Preservation of neurocognition in the era of high precision radiotherapy - a short review
Uday Krishna and Rakesh Jalali

Introduction
The anatomic and pathologic features of invasion of most the glial tumours is a limitation for complete surgical excision. Radiotherapy hence remains a vital and most effective adjunct to surgery in the CNS malignancies. In a landmark publication in 1978 by Walker et al of the Brain tumour study group confirmed a survival benefit of radiotherapy in malignant gliomas. A systematic review by Laperte et al has clearly shown that post-operative external beam radiotherapy is recommended as standard therapy for patients with malignant glioma. In low grade gliomas, the EORTC, RTOG and other studies have shown clear role of radiotherapy in delay of the time to recurrence, symptom control and survival benefit.

Poor penetration of chemotherapeutic agents of the blood brain barrier makes radiotherapy the ideal modality of treatment in brain metastasis from systemic malignancy. Addition of prophylactic cranial radiotherapy as an adjunct to systemic chemotherapy has demonstrated survival benefit in patients with small cell and non small cell lung cancer and in children with leukemia. Late effects in the form of endocrine dysfunction, neurocognitive deficits, and second malignant neoplasms have been attributed to RT. The biology of neuro cognition, various theories, effects of RT on cognition and the literature demonstrating role of RT in neurocognitive decline have been discussed.

Biology of neuro cognition and pathogenesis of radiation induced damage
Declarative memory (explicit memory/ remembering) is defined as the capacity for conscious recollections of facts and events. The structures of medial temporal lobe are the hippocampus (including the dentate gyrus) and adjacent anatomically related cortical areas, the entorhinal, perirhinal and parahippocampal cortices. The perceptual processing in neocortex gets transmitted to the medial temporal lobe structures and persists as long-term memory. The Projections from neocortex arrive initially in the parahippocampal cortex and perirhinal cortex and later to the entorhinal cortex and the hippocampal formation, thereby relating these structures get access to ongoing cortical activity. Diencephalon and mammillary bodies also receive inputs from the hippocampus. The medial temporal lobe and medial thalamus, thus constitute the neural system essential for the formation of long-term memory.

In the hippocampus, memory function is associated with principal cells which includes pyramidal and granule cells of the dentate gyrus. New granule cells formed from the stem cells in the sub granular zone, migrate to the granular cell layer, develop granule cell morphology, neuronal markers and connect to their target area. Cranial irradiation can lead to significant injury to normal brain structures. These effects are although imminent at higher doses of radiation, cognitive dysfunction without a structural damage is seen at low doses, in both adult and paediatric population. Cognitive decline manifests as deficit in memory, learning and spatial information processing.

Monje et al at the UCSF have demonstrated this phenomenon of “stem cell hypotheses” in mice. Apoptosis of the hippocampus was assessed immunohistochemically using bromodeoxyuridine (BrdUrd), 6-48 h after whole brain radiotherapy. Apoptosis was high 12 h after irradiation and was dose dependent. The proliferating sub granular zone was reduced to 96% at 48 h after irradiation and immature neurons were decreased from 40 to 60% in a dose-dependent fashion. The long term consequences were quantified with neurogenesis 2 months after irradiation with 0, 2, 5, or 10 Gy. The production of new neurons was significantly reduced by irradiation, being dose dependent with no effects on the production of new astrocytes or oligodendrocytes.

Effects of Whole brain radiotherapy on neurocognition
Poor penetration of blood brain barrier by chemotherapy agents and better control of microscopic disease by radiation has defined the role of WBRT in local control of patients with brain metastasis and survival in patients with lung cancer and childhood leukaemia.
Preservation of neurocognition in the era of high precision radiotherapy - a short review

Chang et al. through a phase III randomised study at the MD Andersen cancer centre, showed neurocognitive decline at 4 months in patients who received WBRT after stereotactic radiosurgery (SRS) compared to those patients who received SRS alone. Radiation induced neuronal injury to hippocampus and medial temporal lobe was considered central to neuro cognitive decline.

RTOG 0933 is a prospective phase II study which compared the decline in neurocognitive function by hippocampus sparing WBRT using tomotherapy based IMRT with the historic controls who had received WBRT without sparing hippocampus, as a part of PCI studies for SCLC. Previously, the group had demonstrated that the peri hippocampal region (hippocampus plus 5 mm margin) risk of recurrence of brain metastasis was 8.6%. RTOG 0933 showed better preservation of delayed recall as assessed by Hopkins verbal learning test (HVLT-DR) without compromise on local control in patients who underwent hippocampus sparing IMRT compared to the historic controls. At 4 months post RT, decline in the HVLT-DR was 7% compared to 30% in the historic controls (p=0.003) and only 2% of patients undergoing 6 month post RT evaluation showed further decline.

Temporal lobe and hippocampal dosimetry and correlation with decline in neurocognition for partial brain radiotherapy

A prospective controlled observation study by Gondi et al in adult patients with benign or low grade brain tumours treated with fractionated stereotactic radiotherapy and observed a dose response relationship between radiation dose to hippocampal dentate gyrus and long term memory impairment. A dose greater than 7.3 Gy to 40% of the bilateral hippocampi was associated with long term impairment of delayed verbal recall as measured by Wechsler memory scale. Correlation of dose delivered to the left temporal lobe and decline in neurocognition was initially demonstrated by Jalali et al, initial results of a large randomised controlled trial comparing efficacy of stereotactic conformal radiotherapy (SCRT) versus conventional RT in children and young adults with low grade brain tumours. Neurocognitive decline defined as a >10% drop in baseline intelligence quotient (IQ) correlated with doses more than 43.2 Gy to 13% of the left temporal lobe. Radiation dose levels on the hippocampus and various other brain structures was analysed by Jalali et al to preserve neurocognition in young patients with low grade brain tumours treated with high precision stereotactic conformal radiotherapy (SCRT). Change in the intelligence quotient (IQ) after SCRT was correlated with dose to bilateral hippocampi and other normal brain structures. Comparison of dosimetric data of patients with > 10% drop in baseline IQ with the patients who maintained a normal IQ revealed that in patients receiving > 27 Gy (50% of the prescribed dose) to > 50% volume of the left temporal lobe, showed an IQ decline.

Modifications in neuraxis irradiation in medulloblastoma and neurocognition

Merchant et al. have shown that children with high risk (HR) MB, requiring higher doses of craniospinal irradiation and posterior fossa boost show greater decline in neuro cognition compared to those with average risk (AR) MB (who receive craniospinal irradiation to a dose of 23.4 Gy and posterior fossa boost to a dose of 36 Gy). However this was not consistent in children less than 7 years of age in whom efforts to reduce the posterior fossa boost dose did not translate to cognition preservation.

Hyper fractionated RT provides an advantage of dose escalation while maintaining the therapeutic ratio in terms of increased biological equivalent dose to the cranio-spinal axis, while reducing the biological equivalent dose to the normal nervous system and minimising late effects. Eventually this translates to a higher local control and better relapse free survival and overall survival. This was tested for AR MB by various groups in the world.

HIT-SIOP-PNET4 was large multi institutional randomised trial addressing this issue comparing hyperfractionated RT and conventional RT, and showed that at a median follow up of nearly 6 years, there was no difference in relapse free survival or overall survival. Late effects in terms of ototoxicity were not different in the two arms.

A similar large longitudinal study was conducted by Gupta and Jalali et al. RT was delivered with two daily fractions (1.5Gy/fraction), 6-8 hours apart and 5 days/week. CS axis received 36Gy/36 fractions, followed by conformal tumour bed boost 32Gy/32 fractions for a total tumour bed boost of 68Gy/68 fractions. Cognitive assessment was prospectively performed pre treatment and specified post treatment follow up visits. Early results showed preserved cognition for all tested domains in children evaluable at 2 years after completion of RT with no significant decline over time.

Conclusions

Hippocampus is the seat for processing spatial information along with other structures of the temporal lobe. Clinical studies with SCRT in children and young adults with low grade brain tumours showed greater cognitive decline with higher doses to these structures. With improved local control and survival of patients with systemic cancer metastasising to brain and low risk of recurrence in the peri hippocampal region, techniques to spare hippocampus during WBRT (such as a tomotherapy) to reduce cognitive decline are very promising. Exploring the radiobiological superiority of hyper fractionation in treating the entire craniospinal axis with IMRT (such as tomotherapy) in children with average risk medulloblastoma is proving to be useful. Optimal utility of technological refinement in radiation planning and delivery is necessary to reduce late toxicity like neuro cognition in cranial irradiation.

References

5. Gondi V, Mehta MP, et al, RTOG 0933 Phase II study of Hippocampal avoidance during whole brain radiotherapy for brain metastasis, LBA 1, 55th annual meeting ASTRO, September, 2013.

Tata Memorial Hospital, Mumbai rjalali@tmc.gov.in

 Neuro-Oncology Group and Department of Radiation Oncology,
### AROI FELLOWSHIPS / AWARDS

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<th>S.No.</th>
<th>Name of Fellowship</th>
<th>Nos</th>
<th>For</th>
<th>Age Group (Years)</th>
<th>Fellowship Grant (in Rs)</th>
<th>Basis</th>
<th>LM AROI since (Yrs)</th>
<th>Min. Papers</th>
<th>Regularly Attending AROI conferences</th>
<th>Already availed fellowship in last 5 years</th>
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**Conditions**

1. Applicants have to send a copy of date of birth certificate.
2. Applicants to send a copy of the publications mentioned under each Fellowship.
3. Self certified proclamation that they are working full time in radiotherapy.
4. Fellowship amount will be given to candidates from money received from sponsors after tax deduction and 15% contribution to AROI fund.
5. All the applications for fellowship/ best paper awards be sent along with the letter from head of department/ institute to the office of Secretary General AROI by 5 PM, August 31st, 2014.
6. No Objection certificate from their head of Department if selected to go for fellowship.
7. PG Students shall send their certificates through Head of the Department.
8. For the best paper award, applications should be sent along the full paper.
9. Abstract along with the letter from the head of dept. for publication in JCRT should be sent along with the paper.
10. Radiation Oncology Applicants above age 35 must be member of ICRO.
11. Applicants to send softcopy also thru email.

**Mailing address:**
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Sheela . House No. 67,Near Bhartiya Vidha Mandir School,
Phase III, Urban Estate, Dugri, Ludhiana, 141013, (Punjab.)
Mobile No. 9316919170
Email: Secretaryaroi@gmail.com, Vashistha.aroi@gmail.com, drvashistha@gmail.com
16th ICRO PG Teaching Course at Shimla

16th ICRO PG teaching course was held on 26-27th April, 2014 in Shimla and the theme was “Radiotherapy Planning. From 2D to 3D”.

There was an overwhelming response and total 93 students from all over the country participated. The program was inaugurated by Prof Jayshree Sharma, Director Medical Education, Himachal Pradesh.

The course was started with lecture on basic physics of radiotherapy planning and continued with radiotherapy planning for head and neck cancers, pelvic tumors, Ca breast, Ca esophagus, Ca lung and cranio-spinal axis irradiation.

The faculty was invited from Apollo hospital Hyderabad, HCG Banglore, TMH Mumbai, GCRI Ahmedabad, PGI Chandigarh, PGI Rohtak Fortis Hospital Gurgaon, Medanta Medicity Gurgaon, and IGMC Shimla.

The program was highly appreciated by not only students but also by consultants. Finally quiz based on MCQs from the various lectures delivered in the course, was conducted and two students stood first. One was from TMH Mumbai and other was from IGMC, Shimla.

Input by Dr. Manoj Gupta

Notice

36th Annual conference of AROI (AROICON14) is going to be held in Imphal (Manipur) from 6th Nov to 9th Nov 2014. Main points of discussion will be as follows:

GBM of ICRO
On 6th Nov, 2014 after the completion of ICRO work shop at same hall.

GBM of AROI - I
On 8th Nov. 2014 at 6 PM or after completion of best paper in the main hall at Imphal

Agenda will be given later on.

Agenda for GBM
Amendment of constitution
a. Introduction of the post of “President Elect”
b. Change of tenure of President/Secretary Post/Editor-in-chief.
c. Increase in registration fee for new members.

Detailed agenda will be posted on website and mailed to all members as well.

GBM of AROI - II
30 minute after completion of GBM-I

Active participation of members is solicited.

The conference is to commemorate the 20th anniversary of the establishment of the Apollo Oncology Services in India. As cancer care has become one of the fastest growing health care needs in our country, Apollo Group chairman is keen to bring together the best minds in oncology both from India and overseas under one roof to deliberate on the rapid advances in this field and its practical applications.

The focus of this conclave is on integration of the cutting edge science, technology and emerging advances, into the day to day management of the patient care in the Indian Subcontinent, and the South East Asian region.

The Pre Conference Live workshops and Lung cancer Symposium were held on 6th Feb 2014 at the Hyatt Regency, Chennai. It included Uro oncology surgeries & Upper GI Oncology procedures live from Apollo Hospitals Chennai, Head & Neck Live Workshop and the High precision Radiation therapy live workshop from Apollo Speciality hospital. As a unique, the robotic Live Surgery workshop by Dr. Vipul Patel was live transmitted from Orlando, USA. On 7th Feb ‘14 NeuroSurgery live workshop surgical was live from Apollo Speciality hospital. All the workshops were webcasted in Apollo Cancer Conclave website and we live transmitted to various association and the few institutions.

The academic lecture sessions was started on 7th Feb 2014 at ITC Grand Chola, Chennai. We had 3 parallel tracks for the sessions; We had dedicated Meet the Professor sessions which was structured timetabled form in which 15 registered focused delegates discussed with the International expertise and exchanged their knowledge.

The conclave was inaugurated by the former President of India Dr. APJ Abdul Kalam on 7th Feb’14, Healthy deliberation were done to improve the cancer care in the entire Asian and African region the dignitaries from various countries in detail at Afro Asian Symposium which was held on the same day.

Special Plenary session was held on 8th Feb’14 with the guest of honor Satguru Jaggi Vasudev, Dr. Shantha, Chairman Adyar Cancer Institute & Dr. B. Ajai Kumar, Chairman, HCG cancer hospitals. Women Cancer Symposium and the Conquerors night held on the same day.

Apart from the dedicated scientific sessions we had special sessions on Robotic surgery, High Precision Radiation Therapy, Molecular Biology, Special Plenary sessions, Cancer Screening, women Cancer Symposium and Cancer Conquerors night and Afro Asian Symposium.

The Apollo Cancer Conclave was very successful and had a participation of over 2000 delegates from 28 countries, including 300 faculties with 36 scientific sessions dedicated to each specific area in cancer care.

There was a overwhelming response and the appreciation from all the delegates who really were very satisfied with the high quality academic discussions.

An International Journal has agreed to publish the important outcomes from our Apollo Cancer Conclave. The same can be sent to Govt. of India for the benefit of the medical community of our country.

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### Obituary

**Dr Sanjay Supe (1962 - 2014)**

Born in family of illustrious father Medical Physicist Dr. S J Supe at Mumbai, he destined to be a Medical Physicist.

He was jovial, full of life, research oriented person who was friend, philosopher & guide to so many physicists and oncologists.

For almost three decades he made KMIO Bengaluru as his home and made a distinct name for himself in radiation oncology fraternity.

His sudden loss due to illness has created a great void and we pray to almighty for peace to his departed soul.

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Some comments on facebook on his demise

I am shocked, Sanjay was energetic colleague. Fearlessly frank, brutally honest. My heartfelt condolences to bereaved family.

- K S pathasarthy

Its very sad, we have lost a fine human being.

- Suresh Pamidighantam
Call for participation in 36th AROI conference at Imphal from Nov. 06-09, 2014

The “36th Annual Conference of Association of Radiation Oncologists of India” is being organized by North Eastern Chapter of AROI and being hosted by Department of Radiotherapy, Regional Institute of Medical Sciences, Imphal, Manipur (India) during Nov. 06 – 09, 2014. The theme of the conference is “Collaborate and together we conquer”. The first day of the conference will be devoted to CME on brachytherapy and the remaining days will deliberate on all types of cancer.

Conference Venue:

Collaborate and together we conquer—enjoy this themed conference in the lap of Manipur, the Jeweled Land, full of surprises and rich culture

The conference will be held in “City Convention Centre” which is located in the heart of the city.

Conference Secretariate:

Department of Radiotherapy,
Regional Institute of Medical Sciences,
Imphal, Manipur (India) – 795004
Tel.: 0385-2410901 / Fax: 0385 – 2411703
Email: aroicon2014imphal@gmail.com

Our Newsletter Partners for this issue
AROI members going places

Dr Rakesh Jalali was invited as a **Grand Round Speaker at the MD Anderson Cancer Center**, Houston on 25th November 2013.

The title of his talk was "Pediatric Neuro Oncology: challenges and successes in developing countries".

Dr. Rakesh Jalali Co-chaired the Scientific Committee at the recently held World Federation of Neuro Oncology (WFNO) conference in San Francisco between 21st to 24th November,

Dr. A K Anand, Director, Radiation Oncology moderated a session on Treatment Planning during “Awareness Programme on Radiation Safety & Quality Assurance: Driving the benefits of Innovations in Radio Diagnostic and Therapy” on June 5, 2014

4. Dr. Subhash Gupta, Astt. Prof. gave a lecture on Evolution of Modern Radiation Technologies during above mentioned session.

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**Forthcoming Events 2014**

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**National**

July 2014

12-13  **17th ICRO Teaching Course**
Tata Memorial Centre, KOLKATA

Email: raj.shrimali@tmckolkata.com

August 2014

15-16  **MhCI AROI**
Nagpur

Email: mhci.aroi@gmail.com

September 2014

13  **4th Teaching Course “Basic Radiobiology”**
RCC, IGM, Shimla

Email: mkgupta62@yahoo.co

20-21  **20th NZAROICON-2014**
PGIMS, Rohtak

Email: nzaroicon2014@gmail.com
secretary@nzaroicon2014.com

26-28  **FHNO-2014**
PGIME&R, Chandigarh @ J W Mariott

Email: vamahospitality@hotmail.com
www.fhno2014.com

October 2014

10-11  **12th Annual Radiotherapy Practicum**
Teaching Course in Radiotherapy
Tata Memorial Centre, Mumbai

Email: radonco@tmc.gov.in

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**International Events**

November 2014

28-30  **6th SFO, 2014**
The Leela - Ambience, Gurgaon

Mail: saarconcology14@gmail.com,
akvaid@yahoo.com
Web: www.sfo2014.com

Compilation by: Dr. Pardeep Garg, Faidkot
Fortis Memorial Research Institute holds CME cum Workshop on Electron Therapy- Revisited

FMRI, Gurgaon had a CME cum Workshop on electron application in Radiation Oncology on June 14, 2014. Event covered topics related to physics of electrons, current technologies for its generation, dosimetry, commissioning, beam planning, special therapy procedures and clinical challenges in its application. Eminent faculty from national and international centres participated to address the sessions and give hands on training. A lively debate on whether electron therapy has lost its relevance in modern day therapy was held at the end of day. A large number of Radiation Oncologists and Medical Physicists participated in this event.

Input by T Ganesh & Kanan Jassal

Response to last issue question

Role of evidence based Radiation Treatment Management in current practices?

Evidence based practice is a norm globally and its definition is, “The conscientious, explicit and judicious use of current best evidence in making decisions about the individual patient care”. It means our professional judgements and behaviours should be guided by two independent principles:
- When ever possible practice should be grounded on prior findings that demonstrate empirically...that they are likely to produce predictable, beneficial and effective results.
- Every client system over time should be evaluated.

In radiation oncology, current practice is based on Individual’s clinical expertise supported by NCCN & RTOG guidelines which helps in multi centre trials and evaluations for systematic research Compilation of various current Radiation Oncology practices by Dr. Arun Verma, Consultant, Max Patparganj, Delhi indicates effect of evidence on cancer management as follows:

- A systemic review and meta-analysis recently published in green journal by Marta et al had established role of IMRT over 3D CRT. It showed significant overall benefit of IMRT in xerostomia score grade 2-4 with insignificant trend of improved local control and survival. In another study, Radiotherapy in breast cancer patient added a survival benefit of 3.8% in 15 years in post BCS, 5.4% in 5 years in post mastectomy, node positive patients. Though, newer techniques do not add survival benefit but have role in delivering homogenous doses and reducing late toxicity specially cardiac morbidity, maintaining size of breast / cosmetics.
- Similarly novel technique i.e. SBRT has challenged surgery in T1-2 lung cancer with 95% local control and 66.6% overall survival at 2 year while randomised controlled trial and meta-analysis established chemoradiation as standard of treatment in stage III NSCLC and limited stage SCLC.
- INT 0116 trial made adjuvant chemoradiation standard of treatment in loco-regionally advanced gastric cancer with median OS of 35 months vs 27 months in surgery alone.
- Systemic review and meta-analysis published in JCO 2012, established role of adjuvant RT+CT in R1 operated hepato-biliary tumors, and uncertain benefit for R0 patient with positive node but in contrast there is level 3 evidence of improved survival benefit in postoperative T2-3, NO-1MO gall bladder cancer.
- Although randomised trial showed equal survival benefit with preop or postop RT+CT in rectal cancer but there is added advantages associated with preop RT+CT like increased respectability with down staging, and increased pathological response which may get reflected in increased survival benefit with increased sphincter preservation rate in long term and future trial.
- Prostate cancer is one site where newer technique hypo-fractioned IMRT, IGRT +/- brachytherapy challenged surgery in all three risk group i.e. low, intermediate and high risk.
- Another site is cervical cancer where role of radiotherapy is strongly established and limiting role of surgery in medically fit, stage Ia only. Ib and Iia can be equally treated by surgery or EBRT + Brachytherapy but most of time required adjuvant RT in presence of risk factors. Beyond this RT+CT is gold standard treatment except in IVB.
- Level of evidence, its source, grade of recommendations decide whether guidelines are recommendations, suggestive or no guidelines are possible from the study.

When ever possible practice should be grounded on prior findings that demonstrate empirically...that they are likely to produce predictable, beneficial and effective results.

An article recently published in journal ‘Report of Practical Oncology and Radiotherapy that explored evidence based radiation oncology and emphasized development of new radiotherapy centre and upgradeation of existing centre to improve quality of radiotherapy that get reflected in term of better outcome with good quality of life.
However implementing any new evidence based practice is always a challenge as its relevant advantage, costs, compatibility, complexity, trialability, reinvention, observability of benefits and risk attributes need to be addressed.

Input by Dr. Arun Verma & Deepak Arora

Views expressed are personal by respondent to question of the issue.—Editor

Question of this issue

Are we ready for incident free radiation treatment delivery?

Please send your reply for publication in next issue of AROI newsletter to deepak.arora3@maxhealthcare.com