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**From the Desk of Director Research**

Image-guidance radiation therapy is rapidly revolutionizing the planning and delivery of radiation therapy in the treatment of cancer. The "Special Feature" reports on developments in the era of Imaging in Radiotherapy.

Polymerase Chain Reaction has become the cornerstone of molecular biology and genetic analysis and is used by a wide spectrum of scientists in many areas of science. It has been covered in nutshell under "Perspective".

"In Focus" gives a glimpse of the recent developments in the field of Stem Cell Research in India. A special thanks to Dr Alok C. Bharti, Institute of Cytology & Preventive Oncology, for his inputs in this article. Other regular features covered are "Research & Development", "New Technologies", "Clinical Trials", "Watch-Out" and "Globe Scan".

The Institute has registered over 1,00,000 patients since its foundation in 1996 - a major milestone and a great source of pride-and has also set up an exclusive Department of Preventive Oncology; it has been briefly described.

Merck Serono is the new division of Merck for innovative small molecules and biopharmaceuticals. A special thanks to Merck for funding this issue of the Cancer News.

The Institute gratefully acknowledges the contributions made by Dr A.K. Anand, Prof P.S. Negi, Dr J.B. Sharma, Dr Snehlata Maheshwari, Dr S.L. Jain, Dr Dinesh Bhurani, Dr Himesh Gupta, Dr Vivek Arora, Dr Rajesh Jain, Dr Harpreet Kaur and Dr Rajat Saha.

Dr (Mrs) Ira Ray

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This publication aims at disseminating information on pertinent developments in its specific field of coverage. The information published does not, therefore, imply endorsement of any product/process/producer or technology by RGCI&RC.

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**SPECIAL FEATURE**

**IMAGING IN RADIOTHERAPY**

**Introduction**

Modern advances in computers have fueled parallel strides in imaging technologies. The improvements in imaging have in turn allowed a higher level of complexity to be incorporated into radiotherapy (RT) treatment planning systems. Image-guidance strategies used to reduce set-up error are generally classified as either online or offline procedures. An online approach acquires and assesses information from daily imaging; an offline strategy refers to the frequent acquisition of images without immediate intervention. Online and offline image-guidance strategies reduce geometric uncertainties, which in turn lower the dose delivered to the healthy tissues and might enable dose escalation, hypo-fractionation, reduced toxic effects and enhanced tumour control.

A key issue in RT treatment is how to deliver the prescribed radiation dose to cancer cells, while keeping the dose to normal cells as low as possible. New high-precision RT techniques, such as intensity modulated radiation therapy (IMRT) or hadron therapy, allow better dose distribution within the target and spare a larger portion of normal tissues than conventional RT. These techniques require accurate tumour volume delineation and intrinsic characterization, as well as verification of target localization and monitoring of organ motion and response assessment during treatment. These tasks are strongly dependent on the imaging technologies. Among these, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US) and positron emission tomography (PET) have been applied in high precision RT. The combination of PET-CT to obtain a fused anatomical and functional data-set is now emerging as a promising tool in RT departments for

delineation of tumour volumes and optimization of treatment plans. Another exciting new area is image-guided radiotherapy (IGRT), which focuses on the potential benefit of advanced imaging and image registration to improve daily target localization and monitoring during treatment, thus reducing morbidity and potentially allowing the safe delivery of higher doses.

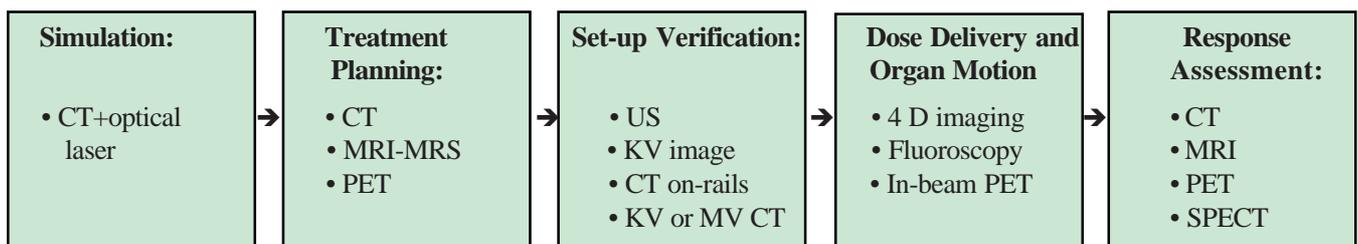
**Phases of High-Precision RT**

Five major phases of high-precision RT are: high quality diagnostic workup, treatment planning, set-up verification, beam delivery and response assessment (Table 1). In the simulation procedure, the patient is positioned (using optical lasers) and immobilized to obtain structural information using CT scan. The CT images, containing three-dimensional (3D) information of patient anatomy, are then transferred to a RT planning system for the treatment planning step in which tumour extension and organ at risks are identified and the target volume to be treated is defined. During this phase, the treatment parameters are determined based on the volumes defined on images and dose prescription. Once a plan that meets the criteria is generated, the parameters are automatically transferred to the treatment machine. In the set-up verification phase, the patient is positioned on the treatment table for each treatment session, in the same way as is done during simulation. This presumes that any components affecting the reproducibility of patient positioning during the course of treatment are known and corrected as needed. In the beam delivery phase, the machine is operated according to the plan parameters. Finally, the response assessment phase of tumour response after RT is evaluated, which is important in determining the treatment success and guiding future patient therapy.

**Imaging Modalities in IGRT**

The modalities may be divided into five groups; Ultrasonography devices, Room-mounted KV X-ray tubes, Traditional multi-slice CT scanners integrated on

**Table 5 Phases of The High-Precision RT Process**



*Imaging modalities used or now investigated in the high-precision RT process (CT-computed tomography, MRI-magnetic resonance imaging, MRS - magnetic resonance spectroscopy, US-ultrasonography, KV-kilovoltage, CBCT-cone beam CT)*

MV cone beam CT scanners with flat-panel technology mounted on linear accelerators.

**Ultrasonography:** is used for daily target localization before treatment, especially for prostate cancers, where a significant positional discrepancy of the prostate exists between the static CT image made for planning and dynamic day-to-day condition of the patient along with rectal and bladder filling.

**MRI & MRS:** MRI has been used extensively for imaging of tumours of the central nervous system, where studies have reported quantitative improvements of up to 80% in target volume definition. Tumour delineation in the regions of nasopharynx, urological and gynaecological cancers have been optimized with the integrated use of MRI. MRS is an emerging modality to identify the extent and position of tumours, aiding delineation of target volumes.

**PET & PET-CT:** [18F] FDG is currently used for tissue characterization and derives helpful information for patient staging, prognosis, treatment planning and monitoring. The role of PET with [18F] FDG in oncology patients has been well investigated in non small cell lung cancers, metastatic disease or mediastinal lymph node spread, esophageal cancer, Hodgkin's lymphoma and head and neck cancer. The main shortcoming of imaging with PET is that exact borders of tumours are not well defined, making visual delineation error prone. Hence, a hybrid imaging system of PET-CT is used for tumour delineation for radiotherapy planning.

**Room-Mounted KV X-Ray Tubes:** These are being increasingly employed for imaging in the treatment room. These images are registered and compared with the reference images to determine the need for set-up corrections. Two dimensional KV imaging performs very well for sites with bony structures, but the necessary imaging contrast for soft tissues is not easy to obtain. One solution is to implant radio-opaque markers in to the target, prior to treatment.

**CT-on-Rails System in Accelerator Room:** In such a CT system, same couch is used for imaging/planning and subsequently, RT treatment by the accelerator. It is a conventional multi-slice KV CT scanner connected via the treatment table with a linear accelerator that can produce 3D images of the patient's anatomy in the exact treatment set-up. CT-on-rails is well suited for target point verification, correction of set-up errors and interfraction target deviations due to

organ motion, as well as for re-calculation of the actual dose given. This device is not suited for adaptation to intra-fractional variations.

### Image-Guided Treatment Machines

**Cone Beam CT Linear Accelerator IGRT:** The first commercially available cone beam CT (CBCT) IGRT system was the Elekta Synergy (Elekta, Crawley, UK). The other medical linear accelerator (Linac) manufacturers have also now embraced the IGRT concept and have either produced their own version of an IGRT Linac, Varian Trilogy (Varian Medical Systems, Palo Alto, Calif, USA) and Siemens Artiste (Siemens Medical Solutions USA, Inc. Malvern, Pa., USA). While Elekta Synergy and Varian Trilogy linear accelerators have integrated KV cone beam CT imaging system, the Siemens Artiste has both KV CBCT as well as MV CBCT systems. The system provides planar, motion and volumetric images. CBCT based IGRT shows great potential for objective, precise positioning of patients for treatment and matching the treatment set-up image model with the planning image model.

**BrainLAB ExacTrac X-ray 6D IGRT System** is a new system, which is mainly an integration of an infrared-based optical positioning system (ExacTrac) and a radiographic KV X-ray imaging system (X-ray 6D). ExacTrac's high resolution X-ray imaging capabilities and millimeter accurate patient set-up enables all existing Linacs to be upgraded to provide IGRT for all patients.

**Helical Tomotherapy (HT)** is an alternative means of delivering IMRT, using a device that combines the features of a linear accelerator with those of a helical CT scanner. The CT images are generated using the same MV radiation beam as the X-ray. MV CT thus obtained provides good 3D soft tissue characterization. Because the unit uses the actual treatment beam as the X-ray source for image acquisition, no surrogate telemetry systems are required to register image space to treatment space.

**The Robotic Cyber Knife™** from Accuray (Sunnyvale, CA, USA) incorporates recent advances in robotics and computerized image recognition. The Cyber Knife mounts a 6-MV lightweight linear accelerator on a robotic arm, that accurately (six degrees of freedom) delivers the RT dose. Deviation from the initial set-up position are automatically compensated by the robotic arm.

**Image-Guided Intensity-Modulated Proton Therapy and Beyond:** Establishing the optimum clinical use of the above described IGRT machines (and their continued development) will require considerable effort over the next several years.

### Imaging for Organ Motion and Dose Delivery Monitoring

The explicit inclusion of temporal changes in anatomy during the whole RT process (imaging, planning and dose delivery) has led to the development of the four-dimensional (4D) radiotherapy based on 4DCT imaging systems and targeting the radiation on tumour related to in situ surrogate markers and/or respiratory phase related imaging. Three different approaches are possible: (a) controlled breath hold; (b) respiratory gating; and (c) tumour tracking. In controlled breath hold, organ motion is abolished during simulation and a static CT image is obtained. Feedback can be either direct measurement of target position by means of fluoroscopy or indirect assessment by measuring other parameters (inhaled volume, optical skin marker position).

### Benefits of IGRT

**Measurement of Tumour Changes:** Changes in the size, shape and position of tumours and healthy tissues have been recorded by serial volumetric imaging during RT of cancers of lung, bladder, liver and head and neck and deliver radiation accordingly. The size and amount of interfraction variation in the amplitude, period and reproducibility of motion of lung and liver cancers because of breathing is also becoming clearer with the increasing use of IGRT.

**Geometric Benefits:** As set-up error and organ motion are reduced and as geometric precision increases, the volume of tissue around the tumour that needs to be irradiated - the planning target-volume margin - can be reduced, leading to a decline in the amount of healthy tissue treated.

**Dosimetric Benefits:** A reduction in irradiated healthy tissue can decrease the probability of toxic effects to these regions and the ability to escalate the dose to tumours might be associated with an increased probability of tumour control.

**Clinical Benefits:** Clinical benefits of technological advances, including IGRT, are challenging to describe. Randomized data for patients treated with and without image guidance is unlikely to ever exist. Careful prospective studies to assess treatment technique and

patterns of recurrence can also provide an insight into the potential clinical benefits of imaging at the time of radiation planning and treatment.

### Limitations of IGRT

Pursuit of fully online adaptive replanning might be tempting, but the desire for sub-millimeter technical precision needs to be balanced with a risk of chasing only modest clinical gains and the possibility of imposing an unacceptable workload on RT planning, delivery and review processes. Clinical needs and infrastructure, human resources, the quality of imaging in the sites at which it is needed and the efficiency, ease of use and support for technology, all need to be considered in the development of an image-guidance strategy. A final limitation of image-guided treatment is the potential for the false reassurance it can provide, if used inappropriately, leading to unsuitable margin reduction and overconfidence.

At present, IGRT does not measure the biological change or healthy tissue function, and image-registration techniques are needed to link the biological imaging with the scans obtained at treatment. However, fluoroscopic imaging causes a significant amount of extra irradiation of the patient. The management of repeated imaging and concomitant doses is the concern of the community, to balance the risk and benefits of IGRT to long term survivors, especially young patients.

### Future Perspectives

Particularly important will be the development of accurate and efficient deformable registration tools that will allow image-guided adaptive radiation therapy to become a routine standard of practice. Image guidance will also facilitate dose guided RT.

### Conclusion

First generation IGRT systems are truly exciting. These are providing an integrated approach to radiation oncology treatment planning, dose delivery and treatment verification. Improvements in image quality, data storage, data import/export and software tools (for specific workflow tasks and data mining) are needed. Most importantly, IGRT machine reliability (i.e. 99% uptime) is absolutely critical. There is considerably more research and developmental work to do, as we move from these new frontiers to new standards of practice.

*(The Institute appreciates Dr. A.K. Anand and Prof. P.S. Negi for their contribution to this 'Special Feature' on Imaging in Radiotherapy).*

## PERSPECTIVE

### POLYMERASE CHAIN REACTION

#### Introduction

The polymerase chain reaction (PCR) is an in vitro molecular technique which can generate millions of copies of the desired DNA or RNA segment from any source, i.e, bacterial, viral, plant or animal, in a few hours. Introduced in 1985 by Kary Mullis, the technique was made possible by the discovery of Taq polymerase (heat stable DNA polymerase) isolated from the bacterium *Thermus aquaticus*. PCR has revolutionized the way DNA analyses are performed and has become a cornerstone of molecular biology and genetic analysis.

PCR technique utilizes the DNA preparation containing the desired segment to be amplified (target sequence), enzyme Taq polymerase and 2 primers (20 to 35 nucleotides long). These primers have complementary sequence to the nucleotide sequence of short segments present at or beyond the 3' ends of two strands called flanking sequences.

#### Steps of PCR

1) *Denaturation*: The DNA to be amplified is heated to a temperature between 90°C-98°C (commonly 94°C) to separate the double stranded target DNA into single strand (duration 2 minutes).

2) *Annealing*: The separated strands are cooled to a temperature between 40-60°C and allowed to anneal to the two primers (duration 1 minute).

3) *Primer Extension*: DNA polymers synthesize the complementary strand by utilizing 3'OH of primers and deoxyribonucleoside triphosphates. The optimum temperature for synthesis is 75°C (duration 2 minutes).

4) *Final Extension*: After the last cycle, the samples are usually incubated at 72°C for 5-15 minutes to fill in the protruding ends of newly synthesized PCR products.

#### Types of PCR

PCR is a highly versatile technique. It has been modified in a variety of ways to suit specific situations and applications. Some important variations of PCR are inverse PCR (amplify the sequences flanking a segment, the border sequences of which are known); anchored PCR (when sequence of only one end of desired segment or gene is known); reverse transcriptase PCR (amplify RNA sequence into DNA duplexes); overlap-extension

PCR (used to induced modification within internal site of gene); asymmetric PCR (generated single strand copy of one strand of template DNA), thermal cycle sequencing PCR (primers are radio or fluorescence labeled and base sequence of template DNA is determined by polyacrylamide gel electrophoresis), nested PCR (after amplification of target sequence, portion of the amplification product is re-amplified using another pair of primers); touchdown PCR (increase the specificity of PCR without lowering the efficiency); and real time PCR (permits the analysis of the products while the reaction is actually in progress).

#### Applications

Amplification through PCR, a key component of molecular diagnostics, can be done from a variety of tissue sources, including blood samples, biopsies, surgical or autopsy specimens. It can be used to search for mutations by a wide array of techniques, including DNA sequencing, to induce the desired mutations at specified sites in a gene (site directed mutagenesis). PCR can amplify highly polymorphic alleles to be traced in genetic linkage or association studies and is increasingly used to diagnose various microbial pathogens. In forensic science, it plays a major role in the analysis of DNA samples isolated from a single human hair or blood to determine whether the samples come from a specific individual. It has played a key role in the human genome project.

#### Limitations

While a very powerful technique, PCR can also be very tricky. Primer design and constitution is extremely important for effective amplification, and must be very specific for the template to be amplified in a reaction. Due to extremely high sensitivity of PCR, contamination from non-template PCR presenting lab environment (from bacteria, viruses) presents a real problem.

#### Future Perspectives

In the near future, chip based devices will hasten the day when scientists can take them on the road and patients will be able to get on the spot readouts of their DNA. Before long it may be quite routine to diagnose an infection, genetic disorder or even detect an inherited predisposition to cancer and heart disease, right in the doctor's office.

*(The Institute appreciates Dr. Vivek Arora for his contribution to the 'Perspective' on Polymerase Chain Reaction).*

## RESEARCH AND DEVELOPMENT

### Control Switches

Researchers from Washington University School of Medicine in St. Louis have shown that a single protein, HS1, enables key functions of natural killer (NK) cells, which kill early cancers and fight off viral infections. The protein allows the NK cells to pursue their targets, latch on to them and configure the cellular machinery it uses to kill them. Further study of how HS1 controls these processes may open up new possibilities for reviving the NK cells to fight infection and cancer. The researchers may also be able to use this same protein to inhibit the activities of other immune cells and prevent them from contributing to autoimmune conditions.

The cell sits down on the bone, seals tightly and then starts secreting the acid and other compounds that break down the bone. NK cells have to form a similar plunger-like bond, known as lytic synapse, with the targets they attack. The researchers wanted to see what would happen to NK cells in human blood samples if they turned down their ability to make HS1. The resulting cells were severely disabled. They couldn't effectively pursue the target cells, bind to them or prepare to kill them. NK cells are very good at nipping early cancers in the bud. Understanding their activation mechanism could lead to ways to make them better killers of cancers and cells infected by viruses and other invaders.

*(Science Daily, July 11, 2008)*

### Novel Treatment for Melanoma

Researchers at the NYU Cancer Institute, New York, have screened a library of already approved drugs for activity against the most deadly form of skin cancers. They have identified mebendazole, a drug used globally to treat parasitic infections, as a novel investigational agent for the treatment of chemotherapy-resistant malignant melanoma.

A novel assay found that mebendazole targets cancer causing proteins. Melanomas produce high levels of a protein called Bcl-2, which is known to protect cancer cells from apoptosis. The team saw that when a melanoma cancer cell was exposed to mebendazole, it resulted in inactivation of Bcl-2, allowing apoptosis to occur. The researchers are now focused on determining the range of doses to be tested in the clinic, whether specific types of

melanoma will respond better than others and whether combining mebendazole with other agents will be of further benefit.

*(Molecular Cancer Research, Aug 2008)*

### Potential Molecular Markers

Researchers at Rhode Island Hospital have identified two potential molecular markers that may predict outcomes for patients with stomach cancer, one of the most common and fatal cancers worldwide. According to the study, patients who had poor outcomes following surgery for stomach cancer, also had extremely low amounts of two proteins, known as gastrokine 1 and 2 (GKN1 and GKN2), which are produced by the normal stomach cells.

This is the first known study to link these low protein levels with outcomes following stomach cancer surgery. This discovery could eventually help physicians better determine and individualize therapy for stomach cancer, including which patients should be offered chemotherapy with other treatments in addition to surgery, to help them live longer and more comfortably. Further studies are needed to demonstrate the mechanisms responsible for the loss of GKN1 and GKN2 in this patient population as well as the clinical biomarker potential of these two proteins.

*(Medical News Today, July 18, 2008)*

### Promising Treatment for Leukemia

Leukemia is a type of cancer that originates in the blood cells. One therapeutic option for patients with acute type of leukemia is stem cell transplant. Researchers from Italy recently evaluated the effectiveness of umbilical cord stem cells that are injected directly into the bone marrow of patients with leukemia and the results appear promising. However, longer followup is necessary to determine the outcomes for these patients. They found that no complications occurred during the infusion of stem cells into the bone marrow. No patient developed acute, severe graft-versus-host disease, which attacks the patient's healthy tissue. At 13 months, 16 patients were alive and in complete remission, 5 patients died from treatment related complications of the transplant, 7 died from infection and 4 died from relapse of disease. According to the researchers, these results lead to the possibility of using this technique in a larger number of patients.

*(Lancet Oncology, Aug 9, 2008)*

## NEW TECHNOLOGIES

### DIAGNOSTICS

#### CK19 mRNA

Measurement of CK19 mRNA expression intraoperatively, can be used as a rapid diagnostic method to detect lymph node (LN) metastases in women with breast cancer. The cytoskeleton protein CK19 is expressed by virtually all breast cancers and one step nucleic acid amplification (OSNA) can be used to quantify CK19 mRNA expression in LN samples within 30 to 40 minutes.

Scientists from the VU Medical Centre, Amsterdam, tested the performance of OSNA for CK19 mRNA in comparison with the standard histological methods for identifying LN metastases in 346 axillary LN from 32 Dutch breast cancer patients undergoing axillary LN dissection. OSNA and histology results were concordant for 267 negative samples and 61 positive samples, while 18 were discordant. In 7 of the 18 discordant samples, sampling bias was thought to account for the disparate results. The OSNA method is an attractive intra-operative tool for LN metastases detection in breast cancer patients.

*(Cancer News-ASCO, Jul 2008)*

#### MicroRNA as Biomarker

Scientists at Fred Hutchinson Cancer Research Center have discovered that microRNA's molecular workhorses that regulate gene expression, are released by cancer cells and circulate in the blood, which gives them the potential to become a new class of biomarkers to detect cancer at its earliest stages. MicroRNAs have some advantages over protein based early detection systems. They can be detected potentially in smaller quantities and that the technology exists to rapidly develop microRNA based early detection tests.

For the study, the researchers tested blood from mice and humans with advanced prostate cancers, as well as those from healthy controls. They measured microRNAs made by the tumors in both cases and controls and they could distinguish which individuals had cancer, based on the blood microRNA measurement. The next step would be to identify specific microRNAs that can signal the presence of a variety of solid tumors at an early stage.

*(Science Daily, July 28, 2008)*

#### New Test for Herceptin

The US Food and Drug Administration has approved a novel genetic test, SPOT-Light, for determining whether breast cancer patients are good candidates for treatment with trastuzumab, Herceptin. When used with other clinical information and laboratory tests, this test can provide healthcare professionals with additional insight on treatment decisions for patients with breast cancer.

Herceptin, manufactured by Genentech, is given to breast cancer patients whose cancer cells have a lot of copies of the HER2/neu gene and usually have cancers that grow more aggressively than other breast cancers. Herceptin has been shown to dramatically slow that growth and help women live longer. However, the drug is expensive and can cause side effects. Fluorescent in situ hybridization (FISH) and immunohistochemistry are currently used to figure out if a patient's cancer is HER2-positive and will likely respond to Herceptin. The new test counts copies of the HER2 gene in a patient's tumor tissue similar to FISH. Unlike FISH, SPOT-Light uses a stain that can be viewed with standard microscopes and allows labs to store the patients tumor sample at the laboratory for future reference.

*(ACS, July 12, 2008)*

#### Tissue of Origin Test

Pathwork Diagnostics Inc., a molecular diagnostics company focused on oncology, announced that the US FDA has cleared its Pathwork "tissue of origin test" for use in determining the origin of uncertain tumors. The test analyses a tumor's gene expression pattern to help pinpoint the source of hard to identify tumors and is the first test of its kind to receive FDA clearance. It uses a microarray to measure the expression pattern, comprising more than 1,500 genes in the uncertain tumor and compares it to expression patterns of a panel of 15 known tumor types, representing 60 morphologies overall to help determine the tumor's origin.

The growing trend in cancer care is the use of therapies that target specific tissues and their genomic components, rather than relying on one-size-fits-all treatment approach. The FDA-cleared Pathwork, "tissue of origin test" will be available as an in vitro diagnostic kit. The clearance of the Pathwork test is another step in the continued integration of molecular based medicine into standard practice.

*(FDA News, Aug 2, 2008)*

## EQUIPMENTS

### Electa VMAT

Electa VMAT (Volumetric Intensity Modulated Arc Therapy) is a revolutionary new technology that dramatically decreases treatment times, delivering a higher dose to the tumor target without compromising coverage and patient safety. The speed and precision of Electa VMAT is due to the simultaneous manipulation of the gantry position and speed, the multileaf collimator leaves, the dose rate and the collimator angle, all while the radiation is on. Electa VMAT also allows the flexibility of one arc, two arcs, sub-arc or a combination.

From the patient's perspective, faster treatment times often mean improved comfort, which makes it easier to remain still during treatment and increases the likelihood of delivering radiation beams more accurately and safely. From the physician's perspective, the reduction in treatment time makes it much easier to accurately target the tumor and the improved dose sparing offers new options to either increase the cancer-killing dose to a tumor or reduce the side-effects and therefore potentially improve outcomes.

*(Elekta Inc., July 31, 2008)*

### Endoscopic Circumferential Ablation for BEHGD

Endoscopic circumferential ablation with a balloon-based radiofrequency device is a more recently available endoscopic ablation technique for Barrett's esophagus high-grade dysplasia (BEHGD). This procedure burns away the abnormal cells with radiofrequency energy.

A multicenter US registry assessed the safety and effectiveness of this technology for the treatment of BEHGD. Results showed that in 92 patients treated with endoscopic circumferential ablation who had at least one follow-up biopsy session, 90.2% were free of HGD at an average of one-year follow-up and avoided many of the adverse events associated with this disease. The technique compares favorably with photodynamic therapy, wide-field endoscopic mucosal resection (EMR) and esophagectomy, with respect to safety, patient tolerability and the histologic complete response outcomes tracked. Further, there may also be an adjunctive role for circumferential ablation and EMR, with EMR used to remove visible abnormalities for staging, followed by circumferential ablation to eliminate all remaining dysplastic and metaplastic disease.

*(American Society of GI Endoscopy, Aug 3, 2008)*

## New Imaging Technique

Researchers in Massachusetts have reported the development of Fluorescence-Assisted Resection and Exploration system for more precise true image-guided cancer surgery. The unique imaging system uses special chemical dyes called near-infrared (NIR) fluorophores, designed to target cancer cells, when injected into the patients. When exposed to NIR light, the dyes or contrast agents light up the cancer cells and the images are shown on a video monitor superimposed over images of the normal surgical field, allowing surgeons to easily see the cancer cells.

The technique promises improving surgery for breast, prostate and lung cancers, whose tumor boundaries can be difficult to track at advanced stages. The technique can also help cancer surgeons avoid cutting critical structures, such as blood vessels and nerves. In near future, fluorophores could be developed to highlight the nerves and blood vessels in one color, while visualizing cancer cells in a different color, allowing multiple structures to be viewed easily and simultaneously.

*(Medical News Today, Aug 20, 2008)*

## Point of Care Technology

The novel microfluidic CTC-chip, a breakthrough technology, provides 100-fold increased sensitivity and increased purity in detection and isolation of circulating tumor cells in the blood of cancer patients, compared with the existing technology. It is expected that within one to two years when this becomes a point of care technology, it may be possible to monitor cancer non-invasively in terms of responses and drug choices.

Researchers have shown that mutations in the epidermal growth factor receptor (EGFR) gene may arise in circulating lung cancer cells. They analyzed circulating tumor cells from 27 patients with metastatic non-small-cell lung cancer and identified EGFR activation mutation in cells from 11 of 12 patients (92%) and in matched free plasma DNA from four patients (33%). The drug resistance mutation T790M was found in patients with EGFR mutations who had been treated with tyrosine kinase inhibitors. The presence of this mutation in pretreatment tumor-biopsy specimens predicted reduced progression free survival. This technology comes hand in hand with the revolution in targeted cancer therapies.

*(Reuters Health, July 2, 2008)*

## IN FOCUS

### STEM CELL RESEARCH IN INDIA

#### Introduction

Stem cell research has the potential to revolutionize the future of medicine. In addition to offering hope in understanding cancer development and treatment, stem cells are being explored with encouraging results for cure of diabetes, some forms of blindness, heart attack, spinal cord damage, etc. Stem cell research has also been useful in advancing the knowledge of cell fate/lineage determination, embryogenesis and cellular transformation and extensive research is required to harness the enormous potential of stem cells. Considering it as a field of national importance, three priority areas can be identified: (i) basic and translational research, (ii) creation of facilities/infrastructure, and (iii) human resource development.

#### Basic and Clinical Research

India is currently witnessing exponential growth in the frontier areas of stem cell research. A sizeable number of programmes have been formulated and implemented, covering various aspects of both embryonic and adult stem cells, such as limbal, hematopoietic, embryonic, pancreatic, neural, cardiac stem cells, generation of human embryonic stem cell lines, stem cell preservation, *in vitro* differentiation of human embryonic stem cells, hematopoietic stem cells for haplo-identical transplantation, use of limbal stem cells for ocular disorders, isolation and characterization of mesenchymal, liver and cancer stem cells.

#### Infrastructure Development

There has been a substantial public and private sector investment in stem cell research with the establishment of several state-of-the-art stem cell facilities and stem cell banks. “*Centre for Stem Cell Research*” at CMC, Vellore has been established by DBT, Government of India, to carry out translational stem cell research. Similarly, MIRM, Manipal has been created to facilitate cutting edge research in stem cells and tissue engineering. Also, clinical stem cells facilities have been created at PGIMER, Chandigarh; SGPGIMS, Lucknow; LVP Eye Institute, Hyderabad; KEM and TMH, Mumbai; and AIIMS, New Delhi. Modern stem cell facilities have also been established for basic research at NCBS and IISC, Bangalore; NCCS, Pune; NBRC, Manesar; CCMB, Hyderabad; and ICPO (ICMR),

Noida. Recently, several private firms are also showing interest in developing their own stem cell units.

#### Human Resource Development

Efforts have also been made to bring the clinicians and researchers together by organizing a number of research workshops, extensive training programmes, brainstorming sessions and symposia, specifically addressing issues related to stem cell biology and its therapeutic application. “*Stem Cell Research Forum of India*” provides a common platform to the scientists and clinicians for discussion on new developments and for sharing the research outcome. Recently, Panjab University has proposed a new MSc course in Stem Cell Biology which will immensely help in human resource development in this field.

#### Regulatory Issues

To regulate stem cell research in the country, guidelines were formulated by DBT and ICMR in 2007 that are to take the shape of legislation in the near future. According to these guidelines, research on adult and umbilical cord blood stem cells is classified as permissible. However, embryonic stem cell research falls under restricted category. Research pertaining to reproductive cloning and introducing animal embryos in humans is prohibited. For implementation of these guidelines, four independent committees have been constituted, which include: “*Human Studies Committee*” for evaluation and guidance for clinical research; “*National Bioethics Committee*” to ascertain rigid ethical guidelines for conducting research on human beings; “*Task Force on Stem Cells and Regenerative Medicine*” to evaluate and fund basic research; and clinical research and “*Programme Advisory Committee*” to develop Centres of Excellence.

#### Conclusion

With development of required infrastructure, increasing awareness along with adequately formulated laws, India is at the verge of experiencing major boom in stem cell research. However, amalgamation of both basic as well as clinical research delivered in a clinical setting can only facilitate our bench to bedside approach and will strengthen translational research on stem cells in India.

*(The Institute appreciates Dr. Alok C. Bharti, Asst. Director & Chief, Div. of Molecular Oncology, ICPO (ICMR), Noida for his contribution to this write-up on Stem Cell Research in India)*

## CLINICAL TRIALS

### Eradication of *H. Pylori*

*Helicobacter pylori* is a bacteria that usually infects the stomach or small intestines. Once the initial cancer has been removed, another cancer may appear in a different part of the stomach. Removing *H. pylori* bacteria from gastric cancer patients after surgery can reduce the odds of cancer redevelopment dramatically.

Japan Gast Study Group performed a randomized controlled trial of 544 patients. Each patient was either newly diagnosed with stomach cancer and planning to have endoscopic treatment or was in post-resection follow-up after this treatment. Subjects were randomly assigned to one of the two groups: a test population administered 30 mg lansoprazole twice per day, 750 mg amoxicillin twice per day and 200 mg clarithromycin twice daily for a week and a control population administered standard care but no additional treatment to eradicate *H. pylori*. During a three year follow-up, metachronous gastric cancer developed in 9 patients in the eradication group (3.3%) and 24 in the control group (8.8%). Overall, the risk was reduced to one-third of the control risk using this treatment. This study suggests that the treatment to eradicate *H. pylori* reduces the risk of developing new gastric carcinoma in patients who have a history of such disease.

(*Lancet*, Aug 22, 2008)

### Non-Hodgkin's Lymphoma

The treatment combination consisting of treanda (bendamustine) plus rituxan (rituximab) provides effective therapy for patients with non-Hodgkin's lymphoma (NHL) that has stopped responding to prior treatment. There are approximately 30 different types of NHL, all characterized by the excessive accumulation of atypical (cancerous) immune cells. The most common type of immune cells that become cancerous are called lymphocytes. Cancerous lymphocytes can crowd the lymph system and suppress the formation and function of other immune and blood cells. Treanda is a chemotherapy agent that was recently approved for the treatment of chronic lymphocytic leukemia. Treanda is also being evaluated in other types of cancers, such as NHL. One advantage of treanda is that it does not interfere with another commonly used form of chemotherapy known as alkylating agents.

Researchers from Canada and United States recently conducted a clinical trial to further evaluate the effectiveness of treanda among patients with recurrent NHL. This trial included 66 patients with recurrent mantle cell lymphoma or indolent B-cell NHL. The patients were treated with treanda plus rituxan. Anticancer responses were achieved in 92% of the patients, 41% of the patients achieved a complete disappearance of detectable cancer. Median duration of anticancer responses was 21 months. Median progression free survival was nearly two years (23 months). The main side-effect was low levels of blood cells (immune cells and platelets). The researchers concluded that treanda plus rituxan is an active combination in patients with relapsed indolent and mantle cell lymphoma.

(*cancer consultant.com*, July 15, 2008)

### Non-Seminomatous Tumors

Researchers presented the results of a large randomized German trial in men with stage 1 non-seminomatous germ cell tumors (NSGCT). The treatment options for these patients included active surveillance, retroperitoneal lymphadenectomy (RPLND), or one course of bleomycin, etoposide and cisplatin (BEP) chemotherapy. The hypothesis of the study was that one cycle of BEP chemotherapy is efficacious and results in a lower recurrence rate than RPLND.

Men with stage 1 histologically confirmed NSGCT were randomized to arm A; one cycle of BEP chemotherapy or arm B; RPLND. If metastasis were pathologically confirmed from the surgery, 2 cycles of BEP chemotherapy were given as 21-day cycles. Between 1996 and 2005, 382 patients from 61 German centres were randomized to the 2 arms. Arm A and B each enrolled 191 intent to treat patients. The median follow-up was 56 months and all patients had been observed for at least 15 months. There were 2 and 15 recurrences in the chemotherapy and surgery arms, respectively. Considering outcomes in the according-to-protocol population, there were 15 recurrences, 2 in arm A and 13 in arm B. The 2 chemotherapy recurrences were at 15 and 60 months. The surgery recurrences were all in the first 17 months after orchiectomy. The benefit for recurrence-free survival in the chemo patients was statistically significant. The study holds promise for the treatment approach using one course of BEP chemotherapy in this setting.

(*Medical News Today*, July 31, 2008)

## WATCH-OUT

### Inhibition of Cancer Metastasis

Tumor metastasis involves detachment of malignant tumor cells from the primary tumor, escape through the surrounding extracellular matrix, intravasation into microvessels, extravasation from microvessels and proliferation in a foreign environment to form a secondary or metastatic tumor. Most cancer treatment regimes focus on eradicating the malignant tumor cells through surgery, irradiation and/or chemotherapy. There is a great need therefore, for compositions and methods that effectively treat or suppress tumor cell metastasis.

Ware-Jerry (US) have been awarded a US patent No. 2008160024 entitled, "Inhibition of cancer metastasis", published on July 3, 2008. The present invention provides a method for inhibiting tumor cell metastasis in a subject. In particular, the method comprises administering a glycoprotein Ibalph inhibitor to the subject. The method may also be used for reducing tumor cell malignancy or inhibiting formation of a tumor cell embolism.

(esp@cenet.com, Aug 25, 2008)

### Prevention of Ovarian Cancer

There is a need to develop optimal oral contraceptive pills (OCP) and hormonal therapy (HRT) regimens which are protective against ovarian cancer.

Patent No. US 2008167279, published on July 10 and entitled "Prevention of ovarian cancer by administration of products that induce biological effects in the ovarian epithelium" provides a method for preventing the development of epithelial ovarian cancer by administering agents which alter TGF-(beta) expression in ovarian epithelial cells and/or which promote apoptosis of such cells, either alone or in combination with other agents, including agents which increase apoptosis and/or induce effects on TGF-(beta) expression either by increasing expression of TGF-(beta) isoforms such as TGF-(beta)2 and/or TGF-(beta)3, or by downregulating TGF-(beta) isoforms such as TGF-(beta)1, or by doing both, or by altering the ratio of TGF-(beta) isoforms, or by pulsing alterations of one or more TGF-(beta) isoforms. Pharmaceutical compositions and regimens for prevention of ovarian cancer comprises HRT and OCP formulations with the addition of an agent which induces effects on TGF-(beta) expression in the ovarian

epithelium and/or expression of other relevant biomarkers. The regimens, methods and products described herein may have reduced side-effects and/or be more beneficial when administered to perimenopausal women.

(European Patent Office, Aug 16, 2008)

### Promising Anti-Cancer Product

Duke University chemists have patented an efficient technique for synthesizing a marine algae extract in sufficient quantities to now test its ability to inhibit the growth of cancerous cells while leaving the normal cells unaffected. The researchers also deduced that this molecule called largazole acts on cells through the same chemical mechanism as other anticancer compounds in the market or in clinical trials.

Luesche's team at the University of Florida extracted and identified largazole from a marine blue-green algae and demonstrated that largazole could impede breast cancer cell growth better than the anti-tumor drug Taxol, without causing Taxol-like side effects on normal breast tissue. The drawback was that Luesche's group isolated just one milligram that was very difficult to grow. The Duke team devised a method to produce gram-sized quantities with 20% yield. The team discovered that largazole was similar to another molecule called FK 228. These molecules are undergoing trials as anti-cancer drugs. The team is aiming at changing largazole's structure to increase its effects on various cancers.

(Duke University News, Aug 2, 2008)

### Treatment for Cancer

Under USPTO patent No. 7,405,227 dated July 29, 2008, BiPar Science, Inc (Brisbane, CA) have claimed it offers a treatment for cancer. Malignant cancerous growth poses serious challenges for modern medicine. The present invention relates generally to methods of treatment of tumorigenic diseases using aromatic nitrobenzamide compounds and their metabolites. More specifically, it relates to the use of the nitro compound 4-iodo-3-nitrobenzamide or a salt, solvate, isomer, tautomer, metabolite, analog or prodrug thereof in suppressing and inhibiting tumor growth in a mammal.

The treatment further comprises surgery, radiation therapy, chemotherapy, gene therapy, immunotherapy or its combination. The administration of the compound is intravenous. A pharmaceutical composition of the invention may be suitable for administration to a subject.

(USPTO, Aug 26, 2008)

## GLOBE SCAN

### First Step to New Therapies

Scientists at Sydney's Centenary Institute, Australia, have mapped the anatomy of a membrane protein. There are only around 70 membrane proteins out of the potential 10,000 that have ever been mapped. This exciting discovery has the potential to turn the way new drugs are discovered on its head and reduce the development time for new treatments. These membrane proteins are target for 70% of all therapeutic drugs, so an increased understanding of them would help develop better treatments for some of Australia's biggest killers such as cancer. At centenary, the scientists are now trying to map membrane proteins that are involved in pumping drugs out of the cells, thereby reducing the effectiveness of cancer chemotherapy agents and antibiotics among other drugs. By understanding how these membrane proteins work, they have the potential to eliminate the trial and error nature of patient treatment and to create targeted therapies.

(Australia: *Research Australia*, July 15, 2008)

### New Way to Study Cancer

Scientists at Duke University Medical School in Singapore have found a new way to study cancer that could be useful for developing targeted therapies against the disease and possibly many other diseases. Surveying large amounts of genetic data, the scientists analyzed both cancerous and healthy, normal tissues for genes with tightly controlled activity. The samples used came from lung, thyroid, liver, esophagus, colon and breast tissues.

From the analysis, forty-eight genes, that are tightly controlled in tumors, emerged from the analysis referred to as "poised gene cassette (PGC)". They viewed PGC as an exciting new class of genes in which there would be a need to slightly affect gene function to elicit a sizeable effect on the tumor. According to the scientists, it would make the PGC genes attractive targets, which would inhibit protein activity by 10–20% in order to gain the desired effect. This contrasts with the other genes, where a near-complete inhibition (90-100%) might be required before effects on tumors are seen. They found that small changes in PGC expression in tumors may be linked with potent differences in the tumor's ability to be invasive.

(Singapore: *Duke Univ. Med. Centre*, July 20, 2008)

### Promising Path in Cancer Therapy

By using "targeting", Dario Neri from the Institute of Pharmaceutical Sciences at ETH Zurich has followed a promising path in cancer therapy. "Targeting" employs antibodies as delivery vehicles for medicines to carry their active ingredients through the blood circulation and into the tumor. He has presented a new marker, together with three associated monoclonal antibodies as further promising candidates for cancer therapy.

The researchers used markers to help the antibodies find their way into the diseased cells. The search is on for such markers that occur solely in the tumor's blood circulatory system. A marker in a shape of the extra-domain B (EDB) of the protein fibronectin has been found 21 years ago. In the past 10 years, Neri and his team have developed two very promising antibodies, F16 and L19, that can dock on to tumour blood vessels and can be readily loaded with an anti-cancer active agent. Another marker, the fibronectin extra-domain A (EDA) together with three monoclonal antibodies that bind selectively to EDA, has been described. F8 antibody in particular is a promising candidate for this cancer therapy. Clinical studies on humans are taking place for the EDB antibodies F16 and L19.

(Switzerland: *Swiss Fed. Ins. of Tech.*, July 20, 2008)

### Cancer Survival Analysis

Cancer survival varies widely between and within many countries around the world, according to the first worldwide CONCORD study, conducted by Professor Michel Coleman from Cancer Research UK and over 100 colleagues. This study provides directly comparable data on 1.9 million adult cancer patients (aged between 15 and 99) from 101 cancer registries in 31 countries on 5 continents. The study covers cancers of the breast, colon, rectum and prostate. Most of the wide variations in survival are likely to be due to the differences in access to diagnostic and treatment services and factors such as tumour biology, state at diagnosis or compliance with treatment may also be significant. Population based cancer registries are increasingly important in monitoring cancer control efforts and in evaluating cancer survival. It is hoped that the information provided would facilitate better comparisons between rich and poor countries and eventually enable joint evaluation of international trends in cancer incidence, survival and mortality.

(UK: *Lond. Sch. of Hyg. & Trop. Med*, July 17, 2008)

## ACTIVITIES OF RGCI & RC

### DNB SYMPOSIUM ON BONE TUMORS

Rajiv Gandhi Cancer Institute and Research Centre (RGCI&RC) is a recognized academic center. Besides being a state of the art hospital for patient care, it also provides training in all oncology super specialities which are involved in the care of cancer patients.

DNB Symposium is held every two months, away from the busy schedule of the hospital and is seen as an academic activity with a difference where all the DNB students are able to clarify their queries with their colleagues and faculties of the hospital. A DNB Symposium on pediatric and adolescent bone tumors was organized by the Department of Pediatric Hematology & Oncology on 4th July, 2008. The main tumors for discussion were Ewing's sarcoma and Primary osteosarcoma, which together account for 6% of all pediatric malignancies.

Dr Ajay Agarwal from the Department of Radiodiagnosis discussed the various imaging modalities commonly used in evaluation of bone tumors: plain radiograph, computed tomography and MRI, MRI being the method of choice for local staging of tumors. Both osteosarcoma and Ewing's sarcoma have specific presentation on radiology which aids in their diagnosis. Osteosarcoma shows a well organized mass signifying osteoblastic process. Sunburst periosteal reaction and soft tissue mass signifies an aggressive and rapidly growing tumour. In Ewing's sarcoma, periosteal reaction is usually present, and it often has an onion-skin or sunburst pattern, which indicates an aggressive process.

Dr Kumardeep from the Department of Medical Oncology spoke on the advantageous role of preoperative chemotherapy for all patients with osteogenic sarcoma and significance of controlling all foci of macroscopic disease in managing metastatic osteosarcoma. For Ewing's sarcoma, the role of combination chemotherapy with ifosfamide and etoposide alternating with vincristine, adriamycin and endoxan has been the standard in its management. The proposed histopathologic grading to evaluate the effect of chemotherapy on the primary tumor had the strongest correlation to clinical outcome in the patients with osteosarcoma. He also dealt with the prognostic markers of both the tumors from the clinical perspective.

Dr Rakesh Kaul from the Department of Surgical Oncology stressed on the role of limb-sparing resections. The discrepancy in the length of limb which occurs after treating the malignancy is a real problem in pediatric age group and the roles of limb salvage surgery with expandable prosthesis were talked about at length. Local control rates have improved with the introduction of neo-adjuvant chemotherapy. Cryosurgery is being used at a few centres to achieve local control though not with much success. The local recurrence after first surgery carries a poorer prognosis making the initial complete resection with free margins very important. Metastatic disease at presentation is the most important adverse factor in the prognosis of these tumors.

Dr Pankaj Agarwal from the Department of Radiotherapy made a presentation on the role of radiotherapy in the current standard of care for osteosarcoma. Radiotherapy is offered in selected patients who refuse surgery or in whom definitive surgery is not possible, i.e, sites that are not amenable to resection and reconstruction or which have positive margins after resection. Patients with Ewing's sarcoma, treated with reduced-dose radiotherapy, experienced unacceptably high rates of local recurrence.

Dr Harpreet Kaur from Department of Pathology presented the pathological interpretation of pediatric and adolescent bone tumors. She discussed the interpretation of biopsy of the tumor for diagnosis, along with the advantage of taking biopsy from multiple areas in the same tumor. Osteosarcoma is a pleomorphic tumor with multiple molecular derangements. The assessment of necrosis in specimen was discussed in depth, necrosis being an important prognostic factor. Ewing's sarcoma is round cell tumor that shows varying degree of neuroectodermal differentiation. They are now grouped as Ewing's family tumors. All cases show fusion EWS-ETS family and can be used for molecular diagnosis of the same. Finally, the immunohistochemical profiles of all small round blue cell tumors were also discussed.

The presentations were followed by a panel discussion moderated by Dr Himesh Gupta (Pediatric Onco-Surgeon). There were valuable inputs from Dr Gauri Kapoor, Dr AK Chaturvedi and Dr Sunil Kumar. The prizes for the best presentation and best question were awarded to Dr Harpreet Kaur and Dr Preeti Bagga, respectively. Such symposiums have become an integral part of the academic programme of the Institute.

**DR DANIEL G. HALLER'S VISIT**

Dr Daniel G. Haller visited Rajiv Gandhi Cancer Institute & Research Centre on July 14, 2008. He is a Professor of Gastrointestinal Oncology at the University of Pennsylvania, School of Medicine, Philadelphia, USA and Associate Chief of Clinical Affairs and Editor in Chief of the prestigious Journal of Clinical Oncology (JCO). He is an authority on cancers of the digestive system, especially colorectal cancer. Dr Haller had an interactive session with Dr KV Swaminathan, Chairman; Mr KK Mehta, Principal Advisor; Ms Jyotsna Govil, Hony Secretary; Mr DS Negi, Chief Executive Officer; and Dr AK Chaturvedi, Medical Director; Consultants, Resident Doctors and Research Officers of the Institute.

Dr Rajat Saha from the Department of Medical Oncology presented an article published in JCO about phase III trial of trimodality therapy with chemotherapy, radiotherapy and surgery, compared with surgery alone for esophageal cancer. For trimodality therapy, patients with non metastatic esophageal cancer were given concurrent chemotherapy with cisplatin, 5-FU weekly. Radiation therapy was given 50.4 Gy over 5.6 weeks followed by esophagectomy with node dissection. The results showed a median survival of 4.48 years vs 1.79 years and five-year survival of 39% vs 16% in favour of trimodality therapy. Dr Saha highlighted five cases of esophageal carcinoma with different sites of presentation, chemo-protocols and results. In all these cases, radiotherapy was interrupted because of neutropenia or thrombocytopenia. Dr Daniel agreed that the treatment regimen proposed in the article was unduly toxic and individualisation of therapy would be warranted.

Dr Saha presented another case of a 53 year postmenopausal female with right adnexal cyst. Colonic biopsy was moderately differentiated adenocarcinoma. Laparoscopic peritoneal biopsy showed metastatic adenocarcinoma. The patient was given four cycles of FOLFOX 4 regimen and the results showed progression in the form of massive ascites. During follow-up, CT abdomen and levels of CA125, CEA, CA19.9 indicated possibilities of 2 primaries: ovarian progressing and colon regressing. Patient underwent sigmoid colectomy with panhysterectomy and HPE: colon – moderately differentiated adenocarcinoma, cut ends involved, serosal deposits of adenocarcinoma on ovaries. Patient was given 2 cycles of Erbitux + FOLFIRI regimen. She developed intestinal obstruction. A question was raised

about the scope of any palliative therapy, targeted therapy or surgery to alleviate the obstruction. Dr Haller suggested that surgical opinion be taken and patient be considered for resection anastomosis to alleviate her intestinal obstruction.

Dr Devender Pal, DNB Resident from the Department of Medical Oncology, presented the case of a 23-year old patient whose colonoscopy revealed polypoid growth starting 10 cms from anal verge to 20 cms. The histopathology report was well differentiated adeno carcinoma of rectosigmoid region. Laproscopic assisted high anterior resection was done. HPE revealed adenocarcinoma-moderately differentiated. FOLFOX chemotherapy was started 4 weeks after surgery. The patient had received 3 cycles and was admitted for the 4th cycle but withheld because of low absolute neutrophil counts. Questions were raised about the site of cancer (rectal or anal), whether the subcarinal nodes were metastatic and whether surgery was required for the patient. Dr Haller suggested that other FOLFOX regimes need to be tried which probably have low toxicity properties.

Dr Suresh P, DNB Resident from the Department of Medical Oncology, presented the case of a 55-year old male with ulceroproliferative growth, 1cm from anal verge, involving anterior anal and rectal canal. Punch biopsy of rectal wall showed malignant round cell tumor. In PET-CT, circumferential asymmetric mural thickening was seen in rectum and anal canal regions with multiple sub cm & few enlarged pararectal lymph nodes. Patient was planned for concurrent chemotherapy/ RT with 5FU/oxaliplatin. Dr Haller suggested that surgery will be required as later on sphincter preservation may be difficult.

After the case discussions, Dr Haller gave a presentation on how to write a manuscript/article for journals. He initially explained about the "impact factor" of each journal and gave a step by step illustration on how to formulate the thought process of writing an article, abstract writing, full text presentation, reference and conflict of interest permission.

He enlightened the audience with certain new advances in the field of colorectal cancer like the necessity of doing k-ras mutations studies before starting cetuximab. The interactive session ended with a vote of thanks by Dr Chaturvedi. He hoped the Institute would get distinguished guests of his stature on a regular basis.

### SPECIAL TUMOR BOARD

Tumor Board is a quality improvement forum for healthcare providers to discuss the diagnostic, therapeutic and follow-up recommendations for all cancer patients seen in the facility, through multidisciplinary treatment approach.

On 23<sup>rd</sup> July 2008, Prof Aman U. Buzdar MD, FACP, Professor of Medicine and Internist, Department of Breast Medical Oncology, Division of Cancer Medicine, MD Anderson Cancer Centre, and Deputy Chairman, Department of Breast Medical Oncology, Division of Cancer Medicine, MD Anderson Cancer Centre, Houston, Texas, and a specialist in breast cancer, participated in the tumor board discussion of RGCI&RC. The Tumor Board consisted of specific case discussions. It was attended by Medical Director, Senior Consultants, Consultants, Resident Doctors and Research Officers of the Institute.

Dr Rajesh Jain, Surgical Oncology, presented the first case of an early stage hormone positive breast cancer in a 72-year female patient with lump in the breast (T1N0M0 staging). Modified radical mastectomy was done. Post operatively, her report showed ER 80%, PR 100% with no lymphovascular invasion, while the HER report was awaited. The clinicians wanted to know the role of chemotherapy, specially in early stage hormone positive breast cancer. Regarding management, Prof Buzdar said that with strong ER and PR positive status, endocrine therapy- anti-estrogen (tamoxifen or aromatase inhibitors) is favourable. Aromatase inhibitors are better than tamoxifen because of lesser side effects and reduction in recurrence rates. He said that HER is a dominant pathway and for HER positive cases, targeted therapy transtuzumab should be given. Breast conservative surgery should be followed by radiotherapy at this early stage of breast cancer. If lymphovascular invasion is present, the risks of recurrence are more, for which, chemotherapy should be given. For systemic spread, one could go for Oncotype DX. However, if the score is low, then chemotherapy should not be given as it causes neutropenia and thrombocytopenia, while with hormonal therapy, risks are comparatively lesser. However, in ER/PR negative patients, endocrine therapy has no benefits.

The second case was presented by Dr Amit Dhiman of Medical Oncology, of a 43 years old female patient who was diagnosed in 1998 as a carcinoma right breast.

Patient was endocrine dependent and was on tamoxifen. She developed multiple metastasis, first in eye and bone, for which, docetaxel was given. Further, she developed lung and liver metastasis, for which, capecitabine was given. The disease being progressive, patient was given Faslodex. The patient later on developed brain metastasis for which gemcitabine was given. Prof Buzdar suggested that for such chemoresistant cases, one could try progesterone or epothilones and their analogs (Ixempra) which has low susceptibility to tumor resistant mechanisms.

The third case was presented by Dr Devender Pal, Medical Oncology, of a patient with a right axillary lump (5x5cms) with supraclavicular lymph node 2cms, poorly differentiated with positive bone lesions and treated with taxotere, carboplatin and herceptin (TCH) along with G-CSF support. Prof Buzdar suggested that maximum response can be obtained by local therapy in limited disease. Herceptin can be continued for longer periods.

The fourth case presented was of a female patient with right breast lumpectomy and ER 30% and PR 05%. The patient was given two cycles of docetaxel/epirubicin. As the disease was progressive, she was administered 3 cycles of avastin/ gemcitabine/ navelbine, despite which, the disease was progressive. Prof Buzdar suggested that for such patients, trial of endocrine therapy, ablation therapy with bilateral oophrectomy, LH/RH agonist therapy or capecitabine could be tried.

The last case was presented by Dr Rajat Saha, Medical Oncology, of a patient with a lump in right breast diagnosed as inflammatory breast carcinoma with ER/PR negative and HER positive. As the response to taxotere was poor, she was given paclitaxel. Herceptin was given for one year. Prof Buzdar suggested that because of high recurrence rate, radiation therapy should be given and Herceptin should be continued. Radiofrequency ablation or thermal ablation would be an effective means in unifocal well defined disease. TC or TCH could be given but anastrozole should be avoided in HER2Neu negative patients. In triple negative patients, platinum based chemotherapy does not add any benefit. In such patients, 4 cycles of anthracycline based chemotherapy and 5-fluorouracil should be given or weekly dose of taxol.

Prof Buzdar was very much impressed with the Tumor Board in RGCI&RC. The Medical Director thanked Prof Buzdar for the interactive session.

### MYELO DYSPLASTIC SYNDROME

Dr Eva Hellstrom-Lindberg, MD, PhD, Associate Professor, Department of Medicine, Division of Hematology, Karolinska University Hospital, Huddinge, Stockholm, Sweden was invited to the Institute on July 31, 2008. She had an interactive session on Myelo Dysplastic Syndrome (MDS) with Dr A K Chaturvedi, Medical Director, and medical oncologists, hematologists, hemato-pathologists and resident doctors.

The MDS is a diverse collection of hematological conditions united by ineffective production of blood cells and varying risk of transformation to acute myelogenous leukemia (AML). She mentioned that the signs and symptoms in MDS are non-specific and generally related to the blood cytopenias: anemia, granulocytopenia, thrombocytopenia and AML. Epidemiology of adult MDS includes primary - 90% and therapy related - 10%, which includes alkylating agents, anthracycline, topoisomerase group of drugs and radiotherapy.

She described that the WHO modified the FAB classification, introducing several new disease categories and eliminating others. The list of dysplastic syndromes under new WHO systems includes refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, refractory cytopenia with multilineage dysplasia and ringed sideroblast and 5q syndrome. She emphasized the importance of International Prognostic Scoring System used in MDS to predict long term outcome.

For suspected MDS cases, the workup includes full blood count, blood tests to eliminate other common causes of cytopenias, bone marrow for dysplasia, cytogenetics or chromosomal studies and flow cytometry for lymphoproliferative disorders in the marrow. Under pathology, she explained the epigenetic changes in DNA structure in MDS and loss of DNA methylation control.

She explained that the goals of the therapy are to control symptoms, improve quality of life, improve overall survival and decrease progression to AML. She also explained the role of erythropoietin (EPO), treatment model of anemia with GCSF+EPO, immune suppression in MDS, lenalidomide in del 5q MDS, role of 5-azacytidine as hypomethylating agent and allogeneic stem cell transplantation in MDS.

Dr Chaturvedi thanked Dr Lindberg and all the faculty members for the interactive session.

### STEM CELL THERAPY IN MALIGNANCIES

A lecture on "Stem Cell Therapy in Malignancies" was delivered by Dr Indreshpal Kaur, PhD, Assistant Director, Cell Therapy Laboratory, Department of Stem Cell Transplantation & Cellular Therapy, MD Anderson Cancer Center, Houston, Texas, USA on 31<sup>st</sup> July 2008. It was attended by Dr A.K Chaturvedi, Medical Director, senior consultants, resident doctors and research officers of the Institute.

Dr Kaur said that the potential of stem cell as therapy for many untreatable diseases through cellular replacement or tissue engineering is widely recognized. This is a highly interactive field of life sciences and requires close interaction of basic researchers, clinicians and the industry for the overall growth and development. Stem cell therapy plays an important role in the management of hematological malignancies.

There are three main sources of stem cells: bone marrow, mobilized peripheral blood, and cord blood. The main advantages of cord blood stem cell are that it is readily available, more primitive and allows engraftment across immunological barriers more easily. The main disadvantage of cord blood is relatively low dose of stem cells. Dosage of cord blood stem cell can be improved by using multiple cord blood and ex-vivo expansion. Mobilized peripheral blood stem cells collected through apheresis are used more often than bone marrow stem cells. Most patients of multiple myeloma do receive autologous peripheral stem cells.

Dr Kaur said that the graft versus host disease can be controlled by tacrolimus and low dose methotrexate. After transplant, the immune system should be monitored by counting T cells, B cells and NK cells. The factors influencing the outcome of stem cell transplants are disease status at transplantation, recipient's age, co morbid conditions and HLA compatibility.

Regarding stromal stem cells, she explained that they can be derived from many tissues, are easy to grow, non-immunogenic and promote engraftment of CD34+ cells in SCID mice. Stromal cells can also be used for ex-vivo expansion of hemopoietic stem cells.

Dr Kaur also elaborated the use of stem cells for damage in non-hemopoietic organs, especially in cardiac damage. The queries raised by the consultants were discussed. This informative lecture ended with a vote of thanks by Dr Chaturvedi.

### PREVENTIVE ONCOLOGY

Cancer has become one of the ten leading causes of death in India. There are nearly 2.5 million cancer cases at any given point of time, with over 8 lakh new cases and 5.5 lakh deaths occurring each year due to this disease. Common sites for cancer in India are oral cavity, lungs, oesophagus and stomach in males and breast, cervix and oral cavity in females. Over 70% of cases report for diagnostic and treatment services in advanced stages of disease, resulting in poor survival and high mortality rates.

Human suffering due to cancer is enormous. Regardless of prognosis, the initial diagnosis of cancer is perceived by many patients as a life threatening event with over one-third of patients experiencing anxiety and depression. Cancer can be equally distressing for the family's daily functioning and economic situation.

In this era of medical cost containment, oncologists seek to develop not only better treatment for cancer but also effective programmes for cancer prevention.

Prevention should be the key element in any disease control programme. Cancer prevention is the reduction of occurrence of cancer by identifying causes and developing measures to remove or counteract them. Preventive oncology embraces any measures that may be taken to prevent the development or progression of malignant disease. Healthy lifestyle holds the key to cancer prevention; upto 2/3 of all cancers may be preventable by avoiding tobacco and adopting other healthy habits. Regular screenings can help detect many cancers in earlier stages when they can be treated successfully.

A preventive oncology wing in an institute is expected to provide comprehensive cancer screening services based on age and gender, risk assessment, screening, personalised risk reduction strategies, genetic testing, chemoprevention, tobacco cessation and nutrition counseling. Educating people about the disease will help drive away the fears and stigma associated with the disease. It is important to involve all levels of population in educational processes. The contents of cancer education should focus on tobacco control, physical activity and avoidance of obesity, healthy dietary practices, reducing occupational and environmental exposures, reducing alcohol use, immunisation against hepatitis B virus, safe sexual practices to avoid human papilloma virus infection and vaccine against human papilloma virus for carcinoma cervix. Coordinated

public health approaches at national, state and local levels with active involvement by voluntary health services agencies, non-profit organizations and private sector would greatly enhance the success of these activities.

With the sincere efforts of Ms Jyotsna Govil, Hon'y Secretary, a Preventive Oncology Department has been recently set up in the Institute which is headed by Dr Sneh Lata Maheshwari. It primarily focuses on creating awareness among the public about the need to screen for early detection of cancer. Its aims are :

- Early detection of cancer at asymptomatic stage
- Demystify cancer
- Concentrate on organ specific information

The objective can be achieved by the Institute only in collaboration with Government Departments, NGO's and civil society. In this regard, already detailed discussions on the subject with Department of Health and Family Welfare and Department of Women & Child, NCT of Delhi have been held and collaboration with Gender Resource Centres of the NCT of Delhi are being worked on for the following services:

- a) Organize early cancer detection camps, primarily for breast and cervix.
- b) Create awareness especially among women, about the need of screening and early detection, through literature, posters, workshops etc.
- c) Organize training of general practitioners, NGO's and other health workers.

Department of Preventive Oncology in association with Roko Cancer organized a free camp for detection of breast cancer and carcinoma of cervix uterus on August 5, 2008 within the hospital premises. In this camp, mammography & pap smear test were done free of cost apart from free consultation. In future, it is proposed to organize more such camps for the benefit of general public.

It is evident that the current small and piecemeal approach to cancer prevention has had very limited success. Much has been learnt about the nature of the carcinogenic processes at the molecular level. This has, in turn, yielded systems for the detection of carcinogens. Cancer prevention has two readily measured end points, the reduction of the incidence of cancer through early detection and the reduction in mortality. All activities must be directed towards the swift achievement of these goals.