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From the Desk of Director Research

Organ preservation is becoming a major and important concept in the management of patients with cancer. The 9th Annual International Conference "RGCON-2010" being organized by the Institute from March 26th to 28th, has its main theme as "Strategies for Preservation of Organ Structure and Function in Cancer". The conference promises to provide a perfect blend of various clinical specialities, namely Radiation, Surgical and Medical Oncology, complemented by the imaging specialities like Radio-Diagnosis and Nuclear Medicine. The "Special Feature' in this issue complements the theme of "RGCON-2010".

Breast cancer is one of the commonest malignancies encountered in women all over the world and is the leading cause of cancer deaths in females. There has been a paradigm shift towards more conservative surgery in the treatment for breast cancer. A special gratitude to Prof RA Badwe, Director Tata Memorial Hospital and his team, for contributing the "Guest Article" on 'Breast Conservative Surgery in Cancer'.

"Perspective" profiles 'Chromoendoscopy' which refers to the topical application of stains or dyes at the time of endoscopy to detect and characterize gastrointestinal mucosal lesions. Prof Timothy P. Hughes and Dr Devendra Hiwase from Royal Adelaide Hospital, Australia visited the Institute and delivered a lecture on 'Chronic Myeloid Leukemia'. The "Activities of RGCI&RC"gives a brief on the lecture.

The Indian Cancer Society, Delhi, is a community -based voluntary health organization dedicated to eliminating cancer as a major health problem. "In Focus" gives an overview on 'The Indian Cancer Society, Delhi'.

Clinical research is an indispensable part of the drug discovery process to ensure the safety and efficacy of any new drug. The Institute has been conducting clinical trials in the field of Oncology since its inception in the year 1996. An overview of 'Clinical Research' has also been covered in this issue.

A special thanks to Dr Reddy's Laboratories Ltd. for supporting this issue of Cancer News. The Institute gratefully acknowledges the contributions made by the Chairman, Hony Secretary, Clinicians, Scientists and DNB students of this Institute.Views and suggestions from readers on the Cancer News are welcome.

Dr D C Doval

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SPECIAL FEATURE

PRESERVATION OF ORGAN STRUCTURE AND FUNCTION IN CANCER

Introduction

Norm of the day is goal for cure with organ preservation. Challenges for curing cancer in this millennium lie with enhanced diagnostic and imaging modalities, more effective chemotherapy, improved delivery of radiation, predictive assays of response, refinements in surgical techniques and post-operative care, as well as better nutritional support, and prospective quality of life assessment. Preservation of organ structure and function is becoming an integral component in the management of cancer patient.

Strategies involving special therapeutic procedures, state-of-the-art surgical and radiation delivery techniques, diagnostic imaging oncology and latest advances in the multimodal management, hold a great deal of promise for preservation of organ structure and function in cancer.

With better understanding of tumor biology and advent of neo-adjuvant and adjuvant therapies, attempts have been made to do less extensive, cosmetically acceptable, functional and organ preserving surgery without compromising the end results viz. minimally invasive nephron-sparing surgery, robotic partial nephrectomy, etc. Surgeries that have been performed with the **da Vinci robot** include radical prostatectomies, cystectomies, nephrectomies, partial nephrectomies, and adrenalectomies. The use of da Vinci robot is also being explored in the retroperitoneal lymph node dissection for testicular cancer.

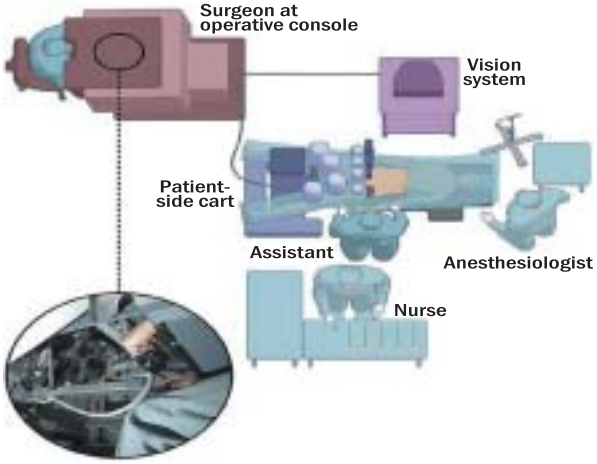

Figure: Sample room layout for robotic surgery

Figure: da Vinci surgical system

Developments in radiation oncology in the last decade have made possible highly conformal radiation delivery techniques, enabling high dose gradients at tumor sites not accessible otherwise.

Cyberknife Stereotactic Radiosurgery

Stereotactic body radiation therapy (SBRT) and Cyberknife take advantage of the technological advancements in image guidance and radiation dose delivery to direct ablative doses to tumors. This requires a high degree of confidence in tumor location provided by high quality diagnostic and near real-time imaging studies along with precise assessment of physiologic tumor motion for accurate treatment delivery with minimal acceptable toxicity.

The **Cyberknife** Stereotactic Radiosurgery System uses computer-assisted, **non-surgical technology** to transmit small beams of radiation from several different angles into a tumor, thereby minimizing the exposure of surrounding healthy tissue. Based on CT scan data of a tumor and the skeletal structure of the body as a reference frame, a high speed computer-controlled robotic arm is used to track patient and tumor positions during treatment and subsequent high precision irradiation.

Carbon ion and proton radiation is expected to offer benefits especially in tumors that are known to show a low radio-responsiveness against photon radiation and are located in normal tissue that is sensitive against photon radiotherapy. These are focused mainly on pediatric tumors, skull base tumors, and head and neck tumors.

At present, most research in nanomedicine remains in the oncology realm. Potential applications involve not only the ability for specific targeted treatment of disease, but also enhanced ability for prevention, early diagnosis, and following disease progression through superior imaging techniques.

Figure: Treatment of lung carcinoma with cyberknife

Neuro-Navigation in Brain Tumors

Advanced magnetic resonance imaging (MRI) techniques, such as magnetic resonance spectroscopy, diffusion MRI, and perfusion MRI, allow for a diverse range of multidimensional information of brain tumor physiology to be obtained in addition to the traditional anatomic images.

Magnetic resonance spectroscopic imaging (MRSI) is a non-invasive imaging technique that provides metabolic information on brain tumor which can be processed and presented as density maps of several metabolites, among them N-acetylaspartate, choline, creatine and myo-inositol provide relevant information in the context of brain tumors. Thus, this technique is a multiparametrical molecular imaging method that can complete the MRI study, enabling the detection of biochemical patterns of different features and aspects of brain tumors. This distinction of neoplastic lesions from non neoplastic and identification of tumor heterogeneity help in subtotal or greater resection and preservation of normal brain function. This facility of neuro-navigation requires a dedicated Brain SUITE.

Organ Preservation

Ocular Tumors

Brachytherapy with ^{125}I and ^{106}Ru plaques as well as radiation with charged particles, such as protons and helium ions, are alternative treatment modalities to surgical eye enucleation in uveal melanomas. Radiotherapy aims at local tumor control and eye retention. Episcleral plaque brachytherapy has been found to be superior to surgery, especially in the treatment of medium-sized choroidal melanomas.

Cancers of Head & Neck

Quality-of-life and function evaluation are recognized as important measures of success of any organ preservation strategy .This is especially relevant because treatment itself can be quite detrimental to speech, deglutition, mastication, respiration, airway protection, and taste, not to mention cosmesis which has now become equally important because of early diagnosis and subsequent increased long-term survival. Combined radiation and chemotherapy have been able to achieve increased rates of disease control and survival and preserve function, thereby decreasing treatment morbidity and increasing quality of life.

Interstitial Brachytherapy in certain early oral and oropharyngeal lesions helps in dose escalation, an important factor in increasing local control, with adequate sparing of adjacent normal tissues. Intensity modulated and image guided external beam radiation, coupled with functional imaging, has further increased precision in radiation delivery and in preserving organ function (specially relief from xerostomia). Larynx presevation strategies include conservation laryngeal surgery, radiation therapy alone, induction chemotherapy followed by radiation therapy, and/or concomitant chemoradiation.

Breast Cancer

Breast conservation is the standard of care in early cancer breast. It is tried even in locally advanced tumours following good response to neo adjuvant chemotherapy. Currently, there is growing consensus for accelerated partial breast irradiation based on recent retrospective studies which suggest that local failure occurs at or near the lumpectomy cavity. Partial breast irradiation is defined as radiation of the site of excision and adjacent breast tissue only. It can be delivered with interstitial and intracavity brachytherapy with the use of a variety of balloon or ''cage-like'' catheter products (MamoSite balloon brachytherapy), or three-dimensional conformal external beam techniques. The potential benefits of such an approach include: (1) better quality of life with marked reduction of treatment time to one day to one week as compared to 5-6 weeks done previously; (2) reducing the underutilization of Breast Conservation Therapy by making it more feasible for patients to

receive radiation, (3) more simplified integration of local and systemic therapies, and (4) decreased long-term complications of radiation by limiting the volume of critical structures irradiated to high dose.

Esophagus Cancer

Historically, radical surgery had been the cornerstone of treatment. Results, however, have been disappointing. Recently, remarkable advances of non-surgical treatments, such as endoscopic treatment and chemoradiotherapy, have been made in the treatment of esophageal carcinoma. Evidence supports the notion that combined modality therapy is effective for localized disease. Preoperative chemoradiation and esophagectomy or definitive chemoradiation are now the standard of care for resectable cancer.

Lung Cancer

Minimal oncologically safe surgical techniques for lung cancer include sleeve resection, a procedure intended both for maintenance of lung function and for radical treatment. It is widely accepted for central tumors for which the other alternative is pneumonectomy. SBRT is now considered standard treatment of choice for stage I, medically inoperable peripheral lung lesions with results equivalent to radical resection. Its potential role as standard of care in early stage cancers is emerging with current use of 4Dimensional-ComputerTomography, respiratory gating and treatment planning, the advantages being highly conformal, escalated dose and reduced treatment time.

Hepatobiliary Cancers

Resection is feasible only in 10-30% of Hepato Cellular Cancers. Various local tumor ablation modalities are being developed to effectively ablate small liver tumors. Of these, percutaneous ethanol injection and radiofrequency ablation (RFA) are highly effective. RFA is currently accepted as an alternative to resection in small (< 3cms) liver malignancy. Proton beam therapy has also been recommended for consideration in patients who have unresectable lesions or in elderly patients where surgical resection is medically contraindicated.

Bladder Cancer

Early superficial low and intermediate grade bladder cancers are managed by Trans Urethral Resection of Bladder (TURB) and intravesical therapy. High grade and muscle invasive bladder tumors are managed by radical cystectomy with or without adjuvant chemotherapy. The main challenge of organ preservation is to maintain a functional bladder while ensuring the same cancer specific outcome of cystectomy. The emerging evidence for bladder preservation strategy has led to development of algorithms for certain solitary muscle invasive lesions without extensive carcinoma in situ wherein initial TURB is followed by chemoradiation.

Prostate Cancer

Preservation of sexual function is one of the main objectives in treatment of prostate cancer. Advances in (1) surgical techniques include bilateral nerve sparing robotic assisted laparoscopic radical prostatectomy, and (2) radiotherapy techniques include low dose rate brachytherapy by Iodine125 seeds, high dose rate accelerated hypofractionation, image guided Intensity Modulated Radiotherapy and stereotactic cyberknife radiation delivery techniques.

Rectal Cancers

Early stage proximal rectal cancers are effectively treated with sphincter preserving mesorectal resection followed by adjuvant treatment depending upon the histopathology. Sphincter preservation has been of concern for locally advanced and distal rectal cancers. Many studies in the past decade have established use of neoadjuvant concurrent chemoradiation followed by total mesorectal excision as a standard approach for managing locally advanced rectal cancers with improved sphincter preservation rates. Also, advancement and increased experience in surgical techniques have contributed to decrease in the surgical morbidity and increased sphincter preservation rates for distal rectal cancers up to 2 cm from anorectal ring.

Conclusion

Organ preservation techniques are now becoming standard of care, especially with (1) increasing rate of early detection of cancer by newer highly sensitive and specific diagnostic modalities, and (2) increasing survival rates amongst early diagnosed tumors with newer multimodality treatment strategies. Innovative techniques for cancer treatment are enabling the organ to be preserved, the cancer to be cured and appropriate function to be retained, thereby improving the quality of life without compromising the treatment outcome.

(Dr Preeti Bagga, Senior Resident; Dr V Bansal, Senior Consultant; Dr N R Datta, Senior Consultant & Co-ordinator, Department of Radiation Oncology)

GUEST ARTICLE

BREAST CONSERVATIVE SURGERY IN CANCER

Introduction

The latter part of the last millennium was a period of new discoveries in science and medicine with a new understanding of the cause and treatment of cancer in general. Over the years there has been a paradigm shift towards more conservative surgery in the treatment for breast cancer.

Hippocrates in 400 BC postulated that breast cancer is a systemic disease from the start and that long-term cure and survival was not influenced by local treatment. The current treatment guidelines are based on this hypothesis and tend towards a more conservative approach for surgery. In 1948, Patey and Dyson published a brief report describing a modification of the Halsted mastectomy[1], modified radical mastectomy (MRM). Several studies[2-5] showed that the modified radical mastectomy was less disfiguring and its results were as good as those for radical mastectomy. Then trials favoring further conservation emerged, like the NSABP B-06 trial[6]. It demonstrated no significant difference in disease free survival (DFS) and overall survival between the three groups, namely MRM, breast conservation surgery (BCS), BCS and RT. Trials[6, 7] have shown similar long-term survival for breast conservation therapy (BCT) compared to mastectomy. However, local radiation therapy is mandatory after breast conserving surgery. Based upon the abundant data, BCT is considered an appropriate treatment of choice for most women with early-stage breast cancer.

Prognostic Factors

The factors associated with worse prognosis like young age, premenopausal status, adequacy of excision and margin status, multifocal or multicentric disease, lymphovascular emboli (LVE), tumor size, lymph node status, negative estrogen receptors, and other histological features like high tumor grade, tumor necrosis, infiltrating lobular histology, and mononuclear cell reaction have been studied for their association with high risk of local recurrence after BCT. The studies have demonstrated that only positive margin status, multicentricity and presence of LVE had a strong association with local relapse[8]. Hereditary breast cancer is another factor found to have a higher frequency of early (2 years) and late (> 5 years) local recurrences following BCT[9].

Adequate surgical excision and obtaining clear margins is the main factor which reduces local recurrence after conservative surgery[10,11]. A 'positive margin'[11] is defined as any amount of tumor at the margins in a low-power field. Extensive intra ductal component (EIC) is defined as the presence of a ductal carcinoma in-situ element in more than 25% of the total invasive tumor volume[12]. A review from M. D. Anderson Cancer Center concluded that EIC, in presence of a negative margin, does not adversely affect disease-free or overall survival or local control rates[13]. Isolated breast tumor recurrence (IBTR) after BCT with younger age, lymph node positivity at initial diagnosis, higher initial tumor stage, shorter time to IBTR, histology of recurrence predicted a lower DFS[14]. Repeated revision of margins may result in poor cosmetic outcome, adverse psychological reactions and delay on starting oncological treatments and higher cost[15, 16]. Thereby stressing on the need for proper selection of patients for breast conservation surgery, adequate surgical excision and obtaining clear margins at the time of the primary surgery.

Technical Aspects in Breast Conservation Surgery

Two separate incisions are generally required: one to remove the primary breast tumor and the other for the axillary dissection. For the excision of the primary tumor, an incision is made directly over the tumor. Tunneling is not recommended. The tumor is excised with an adequate margin (usually a 2cm gross negative margin) upto the pectoralis major muscle. The specimen is then oriented (short suture to mark the superior margin and long at the lateral margin). As no drain is placed in the breast wound, meticulous attention is paid to hemostasis. The skin edges (not the breast tissues) are re-approximated. A seroma generally forms in the wound, but the fluid reabsorbs over a period of several days or weeks which helps in contouring.

The axillary clearance is performed through a separate transverse incision at the lower axillary hairline in a lazy-S fashion starting from the lateral pectoral fold to the fold raised by the lateral border of latissimus dorsi muscle. The axilla is completely cleared with removal of level III nodes. NCCN guidelines recommend level I and II clearance as the standard of care and level III only to be cleared if there is gross involvement of level II nodes[17]. However, there is evidence from small institutional studies which suggest association of the involvement of level III nodes in patients with positive level I and II nodes and increasing tumor size[18,19,20].

Standard Histopathological Reporting

Gross examination should document size of specimen, size of tumor in three dimensions, distance of all margins from tumor. Microscopic evaluation should report the histologic type and grade of tumor, presence and extent of DCIS and EIC, the microscopic presence or absence of tumor at the margins, presence or absence of lymphatic vascular invasion, perineural and perinodal invasion, lymph node status (total dissected and positive nodes). Immunohistochemistry with reporting of estrogen receptor, progesterone receptor and CerbB2 receptor status is also necessary to decide adjuvant systemic therapy[21].

Breast Conservation in Large Tumors Including Locally Advanced Tumors

The earlier trials of breast conservation in Europe had included only tumors of 2.5 cm or less, the NSABP trial later had included tumors up to 4 cm in size. Presently, if the relative size of the tumor to breast volume is adequate, even larger tumours can be considered for BCS. Preoperative chemotherapy in large operable breast cancers and even in locally advanced tumors can result in a significant decrease in tumor size to allow breast conservation with clear margins[22,23]. Neoadjuvant chemotherapy (NACT) in conjunction with surgery and radiation therapy[24,25] is now considered the treatment of choice for patients with locally advanced breast cancer.

The major concerns with offering breast conservation surgery after downsizing the tumor with NACT are due to the lack of objective documentation of actual tumor size (prior to NACT). The concern is that downsized lesions do not always shrink concentrically, which may result in residual disease outside the area of planned excision/ radiotherapy. There are many indigenous methods described to mark tumor margins prior to chemotherapy, which may help perform safe BCT in patients with advanced breast cancer, but none are widely accepted as standard practice[26]. Currently standard practice is to mark the centre of the lump with a core biopsy/ incision biopsy prior to NACT and then to plan surgery later centered on this mark.

Currently there is no level I evidence to support BCT after neo-adjuvant chemotherapy. However there are some prospective studies which support conservation after NACT. One such prospective analysis of 664 women with locally advanced breast cancer who underwent surgery post NACT was conducted at Tata Memorial Hospital[27]. Women undergoing BCT had a superior 3-year DFS as compared to after mastectomy (72% in BCT vs. 52% after mastectomy, $P < 0.001$) with a lower local recurrence (8%). This is not a true representation of the impact of extent of surgery, but a probable result of the selection bias related to response after NACT. However the analysis suggested that BCT can be safely offered after NACT.

Quality of Life: *A* prospective study evaluated the differences in patient's perception of satisfaction with their body image following BCT in comparison with the clinician's appraisal cosmesis[28]. As time elapsed, the appraisal of cosmesis by the clinician showed a trend towards worsening of cosmesis ($p < 0.001$), probably due to late changes in breast appearance (shrinkage) and feel (firmer) related to possible post-radiation fibrosis. In contrast, the trend in patient self-assessment of degree of satisfaction with body image showed a trend towards improvement ($p = 0.84$), suggesting that women who have voluntarily accepted to undergo BCT and are disease-free appear to have a relatively high threshold for accepting ''unsatisfactory'' breast cosmesis.

Contraindications to Breast Conservation Surgery: Absolute contraindications to breast conserving surgery are pregnancy (first and second trimester), extensive, suspicious mammographic microcalcifications, multicentricity, persistent involvement of surgical margins. Also patients, who are not candidates for breast irradiation (early pregnancy, previous breast irradiation, connective tissue diseases) may be treated more appropriately with mastectomy. The relative contraindications are large tumor to-breast volume; multifocal tumors if limited to a single quadrant and centrally located lesions. However, these may be approached by various oncoplastic techniques.

Oncoplastic Surgery: Oncoplasty refers to application of the principles and techniques of plastic surgery to the treatment of breast cancer. It includes local rotation flaps (based on the principles of mastopexy / mammoplasty), e.g. the Grisotti flap.[29] The initial results in support of oncoplasty are promising but there is very little evidence available in published literature to support its use as standard of care[30]. The term oncoplasty also includes breast conservation surgery and pedicle latissimus dorsi flaps for volume correction, which is commonly used for large tumor to-breast volume, multifocal tumors if limited to a single quadrant or centrally located lesions. Other

oncoplastic procedures include dermal fat implantation, lippofill etc. which are all used for volume correction after a breast conserving surgery.

Conservation in Relation to Axillary Surgery

Axillary lymph node dissection is associated with complications of minor lymphedema, pain and parasthesia, seroma formation and shoulder dysfunction. An alternative treatment to axillary clearance is primary axillary radiotherapy[31-33]. However, that gives no information of axillary status and induces a high morbidity comparable to that of surgical dissection[34].

Thus over time the gold standard of level III axillary lymph node dissection has given way to more conservative procedures like sentinel lymph node biopsy (SLNB). The sentinel lymph node (SLN) is defined as the first node in the lymphatic basin that receives the primary lymphatic flow from the tumor. The status of the SLN is thus proposed to reflect the entire lymph node basin. SLNB has emerged as an appropriate method of conservation of the axilla without any long-term follow up data[35-37]. However, it has a learning curve, requires resources (radio-colloid) and is yet to be validated in the Indian setting. Also, currently there is no long-term safety data available in support of the procedure. This has led to the consideration of other methods of axillary conservation like axillary sampling.

Axillary sampling is a simple technique which involves removal of 4-5 nodes from level I. It may be a simpler and more feasible alternative to sentinel node biopsy. This is important especially in developing countries with limited resources, as it does not involve any additional investment[38]. Currently, a non-randomized efficacy study is underway at the Tata Memorial Centre to compare sentinel lymph node biopsy and axillary sampling in operable breast cancer[39].

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World Cancer Day (4th February 2010)

Cancer is a leading cause of death around the world. Each year, over 12 million people are diagnosed with cancer and 7.6 million people die of the disease. Approximately 40% of cancers are potentially preventable. Every year on 4th February, WHO joins hands with UICC to promote ways to ease the global burden of cancer. This year's theme **"Cancer can be prevented too"** focuses on simple measures to prevent cancer such as: **(1)** No tobacco use, **(2)** A healthy diet and regular exercise, **(3)**Limited alcohol use, **(4)** Protection against cancer causing infections.

The slogan of this year also voices **"Learn about vaccines against viruses that cause cancers (e.g. Hepatitis B Virus vaccine, Human Papilloma Virus vaccine)."**

RGCI&RC has started a year long campaign to work with cancer survivors, their relations, volunteers, and decision makers around the world to create awareness about cancer prevention strategies.

PERSPECTIVE

CHROMOENDOSCOPY

Introduction

Modern diagnostics of the alimentary tract takes advantage of the most modern endoscopic visualization techniques. They include high resolution endoscopy, magnifying endoscopy, double balloon enteroscopy, capsule endoscopy, chromoendoscopy, fluorescein endoscopy, endosonography and other radiological techniques such as virtual colonoscopy.

Chromoendoscopy, or chromoscopy, refers to the topical application of stains or dyes at the time of endoscopy in an effort to enhance tissue characterization, differentiation, or diagnosis. Together with recent interest in new imaging techniques such as magnification, chromoendoscopy should be considered to represent a simple, safe and inexpensive technique that may be useful in identifying premalignant conditions and minute cancerous lesions, estimating their superficial extent and determining the histological type and submucosal invasion.

Principle

Chromoendoscopy and magnification chromoendoscopy are aimed at detecting and characterizing gastrointestinal mucosal lesions, namely its possible neoplastic nature and invasive behaviour. They offer features that allow more and new mucosal details to be seen. The analysis of mucosal surface details is beginning to resemble histologic examination. More accurate recognition of small flat and depressed neoplastic lesions is possible. Endoscopic prediction of neoplastic and nonneoplastic tissue is possible by analysis of surface architecture of the mucosa, which influences the endoscopic management.

Technique

Chromoendoscopy: It concerns the application of stains into the digestive mucosa through the endoscope channel, using a spraying catheter or by direct injection. The method is cheap, the coloring agents are widely accessible, non-toxic and no side effects are noted if used in small quantities and recommended concentrations. For most chromoendoscopic applications, a spray catheter is used to apply a uniform mist of the staining agent onto the mucosa. Several disposable and reusable spray catheters are available for this purpose. There are several solutions used classified according to their way of action:

(1) Absorptive (or vital) stains specifically identify epithelial cell types by preferential absorption or diffusion across the cell membrane (Lugol's iodine, methylene blue, toluidine blue or crystal violet). (2) Reactive stains need chemical reactions with specific cellular constituents (Congo's red or acetic acid) resulting in a color change akin to a pH indicator. (3) Contrast stains that seep through mucosal crevices, enhance surface and delineate mucosal lesions and patterns (indigo carmine). Tattoo staining is permanent staining.

Magnification and High Resolution: Resolution of an endoscopic image is a quality defined as the ability to optically distinguish two closely related points. High pixel density charged coupled devices incorporated into high resolution scopes provide views with greater mucosal detail, making it possible to discriminate objects 10 to 71 microns in diameter. High resolution imaging thus improves the ability to discriminate detail, whereas magnification enlarges the image 150 times through a lens or electronically. For carrying out the magnification procedure, a cap usually is fitted on the distal tip of the endoscope, allowing the mucosa in contact with the cap to be magnified even in motility areas. The degree of magnification ranges from 1.5 to 150 and can be changed with the use of a rotary dial on the control head of the instrument or a thumb operated lever similar to the elevator lever on side viewing duodenoscopes. These features of new endoscopes are used together with chromoendoscopy for current practice to characterize mucosal patterns or in transparency observation of gastrointestinal mucosa. The use of stains is easily available; magnification is available according to the use of specific endoscopes.

Clinical Applications

Chromoendoscopy has been applied in a variety of clinical settings and throughout all gastrointestinal tract segments that are accessible to the endoscope. Interest has been renewed in recent years though in part because of the development of new technologies, such as endoscopic mucosal resection and photodynamic therapy, which require precise visual tissue characterization. Chromoendoscopy is easy to use. Training improves knowledge of limitations, application (definition of end of procedure) and improves reliability.

Esophagus: Squamous Neoplasia

Lugol's use in the esophagus shows very high sensitivity but low specificity for the detection of dysplastic and

squamous neoplastic lesions. Lugol's for the detection of neoplastic lesions may be used in patients with a previous history of head and neck cancers. The extent and delineation of these lesions are also more accurately defined after staining, hence the use of Lugol's solution to guide endoscopic mucosal resection (EMR) of early stage squamous cell carcinoma and to detect recurrences at the EMR sites.The use of magnification showed an increase in specificity in an uncontrolled non-consecutive series of patients.

Esophagus: Barrett's Esophagus (BE)

Methylene blue showed diverse results in the identification of intestinal metaplasia or dysplasia in BE, although several studies showed better results when compared with random biopsies based protocols. Magnification with different stains presented higher specificity when compared with conventional endoscopy at least for patients with short segment BE.

Gastric Neoplasia

Methylene blue staining with magnification endoscopy detected gastric intestinal metaplasia and dysplasia with 84% and 83% accuracy, respectively, in a study involving 136 patients. Congo red staining may be useful for the detection of gastric intestinal metaplasia and cancer.A double staining technique using methylene blue and congo red identified early gastric cancers. The detection of synchronous early gastric cancers increased after methylene blue–congo red staining. The technique also facilitated the detection of carcinomatous foci 4 to 10 mm in size that were not visible with conventional endoscopy. Phenol red staining has been used in detecting H pylori compared with biopsy as the gold standard.

There is no evidence that panchromoendoscopy is superior to current conventional endoscopy. In terms of classification of previously identified lesions, diverse techniques show increased validity comparing to unstained mucosa during conventional endoscopy. There are no comparative studies between those techniques. Magnification chromoendoscopy may be useful in terms of invasiveness prediction as well as for the follow up of patients with intestinal metaplasia.

Colorectal Neoplasia

Pancolonic or targeted indigo carmine staining, with or without magnification or high-resolution endoscopy, is the most widely used chromoendoscopic technique for the detection or differentiation of colon polyps and neoplasms.Indigo carmine staining is not currently considered a substitute for histologic diagnosis. Indigo carmine staining combined with magnification endoscopy appears to be a useful technique for the detection of aberrant crypt foci in the rectum and has increased the detection rate of adenomas in hereditary nonpolyposis colorectal cancer syndrome.A double-staining technique using indigo carmine and crystal violet with magnification endoscopy predicted incomplete endoscopic mucosal resection of flat, sessile colonic neoplasms with high accuracy.

Panchromoendoscopy is not recommended in a routine setting.After the identification of lesions, the use of chromoendoscopy may be useful to further characterize the lesions.In patients with ulcerative colitis, chromoendoscopy may be useful during surveillance for dysplasia diagnosis. For invasiveness, assumption before resection or for completeness of the procedure after resection, the use of magnification may be useful.

Safety

There is no clinical evidence that the use of stains at usual doses with or without magnification increases the risk of the endoscopic procedure.

Barriers

Possible barriers to the dissemination and adoption of this relatively inexpensive and readily available endoscopic technique include the perceived lack of efficacy, the lack of routine training in gastroenterology fellowship programs, the perceived time and technical difficulty of the technique.

Conclusion

Chromoendoscopy is inexpensive, safe, and relatively easy to perform, although the method is not standardized for several stains and the staining patterns are subject to observer interpretation. There is a need to build consensus on the staining techniques and terminology of the mucosal patterns for most applications, in addition to proving efficacy and reproducibility in high-quality, randomized, controlled trials before chromoendoscopy can be incorporated into routine clinical practice. Consensus over the diverse classifications would lead to higher levels of reliability and easiness in training and dissemination of these technique and magnification chromoendoscopy.

(Reviewed by Dr A K Khurana, Senior Consultant, Department of Gastroenterology)

IN FOCUS

THE INDIAN CANCER SOCIETY, DELHI

The Conquest of Cancer by Choice; Not Chance

The Indian Cancer Society (ICS) was founded in Mumbai in 1951 by the renowned oncologist Dr D J Jussawala, with the stated objective of providing cancer awareness and education, as well as offering high quality - low cost cancer screening facilities. Dr Jussawala saw even in those early years that prevention through awareness and understanding was only way to fight the scourge of cancer.

The **Delhi Branch** was set up in 1983 by a group of enlightened citizens, led by Shri KK Mehta, who continues to guide the activities of ICS Delhi.

Cancer Jagriti

The Awareness Group of trained volunteers of Cancer Jagriti organises cancer awareness talks at a wide variety of locations, ranging from schools and colleges, to offices and factories, women's groups, urban slums, villages, along with other socially committed organizations, such as Deepalaya, the Mobile Creches, Lions Club, Rotary Club, etc. Speakers deliver the talks supported by instructive video films, and informative literature, which is given free. This service is available completely free of cost, though a pick-up for speakers is much appreciated. The school program imparts cancer education to a receptive audience. A recent initiative is making use of FM channels to carry this message further afield.

Cancer Screening

ICS offers cancer screening at the Cancer Detection Centre, 42 Babar Road, New Delhi 110 001.The Centre is open on all working days from 0900 to 1200 hours. The Centre is served by 3 specialist doctors of ENT, Gynecology and Surgery, supported by a team of technicians. In a package, which includes blood analysis, chest x-ray, and physical examination by experienced doctors, one can avail screening for cancer at minimal, heavily subsidized cost. No prior appointment is required, and the entire process takes only 35 minutes. In order to detect cancer early and even at a pre-cancer stage, ICS urges that every person over the age of 30 years should have an annual check-up.

Mobile Cancer Screening

Cancer screening at your doorstep! This service is ideal for offices, factories, and other clusters of people who cannot take time off to come to the Babar Road Centre. Forty people are screened in a three hour period by the specialist staff. This service is available on weekends, and on weekday afternoons. Bookings can be made through the office, and a payment is required to be made in advance to confirm the booking. Philanthropic individuals and organizations often sponsor camps for people living in the slums of Delhi. One should check with ICS about the availability of free camps. The Mobile Service is an essential part of the Community Projects. This is undertaken by the ICS in the bastis (slums) around Delhi.

Projects

ICS undertakes Community Screening Projects supported by Corporate houses as part of their Corporate Social Responsibility Projects. Over 2160 women from disadvantaged areas were screened for Cervical Cancer in 2007-08. In addition, Awareness Talks and intensive training for chosen leaders among local women as *Basti Sevikas* are organized with the doctors from IRCH/AIIMS. A series of talks and screening camps were organized for the migrant labour working for various Gas Authority of India Ltd. projects in 2007-08 and 2008-09. A unique initiative under this Project resulted in a translation into Urdu of the main awareness booklet "100 Questions about Cancer".

Cancer Sahyog

Since 1991, this support group has been working for people living with cancer under the umbrella of ICS Delhi. Founded by a cancer survivor, all members of Cancer Sahyog have a personal experience with cancer. Besides offering a listening ear and a shared experience, volunteers provide literature, helpful suggestions and tips regarding the side effects of treatment. **Most of the volunteers in hospitals, all of whom are cancer survivors, offer cheer and hope.** Cancer Sahyog offers a measure of financial assistance to deserving cases. Sahyog's annual seminar addresses issues of importance to cancer survivors. The **Walk for Cancer** is a popular fixture on the calendar, as **Survivors Day**.

Breast Cancer Care

This group of Breast Cancer Survivors has joined the ICS family. They provide badly needed advice on prosthesis and under garments; as well as living life under altered circumstances. They also join Volunteers from Jagriti & Sahyog in spreading awareness about breast cancer.

Prashanti

It is the newest addition to the family. Working under the aegis of ICS, this is a Centre for Healing therapies. Patients and survivors are encouraged to explore the various therapies on offer, and use the one of their choice to better their quality of life.

CanKids

Children with cancer are one of Mother Nature's more deplorable jokes. They throng Delhi hospitals in large numbers. **While the causes of child cancers are largely unexplained, it is known they are often more curable than adult cancers.** The rider is - Early Detection. With early detection and timely treatment, most of these youngsters can look forward to long and healthy lives. Since 2003, CanKids, a part of the ICS, looks after the interests of child patients. Apart from sponsoring treatment costs, it seeks to bring a little sunshine to the lives of these young people with gifts, such as clothes and toys, outings to fun places, and similar other activities. It works in conjunction with Cancer Sahyog, which is also the Emotional Support Group of the ICS. CanKids, seeks to provide assistance with educational needs, occupational therapy during treatment, etc. The CanKids' 'Home Away from Home' for children and their parents became a reality in 2008.

ICS Newsletter "Nargis"

It offers information and has a small but loyal readership of 3000 persons. *Nargis* covers the activities of all ICS units and gives useful information about cancer. It is distributed free of cost in hospital clinics.

Pressure Group

ICS works with tobacco regulation lobbies to stem the easy availability of tobacco, especially to vulnerable youth. ICS has made presentations to the Parliamentary Sub- Committee on Tobacco Regulation,and has put forward its views on the tobacco-cancer connection. The newly passed Bill reflects ICS inputs. ICS successfully lobbied the Defence Forces to include cancer screening as part of the Annual Medical examination of all service personnel. This program is being offered to corporate houses as well. Most recently, ICS has been lobbying the government for protecting new generation cancer drugs, whose prices are sky-high due to the new World Trade Organization requirements. ICS has worked to get warning signs put on bidi and gutka packets. Special programs organised during the year highlighted different cancers Tobacco/Oral (May), Breast (October), Cervix (November).

Cancer Insurance

Recognizing the fact that cancer treatment is protracted and expensive, ICS has been the first to offer Cancer Insurance in collaboration with New India Assurance Company. Presently, there are two slabs of cover available. Details can be obtained from the ICS office. At a time when one in eight Indians is likely to get cancer, insurance to offset the high cost of treatment has become a necessity.

There is ample evidence available suggesting that a majority of cancers are related to lifestyle choices. In India, where over half the cancers are in the head and neck region, it is important for people to recognise the link between tobacco (including chewing tobacco such as gutka, khaini, paan masala) and cancer. Most cancers of the mouth, throat and lung are avoidable. The importance of diet in cancers is increasingly evident. Diet is implicated in cancers, such as those of the breast, stomach, gall bladder, colon and rectum, which are rising as lifestyles include richer diets, and people become more sedentary in their habits. Breast cancer, often referred to as the "empowered woman's cancer", is overtaking cervical cancer as the number one cancer in women in urban areas. **Most cancers are curable if detected early. Many cancers can be avoided by understanding the way lifestyles help create these monsters.**

The Delhi branch of the ICS is proud to be a part of the worldwide effort to combat cancer by striking it before it takes root. **"We need your commitment, in time and money, for this valuable cause."**

It is hoped that everyone will carry the message of cancer prevention through awareness and regular annual screening, to one's circle of friends and loved ones.

"Please Help Us Make Health A Habit"

(Mrs Jyotsna Govil, Hony Secretary, Rajiv Gandhi Cancer Institute & Research Centre, and Hony Additional Secretary, Indian Cancer Society, New Delhi)

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MAJOR ADVANCES IN CANCER

Clinical Cancer Advances Report-2009

The American Society for Clinical Oncology (ASCO) in its 2009 Report has highlighted 51 of the most significant studies in cancer research, including 15 which are considered major advances. Some of the major advances, in the field of Personalized Medicine & Tageted Therapies, New Standards of Care, Cancer Prevention & Screening, are described below.

•***First Targeted Treatment for Gastric Cancer:*** Adding trastuzumab (Herceptin) to standard chemotherapy, for advanced gastric cancer improved survival in patients with increased expression of HER2 neu, compared with chemotherapy alone.

•***First Effective Immunotherapy for Neuroblastoma:*** An antibody-based immunotherapy, called chimeric anti-GD2 antibody ch.14.18, was found to reduce risk of relapse and improved survival by 20% for high-risk neuroblastoma.

• ***Cetuximab Improves Survival for Advanced Head and Neck Cancer:*** Adding the *EGFR*-targeted drug cetuximab (Erbitux) to initial chemotherapy for metastatic head and neck cancer extended survival compared to chemotherapy alone.

• ***Benefit of Gefitinib for Lung Cancer Depends on EGFR Status:*** First-line gefitinib treatment improved survival in patients with non-small cell lung cancer (NSCLC) in Asian non-smokers or light smokers whose tumors had *EGFR* gene mutations at exon 18, 19, but not in those without mutations. Patients without *EGFR* mutations responded better to standard chemotherapy.

• ***Targeted Therapies Approved for Kidney Cancer and Glioblastoma:*** In 2009, the US Food and Drug Administration (FDA) approved bevacizumab (Avastin), as a single agent for previously treated glioblastoma. Bevacizumab was also approved to treat metastatic renal cell carcinoma in combination with interferon. The FDA approved everolimus (Afinitor) for patients with renal cell carcinoma whose disease has progressed despite prior therapy with sunitinib.

• ***First Standard of Care for Biliary Tract Cancer:*** A combination treatment with gemcitabine and cisplatin was shown to improve survival over gemcitabine treatment alone.

• ***Maintenance Pemetrexed Therapy Improves Survival for Advanced Lung Cancer:*** Maintenance therapy with pemetrexed (Alimta) has been established as a new standard of care for patients with advanced nonsquamous NSCLC showing survival benefit.

• ***Radiation Therapy Following Prostatectomy Improves Survival for Early-Stage Prostate Cancer:*** This finding has established a new standard of care for early-stage prostate cancer, which is the most common form of cancer among men.

• ***PSA Testing has Minimal Effect on Reducing Prostate Cancer Mortality:*** Routine Prostate Specific Antigen (PSA) testing has a small, if any, effect on reducing the risk of dying from prostate cancer, and has likely led to over-diagnosis and treatment of the disease. These findings will influence doctor-patient communication about risks and benefits of PSA testing.

• ***Ovarian Cancer Treatment for Recurrence Based on Rising CA-125 Blood Levels does not Improve Outcomes:*** This finding could spare women the anxiety and costs associated with frequent blood testing, as well as the expense and toxicity of earlier treatment.

• ***HPV Vaccine Effective in Older Women:*** Vaccine is currently approved to prevent HPV infection in girls and young women aged 9-26 and the new study report has suggested that vaccination may be beneficial for a larger population of women, including 25-45 age group.

• ***Adjuvant Treatment with Bevacizumab does not Prevent Recurrences of Colon Cancer in Individuals who have Undergone Surgery for Colon Cancer:*** Use of bevacizumab in combination with chemotherapy after surgery in patients with earlier-stage colon cancer did not prevent recurrences.

• ***Standard Three-Drug Chemotherapy is Superior to Single-Drug Regimen in Older Women with Breast Cancer:*** Trial showed that standard chemotherapy (fluorouracil, doxorubicin and cyclophosphamide) halved the risk of death and relapse than capecitabine alone.

Recommendations

- Increase Federal Investment in Cancer Research Funding
- Strengthen the Nation's Clinical Research System
- Ensure Patients Receive High-Quality Care

(J Clin Oncol, Dec 10, 2009)

UICC WORLD CANCER CONGRESS

Introduction

Cancer kills more people than AIDS, tuberculosis, and malaria combined and is predicted to become the world's single leading cause of death . By 2030, it has been estimated, more than 12 million people could die from this disease every year. About 80% of these deaths are likely to occur in low-income and middle income countries, where resources available for cancer control are restricted or non-existent. To improve the situation, a worldwide coordination of effort is needed.

The International Union Against Cancer's (UICC) World Cancer Congress brings together the global cancer community for urgent action to deal with the worldwide cancer problem. Clinicians, practitioners, government agencies and non government organizations (NGOs), patient-care providers and advocates, researchers and behavioral scientists and public health experts focus on transforming the latest knowledge into strategies that countries, communities, institutions and individuals can employ to reduce the cancer burden.

Objectives

- Translating scientific and behavioral research into relevant prevention, early detection, treatment, psychosocial support, palliative care, etc.
- Understanding the economic implications of cancer control interventions in both developed and developing settings and determining which interventions produce the best results
- Promoting the development of national cancer plans as building blocks of a comprehensive anti-cancer strategy worldwide
- Stimulating capacity-building among UICC member organizations and cancer NGOs
- Strategic planning and sharing and exchanging best practices
- Implementing effective tobacco control and public health programs
- Engaging donor organizations in cancer control effort
- Developing north-south partnerships

History

The first International Cancer Congress was held in Madrid in 1933. It led to the foundation of the UICC in 1935. So far, 20 conclaves of the World Cancer Congress have taken place. Since 2006, the World Cancer Congress takes place every other year. China has been selected as the destination for the 21st World Cancer Congress to be held from 18th -21st August 2010. It will review the latest knowledge about cancer causes, prevention, treatment and care, and examine how to optimize plans to control cancer now and influence a nation's or a region's cancer agenda as well as assess the role of cancer organizations in implementing the cancer agenda. The scientific program will be developed along the following tracks: Cancer prevention, Cancer treatment, Supportive care and Tobacco control. Within each track, the content of the Congress will be driven by the 11 targets of the World Cancer Declaration 2008 (WCD) that were elaborated in Geneva at the 2008 Leadership Summit.

WCD Targets to be Achieved by 2020

- Availability of cancer control plans in all countries
- Significantly improve measurement of cancer burden
- Decrease tobacco, alcohol consumption & obesity
- Universal coverage of HPV/HBV vaccine
- Dispel damaging myths & misconceptions
- Substantial improvements in early detection programs
- Improve access to diagnosis, treatment, rehabilitation & palliative care
- Universal availability of effective pain control
- Improve training opportunities in oncology
- Substantial decrease in migration of health workers
- Major improvements in global cancer survival rates

To achieve these targets, WCD outlines actions that should be progressively implemented in health policies and in prevention, treatment and research. The UICC has pledged to present a thorough report on the progress achieved in realising the targets set out in the updated WCD at the 2010 World Cancer Congress.

Future Perspectives

The UICC hopes that member organizations will use the WCD to further accelerate the progress being made by international collaboration in the fight against cancer. The UICC strongly believes that effective national cancer-control plans represent the most powerful method for realizing these goals.

NGOs could be especially helpful in developing pilot projects. The WCD should be viewed as a roadmap for change in the global cancer crisis.

(Reviewed by Dr K V Swaminathan, Chairman, RGCI&RC)

ACTIVITIES OF RGCI&RC

CHRONIC MYELOID LEUKEMIA

Prof Timothy P. Hughes, Head Haematology at SA Pathology, and Consultant Haematology at the Royal Adelaide Hospital, Australia, and Dr Devendra Hiwase from the same organization visited Rajiv Gandhi Cancer Institute & Research Centre on January 29, 2010 and delivered lectures on recent advances in Chronic Myeloid Leukemia (CML). It was attended by Medical Director, Director Research, Consultants, DNB students and Research Officers of the Institute.

CML is the most frequent chronic leukemia of myeloid derivatives and is categorized as clonal myeloproliferative disorder. It is characterised by peripheral blood leucocytosis resulting from an expansion of normally differentiated myeloid cells and typically presents incidentally on routine laboratory testing. It is the first leukemia identified with a causative clonal chromosomal rearrangement t (9:22) or the abl tyrosine kinase next to the breakpoint cluster (bcr) region, yielding the bcr-abl fusion protein. In 1960, the Philadelphia chromosome was identified along with the bcr-abl gene and its conversion into bcr-abl mRNA leading to a 210 kD fusion protein.

The management of CML has been revolutionized through targeted inhibition of bcr-abl protein by the oral tyrosine kinase inhibitor imatinib mesylate (Gleevec). CML therapy continues to rapidly evolve with the advent of new generation of small molecular inhibitors of bcr-abl.

The clinical course of CML is divided into chronic phase with a median survival time of 4-6 years and advanced phases which include the accelerated phase with a median duration of upto 1 year and blast crisis with a median survival of 3-6 months (terminal phase).

History of therapies used to treat CML has evolved from splenectomy, arsenic, radiotherapy, benzene, nitrogen mustards, busulphan, hydroxyurea, ∝-interferon, allograft to imatinib and second generation abl kinase inhibitors. Dr Hughes mentioned the mechanism of activation of bcr-abl protein and how it leads to a signal transduction cascade leading to uncontrolled activity and genetic instability. Imatinib inhibits its activation by binding to the ATP binding domain of the protein.

The strength of imatinib for CML in chronic phase is that it is extremely well-tolerated, most patients achieve >3 log reductions in leukemia cell and there is low risk of resistance if used upfront. Greater kinase inhibition induced earlier response with a reduced risk of progression. However, it doesn't eliminate the leukemia stem cells and is vulnerable to resistance, mainly from kinase domain mutations. In 2001, the first resistance mutation was described which was T 315 I.

Dr Hughes cited the case of a 15-year old boy of CML who presented with epistaxis and syncopal episode. The question was whether to proceed with allograft or medical therapy. Ultimately, the treatment given was imatinib since it is well tolerated and has 4 years survival in > 90% of patients. The patient is now in complete molecular response and may be able to stop therapy one day. Lastly, Dr Hughes spoke on the future prospects with the need for more potent and better targeted kinase inhibitors and combination therapies.

Dr Hiwase presented a few cases of CML and their treatments. The first case was a 71-year old lady who was treated with imatinib and with time developed resistance to it. She was found to have the E 225 K mutation. She was then treated with dasatinib and responded well to it. This case emphasized the importance of molecular assessment of response during treatment. Although imatinib is very effective in newly diagnosed CML- chronic phases patients, some people look their response by acquiring mutations in bcr-abl kinase domain. The efficacy of nilotinib and dasatinib according to baseline bcr-abl mutations was also described.

The next case highlighted the significance of loss of Y chromosome which may be due to clonal evolution or it may be age related change, not clinically significant. The evaluation of thrombocytosis was done to rule out evidence of iron deficiency anaemia, active bleeding and active infection. Dr Hiwase concluded by saying that although uncommon, two clones of myeloprofenative disease can exist in single patient and JAK kinase inhibitors may be helpful in such patients. However, currently, these patients can be treated with hydroxyurea and abl kinase inhibitors.

The Medical Director thanked Prof Hughes and Dr Hiwase for their visit to RGCI&RC and their informative presentations.

(Reviewed by Dr Dinesh Bhurani, Senior Consultant, Department of Medical Oncology)

CLINICAL RESEARCH

Clinical Research and Clinical Trial

Healthcare is guided by inputs from a wide array of agencies. Research on new molecules is conducted by pharmaceutical companies through a series of drug development processes. Clinicians become a part of these processes in what is termed as Clinical Research (CR), through conduct of clinical trials.

The National Institutes of Health (NIH), USA, defines CR as "**patient-oriented research,"** research conducted on human subjects (or on a material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator directly interacts with human subjects. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies.

A clinical trial is any research study that ***prospectively*** assigns human participants or groups of humans to one or more health-related ***interventions*** to evaluate the effects on health ***outcomes***. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.

Clinical research is an intrinsic component of clinical practice. It enriches practice by creating knowledge which is then applied to improve prophylactic, diagnostic and therapeutic procedures as also to improve understanding of the etiology and pathogenesis of disease. By challenging custom and questioning convention, and focusing on groups rather than individuals, it systemically creates evidence that compels changes in practice.

Trials are conducted step-by-step, i.e. in phases. In oncology, Phase I trials are done on 10-15 patients, and aim to determine the safety of the drug and define an optimal dose. Phase II trials continue to refine safety evaluation as well as get an idea of the efficacy aspects in a slightly larger (a few scores) patient population. It is the Phase III studies-Randomised Controlled Trials-where a few hundred to a couple of thousands, or even more, patients participate, which define the efficacy as compared to standard practices. Novel designs are being developed to minimise the 'at-risk' population while obtaining meaningful (conclusive) results.

Scenario in India

A large, treatment-naïve patient population, and the availability of a talented pool of English-speaking trained professionals leading to ease and speed of conducting trials with cheap labour costs, attract multinational companies to countries like India. However, this makes it even more necessary to ensure proper conduct of trials.

Drug trials may be conducted in India after permission from the Drug Controller General of India (DCGI). A clinical set-up referred to as 'site' may conduct any particular study only after the Institutional Review Board/ Ethics Committee (EC) approves it. In institutions, where there is no provision for such a committee, review is sought of Independent ECs. Whether institutional or independent, guidelines laid down by regulatory and advisory bodies (DCGI and Indian Council of Medical Research- ICMR) for the constitution and functioning of such Ethics Committees are followed in the review process to ensure that patient well-being remains the focus and there is no abuse of science by compromising ethics.

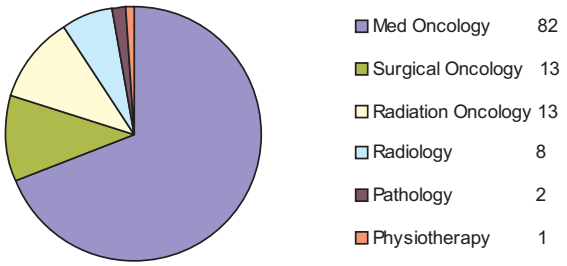
History is replete with many horrendous examples of clinical trials having been conducted in the most unethical manner. These examples have subsequently led to worldwide sensitization of the ethical issues involved. They took shape in the form of Good Clinical Practices (GCP) guidelines at the International Conference on Harmonization (ICH), and universally accepted as a beacon for the conduct of clinical trials. The trial is introduced, explained verbally and through an approved consent document which a patient can read and/or understand. It is the responsibility of the investigator / delegated person to ensure that patients take an independent, well-informed decision to consent for participation in a clinical trial and are not coerced into it. The mandate for registering clinical trials with the Clinical Trials Registry of India implemented since June 2008, ensures that knowledge about trials is in public domain.

Clinical Research at RGCI&RC

Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC) embarked on an eventful journey in Clinical Research after the constitution of the Institutional Review Board (IRB) in 1997. Currently, the IRB composition follows the mandate of Schedule Y by the DCGI. Issues related to ensuring patients' safety and well-being govern the actions of the IRB.

The RGCI&RC has earned the reputation of being a destination of choice, or a preferred research centre for many pharmaceutical companies and contract research organizations (CRO). It has attracted several international academic groups, like EORTC, GELA, BCIRG etc, as well as Indian universities like Delhi University and Jawaharlal Nehru University.

A department-wise break-up of clinical trial activities at the hospital are shown in Figure A.



The first Phase I oncology trial that was conducted in India was at this Institute about a decade ago. RGCI&RC has had an exposure to early phase studies, but advanced phase trials have predominated as depicted in Figure B.

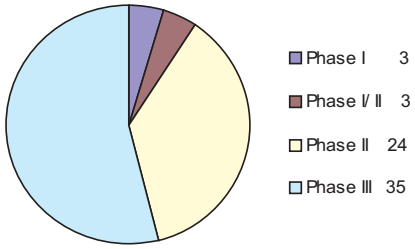


Figure B: Clinical Trials – Phase-Wise Break-Up

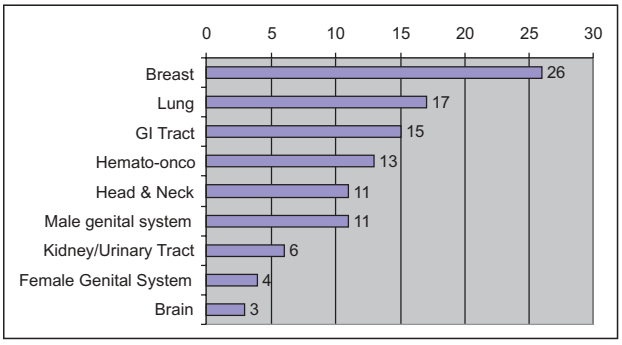


Figure C: Number of Drug Trials - Indication-Wise (Rest of the studies have been for cancers in general/ as supportive therapy during cancer treatment/ not drug trialsetc etc.)

The thrust of clinical research at RGCI&RC, in line with trends in the developed world, has been on targeted therapies-monoclonal antibodies like Trastuzumab, Rituximab; Tyrosine kinase inhibitors (Imatinib); EGFR inhibitors, namely, Gefitinib, Erlotinib, Lapatinib; VEGF inhibitors like Bevacizumab. Besides, novel chemotherapy agents like Alimta and Ixempra have also been used successfully in trials. A landmark study on the use of Gemcitabine in gall bladder (GB) cancer way back in 1999, led to publication of results in *BJC* in 2004, which further inspired many similar studies. Based on the evidence gathered, the Institute's investigator conceptualized a Phase II project investigating the role of neo-adjuvant chemotherapy (Gemcitabine and Cisplatin) in poor prognosis but potentially resectable GB cancer. Today, not only is the protocol followed as a standard of care, but also used as a comparator arm in other drug studies for this indication. Further, a recent Phase III trial by a group of British scientists, published at the ASCO, 2009, has established the protocol as the standard of care. Considering that the incidence of GB cancer in Delhi, and in general in the Gangetic belt, particularly in women, is among the highest in the world, this study has been truly path-breaking. Breast cancer trials of various phases in adjuvant and metastatic settings are also being conducted regularly and about 3-4 trials for this indication are running at any given point of time.

Novel therapies (after exhausting available standard options), like immuno-therapies, have been tried in lung cancer, renal cell carcinomas. Many clinical trials are also means of providing patients an expanded access to the otherwise "inaccessible" drugs.

Supportive care in oncology has seen major advances in the past two decades. Clinical trials in growth factors, observational studies in patients' psychological needs and challenges, quality of life and surveys in patterns of utilisation of complementary medicines, all highlight the various complex aspects of patient care.

The Surgical and Radiation Oncology teams have had a variety of technique, device and drugs trials. Among the drug trials conducted by the team, prostate has dominated the scene (13 trials).

Diagnostic studies in imaging and pathology/ microscopy / molecular diagnostics have been important in the understanding of patients' disease profile. This includes pediatric patients also.

The various Registries (national and international) and other epidemiological data collection are relatively rudimentary in India. RGCI&RC has been consistent in providing data through a handful of such studies.

Organisation of CR Activities at RGCI&RC

Clinical Research is a data-rich, labour-intensive activity. The set of skills required of researchers is not

just the domain knowledge, but also a hawk's eye for detail without losing sight of the larger picture. Research methodology, project management, data and time management are among the other essential skills. Above all, the most essential quality is commitment to understanding and reflecting only the truth. At RGCI&RC, the CR team comprises doctors, nurses, managers, office assistants. A PhD (underway), post-graduates in medical/ life sciences or management, graduates comprising 14 people have been on the job. The functions include patient management, data collection and transcription, pharmacovigilance activities etc. The site has faced a number of independent as well as sponsor / CRO driven audits. The team is geared for DCGI and other regulatory audits. The work done has been recognized by peer groups as evidenced by (a) abstracts presented at international meetings - 25, co-authored - 15; (b) full papers published - 10, and author citations- 7. The team regularly updates its capacities in terms of training and education. Some of the senior members have been part of the consultative group that made a set of recommendations to the ICMR, contributing to formulating the ICMR Ethical Guidelines for Biomedical Research on Human Subjects in the year 2000.

Funding

Clinical Research is a self-sustaining activity at RGCI&RC. It is funded by various agencies – sponsor initiated trials through the sponsor companies; academia-initiated studies through various interested academic groups. The hospital pools the financial resources through which all funds are disbursed as per the individual protocol required tests and procedures as well as for the personnel. Support has also come from the Department of Science & Technology, Government of India.

Future Perspectives

Research has always had a prominent role in the hospital activities at RGCI&RC and leaders have been playing inspirational roles for the team. Besides, it has helped inculcate a culture of detailed documentation and has provided some new technological capabilities to the hospital. Infrastructural and, at times, technology deficiencies, if managed in optimal time appropriately, will give Clinical Research a cutting edge knowledge advantage to lead future practices in clinical work.

(Dr Rashmi Shirali, Physician, Investigator – Clinical Research; Dr D C Doval, Chief, Department of Medical Oncology & Director Research)

EXPERTS CONVERGE

ESMO Conference: 11th World Congress on Gastrointestinal Cancer
Date: 24-27 June 2010
Venue: Barcelona, Spain
Inf: European Society for Medical Oncology (ESMO)
c/o Imedex Customer Service
Alpharetta, GA, United States
E-mail: meetings@imedex.com
www.worldgicancer.com/WCGI/index.html

13th World Congress on Pain
Date: 29 July-02 August 2010
Venue: Montreal, QC, Canada
Inf: International Association for the Study of Pain (IASP)
c/o JPdL MontrealMontreal, QC, Canada
E-mail: iasp2010@jpdl.com
www.iasp-pain.org/Montreal

15th Congress of the European Society of Surgical Oncology (ESSO)
Date: 15-17 September 2010
Venue: Bordeaux, France
Inf: ECCO- the European CanCer Organisation
Brussels, Belgium
E-mail: esso2010@ecco-org.eu
www.ecco-org.eu/Conferences-and-Events/ESSO-2010/page.aspx/1135

APACT 2010
Date: 06-09 October 2010
Venue: Sydney, Australia
Inf: Asia Pacific Association for the Control of Tobacco c/o Event Planners Australia
Ultimo, Australia
E-mail: info@apact2010.org
www.apact2010.org

22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics
Date: 16-19 November 2010
Venue: Berlin, Germany
Inf: EORTC, NCI and AACR
Brussels, Belgium
E-mail: ena2010@ecco-org.eu
www.ecco-org.eu/Conferences-and-Events/EORTC-NCI-AACR-2010/page.aspx/1386