁴. In contrast, addictive potential of fentanyl and other potent opioids is great any carry enormous risk of becoming drug dependent: A single experience with sufentanil is so overwhelming that it is impossible to stop using the drug. Once abuse begins, one needs very high dose to prevent withdrawal symptoms, mainly due to rapidly developing tolerance. The use of 50-100 ml of fentanyl or 10-20 ml of sufentanil per day is common in addicted individuals. This happens within a few months for fentanyl and a few weeks in case of sufentanil.

Miscellaneous factors : Just an experimntal use of drugs increases the risk of future addiction¹⁴. Progression from drug abuse to addiction has genetic basis, too. Denial that drug abuse can lead to addiction, lack of self-respect and assumption that knowledge of drug actions will prevent addiction, are other causative factors.

Signs and Symptoms

Till the disease reaches its late stage and performance is impaired at work place it is difficult to identify the drug abuser. In earlier stage of disease, usual sequence of events may help in identification (Table 1)¹⁵. First sign, usually is withdrawal from outside interests. Examples are giving up athletics, social activities and get-togethers. Next feature is increased turmoil at home. Domestic arguments, lack of interest in family matters and sexual problems are common. Next are unexplained illnesses, personality changes and multiple jobs. All this happens in addiction, which are slow to develop.

With rapid onset addictions, such as to fentanyl and sufentanil, above features are uncommon.

The last activity to be affected is performance at work place (Table 2). Page operators and nurses may be the first to recognise behavioural changes. Record keeping becomes sloppy. Excessive use of certain drugs becomes obvious and difficult to explain the need of these drugs in patient management. Direct observation of self-administration by colleagues confirms the diagnosis but it is not common¹⁶. Keystone of disease is denial. The affected physicians put forward not so logic reasons to explain their bizarre behaviour. Colleagues, too accept these explanations rather than considering the affected colleague to be a drug addict. For these reasons, diagnosis is not made until the manifestations are very obvious.

Intervention

The first step is to seek help from someone experienced in managing drug abusing physicians¹⁷. In United States; all state medical societies have 'committees on impaired physicians'. They give advice to the sick physician and act as buffer between him and the medical board or licensing agency. They also help in conforming the diagnosis and then refer to appropriate centres. Intervention is the process of apprising a drug dependent person that he or she is ill and needs treatment¹⁸. Intervention is attempted by at least

Table 1 : Features of drug abuse outside workplace.

1. Wide mood swings
2. Arguments at home
3. Withdrawal from family, friends and social activities.
4. Unexplained illness (more in alcoholism)
5. Extramarital affairs
6. Drugs/Syringes found in home
7. Weight loss
8. Pinpoint pupils (opioid addicts)
9. Withdrawal symptoms (Tremulousness, diaphoresis)

two persons experienced and preferably member of State Committee. The key is to be caring and compassionate in spite of patient's arguments. The addicted physician is a superb con artist. He is able to counter all ploys attempted by a single individual and gives the people a good workout. Information is collected from co-workers, family and friends. Related pharmacy records and anaesthetic records are gathered to document the illness. A recovering physician may be an invaluable role model for intervention. When all is in order, physician is invited into

Table 2 : Features of drug abuse at workplace.

1. Wide mood swings
2. Gossip by others
3. Increase in particular narcotic use
4. Preference for working alone
5. Poor record keeping
6. Frequent bathroom breaks
7. Appears in hospital when on call
8. Excessive postoperative pain in patients managed by individual
9. Pinpoint pupils
10. Weight loss
11. Witnessed self-administration (conforms)
12. Found comatose

a room where other participants are already seated. Each should describe the aberrant behaviour he or she has observed. If necessary, documents at hand can be shown. Basics of disease and its treatment should be explained and patient should be urged to accept the proposed plan. If he refuses, he should be informed that a group of specialists will examine him and if he is found normal, he will be discharged. If he still is reluctant, the intervners should tell him that medical board and 'controlled drug authorities'

would have to be informed. The patient has diverted narcotics, which is a ground for prosecution.

To prevent the self-inflicted injury by the patient, someone should stay with him after the intervention. Most interventions are successful, if adequate preparation is done.

Basic of Treatment

The treatment includes thorough evaluation followed by therapy, which is both inpatient and outpatient. Therapy may even last for several months¹⁹. Majority feel guilty, ashamed and totally alone on admission. Just seeing that other physicians share their disease is therapeutic. Goal of treatment is to provide the recovering physician with the ability to remain sober. He is encouraged to develop a strong relationship with peer support groups, such as 'Alcoholics Anonymous' and 'Narcotics Anonymous'. In the last stage, the physician may become involved in evaluating new patients that allows personal reflection on his own course, referred as 'mirror imaging'.

Return from Treatment

For a recovering physician, return from treatment is a difficult process. At treatment centre, environment is different from work place. After his discharge, he faces colleagues who are less knowledgeable about his disease and are fearful of him and disease. So, he needs understanding and compassionate colleagues for his re-entry to work place. Gradual return to work, with others managing administration of narcotics, is important. Without this support, changes of relapse are high. Committee on impaired physicians plays a vital role in recovering. After discharge from formal treatment, committee keeps in touch with recovering physician through 'aftercare contract' and physician follows the committee's recommendations. Committee may take random urine samples and in case relapse occurs, certain procedures are followed²⁰. Many recovery programmes recommend naltrexone or disulfiram or both for six months after returning. Few new drugs, such as acamprosate, bromocriptine and bupropion are under investigation²¹. Federal law in United States considers successfully treated and capable of working individuals as 'qualified individuals with a disability'. "Americans with Disability Act" (ADA) defines a history of drug dependence as a disability. This act does not force the employer to get the individual treated but requires that 'reasonable accommodation' be made for qualified individual who wants to return to practice. For a recovering physician, a modified work schedule may be made, such as no call for a few months and assistance with administration of narcotics. The employer is entitled to refuse accommodation with legal argument that return of recovered physician may have negative impact on other employees or could result in prohibitive costs for the employer.

Outcome

Most recovering physicians are able to return to a productive professional life, as reported by various treatment programmes²². Successful outcome depends on lifelong participation in aftercare programmes and a total abstinence from drugs and alcohol. Prognosis for long-term sobriety in anaesthesiologists depends on age and status of the physician at the time of identification. Residents who have been dependent on fentanyl have a significant rate of relapse¹⁰. In case of junior residents, who become addicted to potent opioids, change of speciality should be strongly considered. The American Board of Anaesthesiology requires a physician recovering from alcoholism or other drug dependence to take both written and oral examination, even if he is otherwise qualified. On the result of such examination the board decides whether to award certification or defer it so that he does not pose

a threat to the health and safety of others²³. Length of time the candidate's certification is deferred depends on the individual history of alcoholism or other drug dependence. Addiction is a lifelong disease. Its immediate effects may be overcome, but its sequelae leave an indelible mark on each victim. The disease makes the recovering physician guilty in the eyes of others, forcing them to prove their innocence whenever they are challenged. As there is no way to ensure that drug abuse will not lead to addiction, the only method to prevent is to absolutely avoid the abuse of drugs.

In conclusion, it has been shown that the lives and work of a significant number of physicians in general and anaesthetists in particular have suffered from the effects of misusing drugs and alcohol. The impact of intervention and treatment in cases of drug abuse as well as early recognition may improve the outcome. There is a need for training and education for all doctors for their personal and professional development²⁴.

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