AROI NEWSLETTER



June 2020 Vol.16, Issue 2

From the office of AROI

Dear Friends,

Hoping you and your family to be safe. As you are aware the world is facing a pandemic and the usual lifestyle is changing....

- We at AROI—ICRO are concerned about the safety of our members but at the same time, have an equal responsibility to disseminate teaching for the PG's and young members of AROI.
- ☐ Due to ongoing COVID situation it is becoming difficult to hold one to one meetings/ teaching programs on regular basis.
- ☐ However executive committee of AROI has taken a decision that even during this situation we have to carry on with our teaching activities under ICRO.
- ☐ Our ICRO chairman Dr. Satyajit Pradhan & ICRO secretary Dr. Srinivasan has taken responsibility to hold our teaching programs in each group.
- ☐ Decision has been taken to conduct online the

following teaching programs:

- ☐ AROI-ICRO PRODVANCE (supported by Sun Oncology)
- ☐ AROI-ICRO PG teaching course (supported by Sun Oncology)
- ☐ AROI-ICRO Radiobiology course (supported by Intas)
- ☐ After assessing the response & effectiveness of these programs, further programs will be decided.
- ☐ This year AROICON at Delhi, has been postponed.
- ☐ 3rd ICC in 2021 at Mumbai is also postponed.
- ☐ So AROICON 2020 at Delhi will now be held in 2021/2020 at Delhi under guidelines of Dr. Kumar Tapash Bhowmik, depends on the 3rd ICC status.
- ☐ In the end we wish all of you & your family to be safe & healthy.
- ☐ Take precautions Mask, Social distancing, Sanitise yourself & your department & take care of your colleagues.
- ☐ After working hours stay Home –Stay Safe...

ALL THE BEST

Dr. Rajesh VashisthaDr. G.V. GiriDr. Manoj GuptaPresident AROISecretary General AROIPresident Elect AROI

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AROI EC Meeting



Executive Committee Meeting Minutes

Dear Friends,

The online Executive committee meeting was held on 2nd June 2020 at 2:30 pm keeping in mind the safety of us all, time consideration and to discuss the academic activities to be conducted.

1. AROI-ICRO PRODVANCE Course:

The EC decided to conduct the program as a webinar over 2-3 days with 2-3 hrs Session per day, with topic being Stereotaxy. The Central committee of ICRO will organize the program, Dr Pradhan and Dr Srinivasan will take the responsibility of the program content and duration. Mr. Suri has agreed to get the logistics for the program through SUN pharma educational grant.

Tentative dates: Mid June, all the members agreed to the above.

2. SUN ICRO Program:

The EC discussed and decided to have SUN ICRO as webinar. The topic will be Genito Urinary; program will be done over 3 days with 2 to 3 hrs of daily sessions. The ICRO Central committee will take the responsibility of Organizing the event. After accessing the response of this program the decision regarding further Programs will be taken. SUN Pharma will provide the required logistics for the program (Up to 4 hrs of online slot daily for 3 or more days, along with platform for Q & A and other Interactions)

3. Radiobiology Program:

The EC again approved to conduct Radiobiology course online. Dr Manoj Gupta proposed to hold one online meeting of radiobiology in third week of June as a staggered program, based on the response will decide about holding further programs. Dr Vashistha said he has spoken to INTAS Pharma and they have agreed to take Care of the logistics of this program.

All AROI-ICRO teaching programs this year (2020) will be conducted by central ICRO and AROI only. It was also decided that the local chapters who were given responsibility of hosting the AROI- ICRO programs for this year(2020)

AROI-ICRO PRODVANCE

AROI ICRO SUN PG teaching course

AROI ICRO Intas Radiobiology course;

will host it as per revised schedule next year(2021).

4. AROI -ESTRO Advanced Technology Course:

The Executive committee decided that the upcoming advanced technology Course to be held in Kolkata will be postponed to December 2021. The same will be communicated to ESTRO.

5. AROI -ESTRO Gyn Teaching Course:

The above course is scheduled in March 2021. Young Radiation oncology meeting- to be held in January 2021. The EC decided to review the situation in August regarding these meetings. The committee decided that it will meet again to decide regarding this program after 2-3 months depending on the COVID situation.

6. AROICON 2020:

In view of the current COVID crisis, AROICON stands cancelled for this year, however it will be held in Delhi under the North Zone either in 2021 or 2022 depending on the schedule of 3rd ICC.

7. 3rd ICC:

The committee discussed the probability of 3rd ICC 2021 also getting postponed but the final decision will taken by the ICC committee in this month.

8. Invitation for AROI Fellowships:

For this year & extension of completion of fellowships of 2019

The Executive committee decided not to call for AROI fellowships this year as the fellowships provided in AROICON 2019 have not been completed and these fellows will be given one more year extension to complete their fellowship.

9. FICRO Awards:

The committee decided to invite the applications for FICRO awards. The selected Members will be given the fellowship in the subsequent AROICON. Dr Pradhan and Dr Srinivasan will take the responsibility of FICRO.

10. Elections:

The EC decided that no elections will be held this year due to extra ordinary circumstances and also the new EC will not be able to take over in the GBM as AROICON 2020 stands cancelled. It was unanimously decided for the same executive to continue till next year and to call elections in 2021 as per date schedule, also that state chapters also can follow the same procedure adopted by central committee.

AROI EC Meeting



Executive Committee Meeting Minutes

11. Best of ASTRO Amritsar:

It will be decided by Dr. Neeraj Jain to hold as virtual meeting or postpone. He will inform within this month

12. Regarding Funding for JCRT:

Dr Vashishta informed the EC and Dr Kishore Singh that

Rs 5 lakh has been deposited in the JCRT account (published by wolters kluwer) and further fund will be transferred shortly in July end /August 1st week.

The decisions taken during the meeting are here for your consideration and approval.

FICRO awards Fellowship - Indian College of Radiation Oncology

Guidelines and Instructions for nomination of candidates An individual elected as a Fellow of the Indian College of Radiation Oncology is expected to:

- (a) Stand out among peers in the profession as a person of distinction at the national/international level.
- (b) Have distinguished himself/herself in the profession:
- (i) as a physician in his / her specialty; and/or
- (ii) in service to Medicine in patient care, teaching, public health work and/or health administration.

The Eligibility Criteria for the Fellowship of Indian College of Radiation Oncology:

1. Founder Members of the ICRO

OR

Admission Fees.

- 2. Membership of the ICRO for at least 5 years and possessing more than 15 years of experience after post-graduation.
- A. Founder members are automatically eligible for award of the Fellowship, subject to submission of
- Application and the payment of the Admission Fees for the Fellowship. (Fellowship Fees-6500/- INR.)
- B. For other than Founder Members, Application needs to be submitted and after Election as a Fellow, a communication will be sent to the Elected Fellows for depositing the Admission Fees for the Fellowship, by the due date as per the communication.
- C. Fellowships will be awarded after the receipt of the

Format of the Application Form and the Instructions can be downloaded from the AROI Website. A

soft copy of the application is to reach Dr. V Srinivasan,

Secretary ICRO through e.mail

(secretaryicro@gmail.com) so as to reach him not later than 12 midnight of 31st July, 2020. A hard copy of the application along with all supporting documents is to reach the Secretary, ICRO (Address given in the application form) at the earliest but not later than 10th August, 2020. Late applications will be considered only for the Election of Fellows for the subsequent year. Admission Fees for ICRO Fellows:

Rs 6500/-(Rupees Six thousand and Five hundred only) through DD/ Onilne Bank Transfer to "AROIICRO",

Name of A/C: AROI-ICRO Bank: State Bank of India

Bank Address: Millerganj, Ludhiana, Punjab-141001

Account No: 30619770736

IFSC: SBIN0000731 Type of Account: Savings

The Nominees are to be Proposed and Seconded by Members of AROI of GOOD STANDING of

FIFTEEN YEARS duration. The PROPOSERS AND

SECONDERS MUST BE ICRO MEMBERS.

Soft copy of the Application must reach the Secretary, ICRO by midnight of 31st July of the year of

Election, with a copy to the Chairman, Documentary evidence of all

Statements/Experience/Awards must be attached to the HARD COPY of the Application and is to be

sent to the Secretary, ICRO so as reach him/her on or before 10th August of the year of Election.

FICRO awards



Fellowship - Indian College of Radiation Oncology

The attention of the Proposer and Seconder making the nomination is invited to the Guidelines and Instructions laid down for the purpose.

- 1. The Proposer and Seconder nominating the candidate should certify from personal knowledge the professional and scientific standing/achievements of the candidate
- 2. Every candidate shall be proposed and seconded by a statement in writing signed by at least two Life Members of AROI of GOOD STANDING of FIFTEEN YEARS duration. The proposers and Seconders must be ICRO members.

Instructions

- 1. Five copies each and a CD/DVD of the following documents must accompany the application for nomination
- (i) A precise statement limited to 120 words on nominee's professional and scientific standing/achievements which form the basis for nomination signed by proposer/seconder.
- (ii) Information as per format prescribed, duly completed. Follow the same section numbers in their submission as in the nomination form avoiding reference to enclosed appendices.
- (iii) List of publications:
- (a) Two separate lists of publications i.e. one in Journals included in Medical Databases, Medical Literature analysis and retrieval system (Medlar) etc. and other one in Journals, not included in medical database but published in Journals of National Societies/Professional Associations.
- (b) Be written in chronological order and should include
- (1) Names and initials of all authors, (2) Title

of article, (3) Title of publication abbreviated, (4) Volume number, (5) First and last page number, (6) Years of publication.

Reference to books should include: (1) City of publication (2) Name of Publisher (3) Year of Publications.

Abstracts and Proceedings of Conferences etc. should not be included in the list of publications.

2. Five copies each of six published papers considered to be best by the proposer. The Citation Index of six best published papers of the nominee and Average Impact Factor of the Journals in which the six best papers have been published may also be provided along with nomination for Fellowship. (Impact factor of the Journal in the year of publication of the concerned article).

The under-mentioned guidelines may also please be noted in this connection:

- 1. Only Life Members of AROI of GOOD STANDING of FIFTEEN YEARS duration and who are
- ICRO Members can Propose or Second the Nominee.
- 2. A Member may not propose more than three names for Fellowship in a year. He/She may, however, second any number of proposals.
- 3. The candidate shall be Indian citizen. Exceptionally a foreign national who may have done outstanding work in India or for India in his/her own country may be considered.

Note: Nominations which are either incomplete or not according to the prescribed format will not be processed., seconded by- Dr Suresh Kumar -House Approved



Secretary – ICRO Dr. V Srinivasan



Vice Chairman – ICRO Dr. D N Sharma



Chairman - ICRO Dr. Satyajit Pradhan

HONOURS & AWARDS



Congratulations



DR UMESH MAHANTSHETTY,

DMRT, MD, DNB (RT)

Director, Homi Bhabha Cancer Hospital & Research

Centre,

(A Unit of Tata Memorial Centre, under Department of Atomic Energy, Govt. of India)

Dr Umesh Mahantshetty is working as Professor and Senior Consultant Radiation Oncologist at Tata Memorial Centre, Mumbai India - one of the largest comprehensive cancer center in Asia. After completion of MD and Senior Residency at Tata Memorial Hospital, has completed fellowships in brachytherapy and newer imaging at Erasmus Medical Centre, Rotterdam NL and MD Anderson Cancer Center, Houston, USA.

Dr. Mahantshetty is specialized and highly recognized in the field of Gyecology Oncology and is one of the key opinion recognized leader globally in the field of GYN Oncology including high precision radiation techniques and Image Based Brachytherapy. His numerous achievements include Expert for establishing guidelines at national (ICMR Guidelines for Cervical Cancer) and international (ESGO / ESTRO guidelines for vulvar and cervical cancer management) bodies, a consultant to the recent ICRU 89 Report on GYN Brachytherapy and Senior Editor of various prestigious International and National Journals.

At present leading the GYN Radiation Oncology group at Tata Memorial Hospital, he is involved numerous projects and research protocols which have high impact on both the developing and developed world. He has also been instrumental in building up the Indian Brachytherapy Society (IBS) in the capacity of Secretary since 2013 and part of Executive Committees of Association of Radiation Oncologists of India (AROI) and GYN Oncologists of India (AGOI) since many years.

As an Invited speaker, he has delivered numerous lectures at various national and international scientific forums and has been actively involved as faculty of ESTRO School for GYN Radiation Oncology and Advanced Technologies teaching courses, IAEA training Activities and is Director of AROI – ESTRO Course in India.

Dr. Mahantshetty's numerous research publications (more than 180 original articles) in high impact journals such as JAMA Oncology, Lancet Oncology, JCO, IJROBP, Radiotherapy Oncology etc; have been instrumental in guiding treatment philosophies in the management of cervical cancers. In particular, his work on practice changing studies in cervical cancers, collaborative research with GYN ESTRO, UCSD groups, image based brachytherapy in cervical cancers, has been keenly observed and acknowledged by researchers world-wide. Till date he has approximately 200 original publications in peer reviewed journals and as text book chapters.

Dr Mahantshetty is also actively involved in various green projects, TMC Cancer satellite centers (Varnanasi, Viashakapatanam, Sangrur, Mullanpur etc.) right from conception to operational processes for Radiation Oncology Units.

In summary, Dr Mahantshetty is an Internationally acclaimed Oncologist, well known in Radiation Oncology Community for his contribution in GYN Oncology and a responsible, dedicated, and a well known leader in Oncology.

Since 1st April 2020,he has been appointed as Director of Homi Bhabha Cancer Hospital & Research Centre, Visakhapatnam which is A Unit ff Tata Memorial Hospital under Department of Atomic Energy Government of India

This issue is brought to you by

Dr. Vikas Jagtap

Associate Professor & HOD

drvikasj@yahoo.co.in , +91 - 88222-31236, NEIGRIHMS – Shillong
On behalf of Association of Radiation Oncologists of India (AROI)

HONOURS & AWARDS



Congratulations



Dr. Rajiv Kumar Devgan

Appointed as Principal and Controller of Government Medical College, Amritsar

Brief History of Government Medical College, Amritsar

Government Medical College, Amritsar comes into being as a Medical School in Lahore in 1864.

The School was upgraded to the status of Medical College in 1943. The Medical College was named after His Excellency Sir Bertrand James Glancy, the then Governor of the state. The new Medical College started awarding the M.B.B.S. degrees which empowered the holders to practise Medicine and Surgery in 1944.

More than 1100 beds are available for teaching and training of under graduate, post graduate and paramedical students.

The Medical College and Guru Nanak Dev Hospital is spread over an area of 163 acres and has sufficient land for future expansion. The Institution has also provided brilliant doctors and medical scientists, not only to prestigious institution of India like All India Institute of Medical Sciences, New Delhi and Postgraduate Institute of Medical Education & Research, Chandigarh but also many Institutes in the world, particularly U.K, U.S.A and Canada.



Prostate Permanent Implant Brachytherapy



Dr. V. Lokesh M.D.
Professor & Head
Department of Radiation Oncology
Kidwai Memorial Institute of
Oncology, Bangalore

V. Lokesh*, S. Palled*, S. Mandal*, P.Tanveer, T.Naveen, V.Bindhu, R.A.Sunil, S. Sathyan#, K. M. Ganesh#, (*-Department of Radiation Oncology. #- Department of Radiation Physics)

The Department of Radiation Oncology at Kidwai Memorial Institute of Oncology (KMIO) RCC, Benguluru has recently started permanent implant brachytherapy, making it the first state to offer this treatment free of cost with use of indigenous I-125, BARC Ocu-Pro seed.

We are expecting to use iodine seeds for the implant procedure for approximately 20-30 patients annually. I-125 seeds implant brachytherapy is commonly used for prostate cancer, but can also be used in certain scenario of pancreatic cancer, bladder cancer, lung cancer, breast cancer, liver cancer, bone and soft tissue sarcomas. Several guidelines outline the indications and procedure of permanent implant brachytherapy forprostate cancers (1,2,3,4).

Prostate LDR Brachytherapy Technique at KMIO, Bengaluru:

A. Pre-plan volume study

Before seed implantation, the patient. will undergo a prostate volume study usingdedicated trans-rectal ultrasound (TRUS). The images are transferred to The Best® NOMOS (DBA: Best Medical International, Inc., Pittsburgh, PA), treatment planning systems (TPS) dual Activity Module creates treatment plans. This helps for optimal source placement to maximize coverage of the target volume, the exact number of seeds required, also pubic arch interface and patients with large gland can be sent for cytoreduction.

The Best@ Sonalisultrasound with high resolution using frequencies between $5-12\,\text{MhZ}$ with a biplanar system, to allow sagittal and axial visualization. Stabilizer and Stepping unit support system containing a cradle to hold the ultrasound probe and allow three-dimensional axes.

The unit can be mounted on the operating table. Perineal template that will be fixed onto the stepping system and calibrated accurately match the grid displayed on the ultrasound image. The QA of USG machine commissioning and acceptance was carried out.

B. Brachytherapy Implant procedure

Implantation needles with 18G and 20cm long are used to implant I-125 seeds using Stepping unit source system and Mick's applicator. Locking (stabilisation) needles are optional. Foley catheter helps to visualize the urethra on TRUS. We performed after loading implant technique i.e., the needles are positioned in prostate first, and then seeds are implanted into prostate gland using the Mick's applicator with preloaded I-125 seeds into the cartridge. A fluoroscopic image is taken and ultrasound scan from

A fluoroscopic image is taken and ultrasound scan from base to apex to ensure all seeds are accounted for before leaving the operating room. All the radiation safety measure was ensured before, during and after the procedure.

C. Post-plan dosimetry

The timing of post implant imaging will produce different results in post implant dosimetry due to varying degree of trauma related prostatic oedema. ABS recommends CT based post implant dosimetry depending on the radionuclide used: 16±4 days for palladium-103 and 30±7 days for iodine-125.

Patient withstood treatment well without any major complication and is under close follow up. The permanent I-125 seeds implant brachytherapy has the potential to grow on wider scale and multiple indications, delivering higher doses of radiation to the tumour with lesser side effects.

Case Illustration

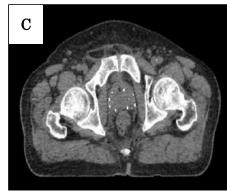
A 78yr old gentleman with newly diagnosed prostate adenocarcinoma stage-T3aNOMO, grade II, Gleason score 7 and PSA – 20ng/ml. He was treated with neoadjuvant hormonal therapy with Inj Leuprolide followed by Definitive Radiotherapy with a dose of 50Gy/25fr to whole pelvis by VMAT technique and boost 110Gy to prostate alone by I-125 seeds implant permanent brachytherapy in Oct, 2019. He achieved good biochemical response at six months follow up.

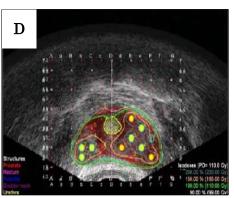


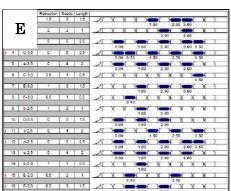
Prostate Permanent Implant Brachytherapy

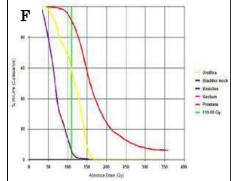












- A. Prostate Permanent BT procedure using Mick Applicator, Stepping Source unit, TRUS &I-125 seeds
- B. Scout AP image showing radio opaque I-125 seeds implanted in prostate
- C.CT axial image showing patterns of I-125 seed implant in prostate
- D. Isodose profile of prostate I-125 brachytherapy
- E. Needle and source information sheet showing its total number & positions
- F. DVH showing D90 of target volume is 107.5Gy and dose to OARs within limits

References

1) Davis BJ, Horwitz EW, Lee WR, et al. American Brachytherapy Society consensus guidelines for

transrectal ultrasound-guided permanent prostate brachytherapy. Brachytherapy (2012), 11(1):6–19.

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- 3)Ash D, Flynn A, Battermann J, et al. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. RadiotherOncol (2000) 57(3): 315–321.
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De-Intensification Strategies In HPV Positive Carcinoma Oropharynx- Where Do We Stand?



Dr.Cessal Thommachan Kainickal Additional Professor Regional Cancer Centre Trivandrum, Kerala,India



Dr.Aprana Sannu MPAssistant Professor
Regional Cancer Centre
Trivandrum, Kerala,India

Dr. Aparna M.P, Dr.Ramadas.K, Dr.Rejnish Kumar, Dr.Malu Rafi, Dr.Naveen Kumar .P, Dr.Geethu Babu, Dr. Kainickal Cessal Thommachan Department of Radiation Oncology Regional Cancer Centre, Thiruvananthapuram Corresponding Author: Dr. Kainickal Cessal Thommachan Email:drcessalthomas@gmail.com

Introduction

Human papilloma virus (HPV) has emerged as an important causative agent for oropharyngeal squamous cell carcinoma with distinct clinical behavior and outcome. The survival of these patients is better and many trials are ongoing to reduce the toxicities associated with treatment. This article tries to summarize the various strategies being tested for better management of HPV positive oropharyngeal carcinoma. Rising incidence of oropharyngeal carcinoma Last few decades has witnessed the reduction in the incidence of laryngeal and oral cavity cancers, mainly due to the reduction in the usage of Tobacco among adults.

tast few decades has witnessed the reduction in the incidence of laryngeal and oral cavity cancers, mainly due to the reduction in the usage of Tobacco among adults. On the contrary there is a recent trend towards increasing number of cancers of the tonsil, tongue etc.Chathurvedi et al based on a Surveillance, Epidemiology, and End Results (SEER) data reported an increase in incidence of oropharyngeal cancers caused by HPV infection [1].They also noticed an improved survival in this subgroup[1].It was further observed that the clinical behavior is different from that of HPV negative subgroup [2].

	IIDV positivo	LIDV magative
	HPV positive	HPV negative
Age	younger	older
gender	3:1 men	3:1 men
Socioeconomic status	high	low
Risk factors	Sexual behavior	Tobacco, alcohol
Co factors	immunosuppression	Diet ,hygiene
incidence	increasing	decreasing
survival	better	worse
Predilection site	Tonsil, base of tongue	none
Histology	basaloid /poorly differentiated	keratinized
T Stage	Lower T stage	Higher T stage
Nodal status	Higher	Lower
Field cancerization	Unknown	Yes
Genetics	P53 inactivated by E6	P53 is mutated
	Rb inactivated byE7	Rb inactivated by cyclin
	P 16 over expressed	D1amplification
		Inactivation of p 16

Table 1. Major differences between HPV positive and negative oropharyngeal cancer



De-Intensification Strategies In HPV Positive Carcinoma Oropharynx- Where Do We Stand?

Many trials have reported survival benefit for HPV positive oropharyngeal carcinoma. In the DAHANCA 5 trial, patients with head and neck cancer were treated with conventional radiotherapy +/-Nimorazole and subset of patients with oropharyngeal carcinoma showing expression of p16 (INK4A) reported better treatment response [3]. RTOG 0129 trial was a randomized trial comparing accelerated-fractionation radiotherapy with standard-fractionation radiotherapy with concurrent cisplatintherapy in patients with locallyadvanced squamous-cell carcinoma of the head and neck. A retrospective analysis of HPV positive oropharyngeal carcinoma patients using DNA ISH (in situ Hybridization) and p16 (INK4A) reported strong association between HPV status and good survival among oropharyngeal carcinoma patients [4]. They risk stratified the patients as having a low, intermediate, or high risk of death based on combination of tumor HPV status, packyears of tobacco smoking and cancer stage. In the low risk group, which included HPV positive and non-smokers, 3 year disease free survival (DFS) was 93% when compared to< 50% in the high risk group which included the HPV negative and smokers. Intermediate risk group included

HPV positive patients with smoking history and HPV negative non -smokers. This led to the thought for Deintensification of multimodality approach for low risk category patients.In the post op setting, German radiation oncology group study showed correlation of HPV positive status with oropharyngeal carcinoma sub site and better outcome in the patients undergoing adjuvantchemo radiation for locally advanced head and neck cancers [5].RTOG 9003, the 4 arm trial comparing standard fractionation versus altered fractionation in head and neck cancers, unplanned retrospective analysis of HPV status using p16 IHC (Immunohistochemistry) showed low 5 year loco regional rates in the HPV positive oropharyngeal carcinoma patients [6]. Retrospective analysis of IMCLstudy, where patients were treated with radiotherapy with or without Cetuximab, the overall survival was better forp16 positive patients [7].Other trials which reported similar outcome includes TAX 324(E6/E7 HPV DNA PCR), TROG 0202(p16 (INK4A IHC, DNA PCR/ISH) and RTOG 0522(p16 (INK4A IHC) etc. [8, 9, 10].

Study	N	Subsite	% HPV	Treatment	Hazard Ratio
Fahkry	96	Oropharynx+Larynx	40	Induction	0.36
ECOG 2399				chemotherapy +	
				chemo radiation	
Lassen	135	Head and Neck	22	Radiotherapy	0.44
DAHANCA 05					
Rischin	172	Oropharynx	57	chemo radiation	0.36
TROG 02.02					
Posner,11	111	Oropharynx	50	Induction	0.20
TAX 324				chemotherapy +	
				chemo radiation	
Gillison	190	Oropharynx	39	Radiotherapy	Nrp<0/001
RTOG 9003					
Ang	323	Oropharynx	64	chemo radiation	0.42
RTOG 0129					
Lassen	769	Head and Neck	-	Radiotherapy	0.54
DAHANCA6, 7					

Table2. Trials that have reported survival improvement for HPV positive oropharyngeal carcinoma

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De-Intensification Strategies In HPV Positive Carcinoma Oropharynx- Where Do We Stand?

The association of HPV positive status with improved outcome was restricted to the oropharyngeal primary site [11]. There was overlap of survival among different stages of HPV positive oropharyngeal carcinoma based on 7th Edition TNM staging system and it was found unsuitable to represent the prognosis according to the stage of the disease. Based on accumulating evidence of prognostic value for HPV-positive OPC new staging system was refined [12, 13].

HPV virus and carcinogenesis

HPV is currently a well-recognized and emerging risk factor for head and neck squamous cell carcinoma [14]. It is a 55nm double stranded DNA(Deoxyribo Nucleic Acid) virus of 8000 base pair length. It is Non enveloped, icosahedral, packed in protein coat. HPV genome contains long control region (10%), early genes (50%) and late genes (40%). Early genes are non-structural proteins encode early proteins E1-E7 that regulate transcription & replication. It is mainly expressed in transformed cells. Whereas late genes are capsid protein that encode late proteins L1-L2 and is expressed in terminally differentiated epithelial cells. The HPV E6 and E7 genes are largely responsible for the onset and persistence of the malignant process in both head and neck squamous cell carcinoma andanogenital cancer. Integration of HPV in to the host genome lead to increased expression of E6 and E7, in turn it inactivates tumour suppressor protein p53 and the Rb pathway resulting in increased proliferation and genomic instability [15].

The epithelial basal cells are the target cells of the virus, where the viral DNA undergoes uncoating and is transported to the nucleus. HPV genome persists as multiple episomal copies with in the nucleus. Once infected E1 and E2 proteins are expressed in the basal cells and they regulate the viral DNA transcription. In high risk HPV infection E6 and E7 proteins are produced from the supra basal layers. In HPV induced carcinogenesis E6 and E7 oncoproteins deregulates cell cycle and apoptosis by acting on p53 [16]. P53 is a tumour suppressor gene which controls G1 transition to S phase in the cell cycle at G1 check point by inducing the expression of cyclin inhibitors p16, p21 and p27 which in turn will block cyclin dependent kinases and progression of the cell cycle at G1/S transition. Inactivation, of p53 gene causes increased cell proliferation.

Rb family of proteins governs the check point between

and Phase. In normal cell cycle hypophosphorylatedRb forms a complex with E2F and makes it unavailable for the DNA synthesis. oncoprotein inactivate Rb family of proteins that causes over expression of E2F thereby produces increased cell proliferation. E7 also down regulates cellular immune responses by down regulation of major histocompatibility complex class 1 and allow HPV to persist in infected epithelial cells. Telomerase is an enzyme that adds hexonucleotide repeats on to the end of chromosome telomere. Absence of telomerase leads to cell senescence. HPV causes activation of telomerase there by prevents shortening of telomere and prolongs life span of infected cell [14].P16 is used as a surrogate marker to detect HPV in samples.

HPV association and treatment response

There are many factors attributed to the survival advantage for p16 positive oropharyngeal carcinoma. Many of the patients are of younger age, they have less comorbidities and less chance of field cancerization in view of reduced smoking history.HPV-positive tumours may harbour fewer or different genetic alterations. HPVpositive tumours have higher radio sensitivity, due to compromised DNA repair capacity. In vitro studies has demonstrated HPV positive cell lines have defect in DNA double-strand break repair associated with a pronounced G2-arrest [17].Other studies have reportedintrinsic radiation sensitivity and increased apoptosis following radiation exposure [18]. Others have reported better degree of sensitivity correlates to Akt activation [19]. Dok et al has reported impaired homologous recombination mediated DNA repair in P16 positive patients [20] further inhibition of Chk1 in HPV positive cells is used to selectively inhibit the cancer cells without injury to normal surrounding cells [21]. Immunologic response may play a role in the improved response to radiotherapy and chemotherapy in HPV-positive tumours.

De-escalating treatment intensity

Current management for locally advanced carcinoma oropharynx by means of concurrent chemo radiation with or without surgery is associated with acute and late toxicities. Since HPV-positive oropharyngeal carcinoma tends to be younger and have prolonged survival, there is a potential to improve the quality of life by means of reducing the toxicities.



De-Intensification Strategies In HPV Positive Carcinoma Oropharynx- Where Do We Stand?

Clinical and Pathological T categories

- T1 Tumour 2 cm or less in greatest dimension
- T2 Tumour more than 2 cm but not more than 4 cm
- T3 Tumour more than 4 cm in or extension to lingual surface of epiglottis
- T4 Tumour invades any of the following: larynx, deep/ extrinsic muscle of tongue(genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, mandible, lateral pterygoid muscle, pterygoid plates, lateralnasopharynx, skull base; or encases carotid artery

Clinical N categories

NO No regional lymph node metastasis

N1 Unilateral metastasis, in lymphnode(s), all 6 cm or less

N2 Contralateral or bilateral metastasis inlymph node(s), all 6 cm or less ingreatest dimension

N3 Metastasis in lymph node(s) greater than 6 cmin dimension

Clinical

Stage I T1,T2 N0,1 M0

Stage II T1,T2 N2 M0

T3 N0,N1,N2M0

Stage III T1-T4 N3 M0

T4 Any N M0

Stage IV Any T Any N M1

There is no T4b in the current classification and carcinoma in-situ is removed as there is absence of a distinct basement membrane in the epithelium of Waldeyer's ring.

Table 3. New classification for HPV positive carcinoma oropharynx based on AJCC Cancer Staging Manual, 8th [22]

Tumor tissue		Serum		
Testing for viral load		Antibody testing		
•	DNA	Cumu	lative viral load	
	Insitu-hybridisation	•	L1	
	Polymerase Chain Reaction	•	Capsid protein	
Gene expression		Expressed oncoprotein		
•	E6,E7 mRNA	•	E6, E7	
Surrogate				
•	Immunohistochemistry-P 16			

Table 4. Various methods used for testing HPV status



De-Intensification Strategies In HPV Positive Carcinoma Oropharynx- Where Do We Stand?

De-intensification strategies have the potential to reduce gastric tube dependence,osteoradionecrosis, dysphagia,xerostomia,dental decay, hypothyroidism, carotid stenosis etc. Application of this knowledge has led to multiple De-escalating Strategies which include the following

- 1. Replace Cisplatin with Cetuximab (along with radiotherapy).
- 2. Neoadjuvant chemotherapy followed by decreased radiotherapy doses.
- 3. Chemo-radiation with decreased radiotherapy and chemotherapy doses.
- 4. Omitting Chemotherapy.
- 5. Protons instead of Photons.
- Less invasive surgery like Trans Oral Robotic Surgery (TORS).

Replace Cisplatin with Cetuximab

In the Subset analysis of Bonners trial, the benefit of cetuximab plus RT was restricted to oropharyngeal sub site [23]. It was later hypothesized to replace Cisplatin with Cetuximab in this favorable group. The three major trials which looked into this aspect were RTOG1016, De-Escalate HPV and the TROG study.

Overall survival was the primary end point in the RTOG 1016 trial, with a non-inferiority margin of 1.45. They included both low risk and intermediate risk patients. Total of 706 patients were randomized to accelerated radiotherapy 70Gy with weekly Cetuximab versus 3 weekly Cisplatin 100mg/m2 [24]. With a median follow up of 4.5 years, the 5 year overall survival was favouring the Cisplatin arm with difference in toxicity pattern. Whereas assessment of toxicity was the main end point in the De Escalate HPV trial.Low risk patients were randomized to conventional radiotherapy 70Gy with weekly Cetuximab or weekly Cisplatin 40 mg/m2 [25]. With a median follow up of 22 months,2 year overall survival was again favoring the Cisplatin arm with no difference in toxicity profile between the two arms. The study conclude that HPV positive disease have good prognosis, there was no difference of toxicity between the two arms ,better overall survival and less recurrence with Cisplatin plus RT arm and Cisplatin plus RT still remains the standard of care in low risk HPV positive disease. The results of TROG 1201 arewaiting [26].

Neoadjuvant chemotherapy followed by decreased radiotherapy doses

E1308 was a phase II trial ,in which patients were selected to reduced RT dose based on complete clinical response to neoadjuvant chemotherapy with Cisplatin +Paclitaxel+Cetuximab [27].Those who achieved complete clinical response was treated to a RT dose of fractions, 5 days a week with concurrentCetuximab for 6 weeks and those patients who achieved partial response or stable disease was treated to a dose of 69.3 Gy in 33 fractions, 5 days a week with concurrent Cetuximab for 7weeks.After a median follow up of 35.4 months, the 2 year progression free survival was 80% in the reduced RT group with improved swallowing and nutritional status.

The Quarter back trial is another trial which is looking in to this aspect. It is a phase III randomized trial comparing reduced dose (IMRT,56Gy in 28 fractions with concurrent Carboplatin weekly) and standard dose radiotherapy (IMRT,70Gy in 35 fractions with concurrent Carboplatin weekly) for locally advanced **HPV** oropharyngealcarcinoma after neoadjuvant chemotherapy with TPF(Cisplatin, Docetaxel and 5-.Primary Flurouracil) regimen[28] end point progression free survival and results are awaited.

Chemo radiation with decreased radiotherapy and chemotherapy doses

In a phase II trial, favourable risk HPV associated oropharyngeal carcinoma patients were randomized to receive 60Gy intensity modulated radiation therapy with concurrent weekly Cisplatin (30 mg/m(2) followed by biopsy from the primary site and planned neck dissection of initially involved site[29]. The primary end point of the study, pathological complete response was 86% and was associated with less toxicity. Few drawbacks of this study is that ,they included early stage cases, short follow up (14 months) and planned neck dissection which was un necessary in some patients. In the follow up study, with the same IMRT dose 60 Gy in 30 fractions, multiple chemotherapy options were there chemotherapy regimens are Cisplatin 30 to 40 mg/m2 (first choice), Cetuximab 250mg/m2 (second choice), Carboplatin AUC 1.5 and paclitaxel 45 mg/m2) and chemotherapy was omitted for patients with T0-2 N0-1 disease, ≤ 10 pack years smoking history [30]. Again neck dissection was advised based on PET/CT weeks .The results are awaited.

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De-Intensification Strategies In HPV Positive Carcinoma Oropharynx- Where Do We Stand?

In the OPTIMA trial both dose reduction and volume descalation was tried where radiation was limited to first echelon of uninvolved nodes [31]. After 3 cycles of neoadjuvant chemotherapy (carboplatin+nab-paclitaxel), low risk patients with $\geq 50\%$ response received 50 Gy RT, low-risk patients with 30%-50% response and high-risk patients with $\geq 50\%$ response received 45 Gy RT + concurrent chemotherapy and patients with lesser response received 75Gy+ concurrent chemotherapy . 2 year progression survival was not compromised compared to historical control.

Omitting chemotherapy

In the HN 002 trial, patients with stage T1- T2, N1-N2b or T3, N0-N2b, p16 positive oropharyngeal carcinoma patients were randomized to receive either IMRT 60 Gy/30 fractions over 6 weeks, or IMRT with concurrent weekly Cisplatin 40 mg/m2[32]. Estimated 2 year survival and late toxicity were similar and acute toxicity was more in the chemotherapy arm.

Protons instead of photons

The goal of the trial was to compare the side effects of 2 radiation treatments; intensity modulated photon beam

therapy 70Gy(RBE) in 33 fractions, with intensity modulated proton beam therapy , 70Gy(RBE) in 33 fractions. Estimated study completion date is in 2024[33].

Less invasive surgery

These trails are trying to assess whether the swallowing function can be improved following minimally invasive surgery like Trans Oral Robotic Surgery (TORS) and to prove non-inferiority of reducing the intensity of adjuvant treatment terms of overall survival .Table 6 shows de intensification trials after surgical intervention. Conclusion

Oropharyngeal carcinoma is on the rise with HPV as important causative factor. Many interesting trials are ongoing to de intensify the treatment protocols in order to reduce the long term morbidities without compromising the outcome. We need to wait for the results with sufficient follow up. As far as now current recommendation is to treat patients according to their stage of disease atpresentation, irrespective of HPV status and to encourage enrollment in to clinical trials.

Trial	Phase	N	Inclusion criteria	Intervention	Results	
RTOG 1016	III	706	T1–2, N2a–3, or T3–4, any N,	Accelerated RT(70Gy)+ plus	5 year survival 77-9% vs.	
			HPV-positive OPSCC	cetuximab (n=425)	84.6%	
				RT+ cisplatin	p=0.5056(non-inferiority)	
				(3 weekly) (n=424)		
De-ESCALaTE HPV) III 334		334	Stage III–IVA HPV-positive OPSCC	Conventional RT+ plus	2-yearoverall survival	
			(T3N0–T4N0, T1N1 –T4N3).	cetuximab (n=168)	89·4% vs. 97·5%	
			Excludes > N2b, >10 PY	RT +cisplatin(weekly)	(p=0.001)	
				(n=166)		
TROG 12.01	III	200	Stage III (excluding T1-2, N1) or	RT+ plus cetuximab	Awaited	
(NCT01855451)			IV (excluding T4, N3, or M1)	RT+ cisplatin (weekly)		
			HPV-positive OPSCC if ≤10 PY. If			
			>10 PY, only N0 –2a			

Table 5. Chemotherapy de-intensification trials



De-Intensification Strategies In HPV Positive Carcinoma Oropharynx- Where Do We Stand?

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stage of disease atpresentation, irrespective of HPV

status and to encourage enrollment in to clinical trials.

Trial	Phase	N	Inclusion criteria	Intervention	Outcome
				(following TORS+ neck dissection)	
ECOG 3311[34]	Ш	377	Resectable stage III–IVB	Low risk- observation	Awaited
			p16-positive OPSCC	Intermediate risk-50Gy/25 fractions	
				or	
				60Gy/30 fractions	
				High risk–chemoRT 66Gy/33	
				fractions	
PATHOS trial[35]	11/111	242	Resectable T1–T3, N0–	Intermediate risk-50Gy/25 fractions	Awaited
			2b HPV-positive OPSCC.	or	
			Excludes active smokers	60Gy/30 fractions	
			with N2b disease	High risk– 60Gy/30 fractions or RT	
				60Gy/30 fractions + weekly Cisplatin	
ADEPT[36]	Ш	500	Transoral resected p16-	RT 60Gy/30 fractions	Awaited
(<u>NCT01687413</u>)			positive OPSCC (R0	or	
			margin), T1–4a, pN	RT 60Gy/30 fractions + weekly	
			positive with ECE	Cisplatin	

Table 6. Trials undergoing De-intensification of surgery/adjuvant therapy

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De-Intensification Strategies In HPV Positive Carcinoma Oropharynx- Where Do We Stand?

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Notice

AROI life Membership Certificates

Those who have not received their Life Membership Certificates

Please contact Dr. Rajesh Vashistha, email - drvashistha@gmail.com

This is for information to all AROI members

WEBINARS



ICRO PRODVANCE 2020 WEBINAR

25th -27th Jun 2020

The year 2020 has been tough for all of us due to COVID 19 Pandemic and unfortunately ICRO, the academic wing of AROI has to postpone all its teaching activities across the country to next year-2021. The AROI-ICRO Executive committee decided that we will continue to teach our members and students in the form of WEBINARS which is the new normal in teaching activities. Thus was born the ICRO PRODVANCE 2020 Webinar on Stereotactic Radiotherapy for Post MD up to 10 years and we also encouraged final year MD Radiation Oncology Students to participate.

The program was designed by ICRO Team and the entire focus was to give the best topics with renowned faculties and to stand above all in teaching activity. We choose the 25th, 26th and 27th of Jun 2020 for the program, three consecutive days and five lectures everyday and planned from 5.00pm to 7.30pm. While there were many Webinars being done every other day in India, We had a astonishing 190 paid registrations and there were nearly 250 participants across India and Bangladesh watching the Webinar every day and the attendance tracker revealed 99% of participants sitting and listening to the entire two and half hours on all three days.

We covered the Brain SRS and SRT including Radiobiology on Day 1, the nuances in Lung SBRT and Spine SBRT on Day 2 and finally Head & Neck SBRT, Liver and Pancreas SBRT on the last day. The Faculties were crystal clear in their presentations and explanations about the topic given to them.

It was designed in such a way that the young professionals sit at home and learn about Stereotactic Radiotherapy which would help them to improve their day to day practice.

All the speakers did an excellent job and the participants were very happy and interactive and were firing questions for every lecture. The final day we organised the PRODVANCE Quiz for the first time and selected the top three and they will be honoured in our next Annual National Conference of AROI.

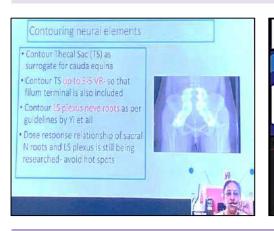
Winners were: First-Dr.Ankita Mehta, SRMS, Bareilly.

Second-Dr.Madan Maitre, HBCH, Sangrur. Third-Dr.Niketa Thakur,GCRI, Ahmedabad.

The three day Webinar ended in a happy note with all the lectures completed on time and lots of appreciations from the delegates saying that they are looking forward to start Stereotactic Radiotherapy in their respective Institutes. This was very motivating to the ICRO team to do more such Webinars in the near future.

Last but not the least our sincere thanks go to Mr. Arvind Suri, SUN oncology who was a strong pillar of support in doing this Webinar and to Webstream World Communications.

Dr.Satyajit Pradan Chairman,ICRO Dr.D.N.Sharma Vice-Chairman,ICRO Dr.V.Srinivasa Secretary,ICRO





Awards



WINNERS OF PRODVANCE 2020 WEBINAR



First Prize
Dr.Ankita Mehta
SRMS, Bareilly



Second Prize
Dr. Madan Maitre
HBCH, Sangrur



Third Prize
Dr. Niketa Thakur
GCRI, Ahmedabad

Conference

UPCOMING...





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UPCOMING...





Indian College of Radiation Oncology (ICRO)

Academic Wing of

Association of Radiation Oncologists of India (AROI)

34th ICRO PG Teaching Program

30th July to 1st August, 2020 Time: 5:00 PM - 7:30 PM

On Genitourinary Malignancies

Organised by, AROI & ICRO



For more information please visit www.aroi.org

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UPCOMING...



Course Goal

The year 2020 has put a full stop to our lives due to COVID 19 Pandemic and as a result of this ICRO, the academic wing of AROI has to postpone its teaching activities across the country to next year-2021. The AROI-ICRO Executive committee decided to teach our PG students in the form of WEBINARS which is the new normal in teaching now. In this context the 34" ICRO SUN PG Teaching Program is being conducted as a Webinar on Genitourinary Malignancies for 2" year and 3" year MD /DNB Radiation Oncology Students to participate.

Genitourinary malignancies are a specialised field focusing on cancers found in the urinary system and the male reproductive system. These include prostate cancer, kidney cancer, bladder cancer, testicular cancer and cancers of the penis. In an Indian study, in both sexes, genitourinary malignancies reported as 20.8% among other cancers.

These malignancies comprise a heterogeneous group of cancers with different cell origins, biological behaviour, and treatments. Although lymphomas and sarcomas are occasionally encountered, in this WEBINAR we will limit the discussion to the more common histological subtypes of carcinomas of the kidney, ureter, bladder, prostate, and testis. Within this group, there is an incredible biological diversity as exemplified by the fact that the management and prognosis of GU malignancies are extremely variable.

For instance, surgical resection alone of the primary cancer may be curative in renal cell cancer, whereas germ cell tumours of the testis are usually curable with chemotherapy alone even in case of widespread metastases. Prostate cancer may be controlled for many years with radiotherapy and hormonal treatment and immunotherapy and targeted therapies are available for Bladder cancers, and for metastatic Renal cell cancers.

The 34th ICRO SUN PG Teaching Webinar is designed in such a way that students can understand the basics as well as evidence based advancements in the management of GU Malignancies. They can also have live interactions with the Faculties who are experts in the field of GU Malignancies during the webinar and get their queries answered.

UPCOMING...



Eligibility & Selection Criteria

- 2nd and 3nd year MD / DNB (Radiation Oncology) Post Graduate students to be nominated by the Head of the Departments / Institutes
- AROI Membership is mandatory to apply for the Course.
- Maximum two students from one Institute.
- Last date for submission of application with CV: 18th July, 2020.
- Candidates who have attended the earlier ICRO program will NOT be given preference.
- Selection will be done by ICRO teaching course committee. Merely applying for the teaching course does not guarantee selection.
- Selected candidates will have to pay Registration fee of Rs. 1,000/- in the form of Demand Draft in favor of "AROI - ICRO, payable at Ludhiana" or can do online payment in below mentioned account details.

Bank: State Bank of India Account Name: AROI - ICRO Account No: 30619770736 Address: Millerganj, Ludhiana IFSC Code: SBIN0000731

- After making the payment, please mail the payment receipt to secretaryicro@gmail.com, drvashistha@gmail.com & arvindsuri@sunpharma.com
- For any correspondence please contact Secretary, ICRO at Secretaryicro@gmail.com or icro.git.2019@gmail.com. The decision of ICRO body will be final and binding