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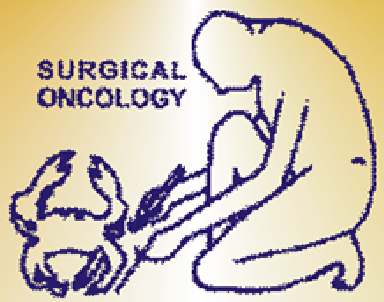
IASO

NEWSLETTER



Indian Association of Surgical Oncology

(A section of The Association of Surgeons of India)

INDIAN ASSOCIATION OF SURGICAL ONCOLOGY (IASO)

List of past presidents and Secretaries of the association

President	Secretary	Year
Dr. D J Jussawala	Dr. Ashok Mehta	1977
Dr. P B Desai	Dr. Ashok Mehta	1979
Dr. M P Vaidya	Dr. N C Misra	1981
Dr. Ashok Mehta	Dr. N C Misra	1983
Dr. D D Patel	Dr. N C Misra	1984
Dr. A P Majumdar	Dr. N C Misra	1985
Dr. R S Rao	Dr. N N Khanna	1986
Dr. N C Misra	Dr. N N Khanna	1987
Dr. N N Khanna	Dr. S G Deshpande	1988
Dr. B M L Kapoor	Dr. S G Deshpande	1989
Dr. S K Sarkar	Dr. S G Deshpande	1990
DR. P M Trivedi	Dr. H S Shukla	1991
Dr. K K Pandey	Dr. H S Shukla	1992
Dr. S K Shukla	Dr. H S Shukla	1993
Dr. J B Venkatrau	Dr. H S Shukla	1994
Dr. Shambhu Pal	Dr. Sandeep Kumar	1995
Dr. C K Gupta	Dr. Sandeep Kumar	1996
Dr. H S Shukla	Dr. Sandeep Kumar	1997
Dr. S P Kharey	Dr. Sandeep Kumar	1998
Dr. P Subhas	Dr. Kiran Kothari	1999
Dr. K K Maudar	Dr. Kiran Kothari	2000
Dr. K Panda	Dr. Ravi Kant	2001
Dr. R I Dave	Dr. Ravi Kant	2002
Dr. K S Gopinath	Dr. L Sarangi	2003
Dr. K Kothari	Dr. L Sarangi	2004
Dr. Sandeep Kumar	Dr. R Karwasara	2005
Dr. Ravi Kant	Dr. R Karwasara	2006
Dr. S. Sadasivan	Dr. Sanjeev Misra	2007

IASO EXECUTIVE COMMITTEE

President	:	Dr. S. Sadasivam, Coimbatore
President Elect	:	Dr. Sanjay Sharma, Mumbai
Vice – President	:	Dr. L. Sarangi, Varanasi
Secretary	:	Dr. Sanjiv Mishra, Lucknow
Editorial Secretary	:	Dr. Manoj Pandey, Varanasi
Assoc. Editor	:	Dr. Jahar Majumdar, Kolkatta
E.C. Members (2006-07)	:	Dr. Ajay Vidyarthi, Ranchi (East Zone) Dr. Naresh Kumar Soni, Jaipur (West Zone) Dr. Pawan Gupta, N. Delhi (North Zone) Dr. Thomas Varghese, Kochin (South Zone)
E.C. Members (2007-08)	:	Dr. Vimal Bhandari, Delhi (North Zone) Dr. Deepender Sarkar, Kolkatta (East Zone) Dr. Mukul Trivedi, Ahmedabad (West Zone) Dr. Jacob Kurian, Manipal (South Zone)
Co-opted Organising Secretaries	:	Dr. H.S Shukla, Varanasi Dr. Satish Jain, Ludhiana
Co-opted Overseas Coordinator	:	Dr. Raghu Pillarsetty, U.K
Past President	:	Dr. Ravi Kant, New Delhi

IASO Newsletter **Vol. 21. Issue 1**

CONTENT

PRESIDENT'S MESSAGE

Dear members,

My warm greetings to all of you. I deem it as a great honor to write to you all as the President of IASO.

Over the last 30 years I have been an active member practicing this Specialty of Surgical Oncology and a witness to the evaluation of this Specialty over the years. Initially Surgical Oncology was practiced by few of the Pioneer General Surgeons who were interested in Cancer Surgery and it was more as a Regional Specialty like Head and Neck, GI, and Urology etc. and that too in only in some of the selected centers in India. But today it has become a Broader Super Specialty which is unique as it covers all the regions of the body. Also additional allied Medical Oncology has born. Many more centers have started to train our Postgraduates for MCh and DNB courses. But this great Nation cannot be served by specially qualified Surgical Specialists for another two decades at least. It is the necessity that General Surgeons who are interested and occupying key positions in Tertiary Care Centers should practice evidence based Surgical Oncology. The IASO should strive hard to educate and train the General surgeons of India to practice the correct Evidence Based Surgical Oncology practice apart from focusing our attention in the research of newer technology. At this juncture our important task should be to make lot more General Surgeons to join into our forum and make them full fledged Surgical Oncologists.

I congratulate the editorial committee for bringing out the IASO News letter

Prof.S.Sadasivam
Consultant Surgical Oncologist
GKNM Hospital
Coimbatore -641 037

SECRETARY'S REPORT

Dear Member,

I welcome you all to the National Conference of the Indian Association of Surgical Oncology at Ludhiana. It is for the first time that the National conference is being organized in the state of Punjab. The growth of our association has been due to the continuous and relentless efforts of the Past Presidents and senior members of the association. We look forward to their guidance and suggestions in future also.

At the beginning of the year we had proposed an agenda for the year 2007. We have moved ahead and have been able to achieve few things.

1. **NATCON 2006** - The NATCON at Varanasi was a successful meeting with large number of delegates attending from India and abroad. It was an International Integrated meeting of Indian Association of Surgical Oncology and WFSOS. The guest lectures by national and international faculty and the symposia on Role of Neoadjuvant treatment in solid tumours, Clinical Research Methodology and Panel discussion on Minimal Invasive vs. Open Surgery for cancer – Big fight was greatly appreciated by the delegates. The Radha Devi Oration was delivered by Dr. Sandeep Kumar, Past President, IASO, Prof. N.C. Misra Oration by Dr. Paul Boulus, UK, and Moti Bhai Oration by Dr. Walley Temple, Canada. The Detroit fellowship was awarded to Dr. Diptender Sarkar from Kolkatta. The members of the association and delegates thanked Dr. H.S. Shukla for an academically fruitful meting and also congratulated him for being elected as the President of WFSOS. Prof. Shukla has contributed Rs. 25,000/- to IASO from the saving of NATCON IASO 2006. We thank him for the same and also request him to raise this amount to at least Rs. 50,000/- or more.

2. **ASICON 2006** – The ASICON 2006 was also held at the holy city of Varanasi. Most of us had the privilege of visiting this oldest living city twice in the same year. It was an honour for the IASO that Prof. K.S. Gopinath, Past President IASO adorned the high office of President ASI for the year 2006 and was in chair during the conference. Thanks to the effort of Prof. K.S. Gopinath the association was given a position of prominence in the sectional programme during the ASICON at Varanasi. The PB Desai – UICC IASO Silver Jubilee Oration was delivered by Dr. Ashoka Shaha from USA. The symposium on Organ/Function preservation in solid tumours and Minimal invasive cancer surgery video symposium were well attended and appreciated.

3. **CME Programme** – I had suggested that at least one CME per zone should be held. As we have members in the executive from east, west, north and south (2 per zone) it is proposed / suggested that these executive members should work as coordinators or should organize CME in their region. This little effort may help in bringing major changes in cancer treatment in the country. IASO and its members should consider it as a part of their commitment to society. This year we have had only one proposal for holding a zonal CME from Col. Sanjay Kapoor, R.R. Hospital, New Delhi on 9th Dec. 07. We request more members to come forward with proposals for CME.

4. **NATCON 2007** – The conference at Ludhiana is expected to be an academically gratifying meeting. Dr. Satish Jain and the organizing committee have done a wonderful job and I am sure everyone

attending the meeting will benefit out of it. On behalf of the IASO I am grateful to all the international and national speakers and delegates attending the conference.

5. **Detroit Fellowship** – Dr. Diptendra Sarkar of Kolkatta has been awarded the Detroit Fellowship at NATCON Varanasi. He will avail the Fellowship in 2008.

6. **Baroda Travelling Fellowship** – Dr. Mithlender Kumar was selected for Baroda Traveling Fellowship. Somehow there is not enough enthusiasm from younger colleagues. I request members to give more publicity to this fellowship.

7. **ASICON 2007 at Bhubaneshwar** – There will be 2 symposia

   (i) What not to do? Common Errors in Cancer Surgery: Convenor – Dr. S.V.S. Deo, New Delhi

   (ii) Carcinoma Ovary – Convenor - Dr. Manoj Pandey, Varanasi

   Those interested in participating in the symposium/ Panel discussion may kindly write to the convenors.

   The speaker for the PB Desai – UICC IASO Silver Jubilee Oration has not yet been decided. I request our members to suggest speakers for it and help in finalising the speaker.

8. **NATCON IASO 2008** - In the GBM it was decided to hold the 2008 Annual Meeting at Hyderabad, the Organizing Secretary being Dr. Raghuram Pillersetti. The dates are 19-21 September 2008. It is planned to be a joint meeting of IASO & BASO.

9. **NATCON IASO 2009** - The venue for 2009 IASO will be decided during the 2007 meeting at Ludhiana. Proposals for the 2009 meeting are invited from the interested members. The interested member should be present to bid for the conference and should send the proposal to the Secretary, IASO. The deadline for submission of proposal is before the Executive meeting which is held during the NATCON 2007. He should be prepared to make a presentation about the proposed venue, accessibility of place by surface and air transport, local infrastructure available, logistics of organizing the meeting etc.

10. **Newsletter** - The IASO newsletter has been fairly standardized. It can improve further with everyone's cooperation. The last issue of the IASO newsletter could not be published due to technical reasons; hopefully it will not happen in future. Dr Manoj Pandey, Editorial Secretary, Varanasi and Dr Jahar Majumdar, Associate Editor, Kolkatta will make special efforts to upgrade it as IASO journal in due course. But this needs quality research articles and reviews to be published in the newsletter. The convenors of symposia should ensure that each speaker contributes to the newsletter his/her presentation as an article. This will improve the quality of article and theme based issues can be brought out.

11. **Finance -** At the time of writing this report I have not yet received the audited accounts of the association till 31 Dec. 2006 from the Past Secretary Dr. R.K. Karwasara in spite of my repeated requests. I hope the audited accounts of the association are presented by him at Ludhiana during NATCON IASO 2007. Dr. H.S. Shukla, Organizing Secretary, NATCON IASO 2006 has contributed a sum of Rs. 25,000/- to the IASO from the conference savings. I request him to increase this amount. The audited accounts of NATCON IASO 2006 are still awaited and hopefully will be received before the Ludhiana meeting. I am hopeful that Dr. Satish Jain will contribute a handsome amount to the IASO. An organization financially viable can comfortably think of achieving greater heights.

12. **WFSOS** - Prof. Sadashivam, President IASO will be the official representative of IASO in WFSOS. The membership subscription arrear has been cleared by him. He will be participating in the next meeting of WFSOS in Russia as IASO's official representative.

13. **Topic for Symposium and Panel Discussion** – For the NATCON IASO 2009 and ASICON 2009 the last date will be 30 August 2008. We have received several topics for Symposium and Panel discussion for NATCON 2008 and ASICON 2008.

14. **IASO Website**- The annual subscription of IASO website is now being made by the Secretary IASO. Those members updating their contact details on the website must send their changed details to the Secretary also. The website address is www.iasoindia.in

15. **Membership Directory and Cards** – The membership directory of the association is in print and will be released at Ludhiana during NATCON. I have tried to have accurate addresses and contact details of members but I am sure that several addresses are likely to be incorrect. I request all members to send their corrected addresses and details (especially e mail address) to me so in future editions corrections can be done. Membership cards are also being planned and will shortly be issued.

16. **Membership drive** - Our membership numbers have increased from before and are increasing. It should be our effort to enroll new members. All trainees in Surgical Oncology should be enrolled as Associate Members and on completion of training they should be made full members of IASO. Practicing Surgical oncologists should be encouraged to join the association.

17. **Future Directions** – The future of the association has in its acceptance by governmental and non governmental agencies as the nodal body for cancer care. The functioning of the association should not only be confined to its role in organising NATCON and Sectional programme for ASICON. The association has to take initiative in organizing national trials for cancer treatment collaborating with international societies and agencies in carrying out trials and research. With bilateral cooperation both associations (International and IASO) will benefit. All these collective efforts can enhance the status of the associations.

I once again thank all members for their help, cooperation and wish the association a bright future.

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EDITORIAL

The Indian Association of Surgical Oncology was established in 1977 with Dr. D J Jussawala as president and Dr. Ashok Mehta as secretary. Two years down the line in 1979, the first one page news letter was published. The news letter improved with each subsequent issue till it reached its present shape. To name a few, the contributions of Dr. Sandeep Kumar, Dr. L. Sarangi, Dr. Sanjeev Misra and Dr. M. Ganguly towards its development are gargantuan.

Getting articles to publish in newsletter has always been a problem and each editorial secretary has to struggle to finalize the content of each issue. This is improving with each subsequent issue and I am sure that this will not be a problem in future. I am sure that the submission rates will further improve if the newsletter becomes a full journal in coming years. I personally feel the members will be more inclined to publish in a peer reviewed journal rather then in a newsletter. Once converted to a journal the circulations too will improve thereby improving the visibility of not only those who publish but also of the Association as well. I am sure that executive committee and general body will take a note of it and will work towards having a journal in our hands by 2008 or 2009.

It has always been debated weather the presentations of NATCON or ASICON can be converted to full articles. The response to such a proposal has been poor but I sincerely believe that this too will improve subsequently though it may require a little more efforts. It is to be noted that in all major scientific meetings sponsored by societies the proceedings are published and act as ready reckoner of development in the field. The Society of Surgical Oncology makes it mandatory for presenters to submit full articles of their presentation for peer review and publications in society journal, the Annals of Surgical Oncology. The proceedings of St. Antonio breast conference and ASCO are very popular and are regularly cited. Members of our society too have to take a strong resolve and ensure conversion of at least the Detroit papers, symposiums and penal discussions into full length articles. The topic of these presentations and the name of presenters are known well in advance.

There was no problem this time as the contributions arrived in time. The delay was from our side as the program of NATCON 2007 could not be finalized in time and waited a long time for audited accounts of society and NATCON 2006 which did not arrive and we decided to go ahead with publication without them. We hope to present these in December issue. A membership form is enclosed in this issue I request all members to fill it and send to us so that we can update the information in our records. This will also help us in updating the membership directory and mailing list of the society, there by improving the communications between secretariat and members. The same information can be uploaded to our web site www.iasoonine.in. This information will also be useful if patients wish to locate a surgical oncologist near their homes.

Lastly we have a great academic feast lined up at NATCON 2007 at Ludhiana and I look forward to meeting you all there.

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IASO
Minutes of Executive Committee Meeting
22nd September, 2006, Varanasi

1. Approval of minutes of the last EC meeting which were circulated in the August 2006, News Letter.

Dr. S.P. Khare pointed out that the condition of 5 years as ordinary member to be elected for executive member already exist in the byelaws and therefore agenda no. 8 part-B should be dropped. Dr. Gopinath proposed and Dr. Kiran Kothari seconded to pass the minutes after doing necessary correction & then minutes were passed unanimously.

2. Eligibility for Vice President.

The matter was discussed at length and it was decided that eligibility for vice president should be minimum 10 years as ordinary member and should have served on any post of the executive.

3. ASICON 2006 – Scientific Program.

Dr. K S Gopinath, President ASI, informed the EC members that ASI program committee has decided to give separate hall to IASO from afternoon of 28th Dec. 2006. Dr. R.K. Karwasra informed the members about the scientific program which has already been sent to ASI headquarter and requested the members to send their proposal for scientific presentation so that program can be finalized within next month.

4. NATCON IASO 2007 – Dates and other issues.

The dates for NATCON-2007 were decided to be 21-23 Sept. 2007. It was also decided that scientific program to be finalized by the scientific committee.

5. NATCON IASO 2008 – Venue to be decided.

The agenda was deferred to be discussed in the General Body meeting.

6. Baroda traveling fellowship – Money.

The Secretary informed the members that Dr. P.M. Trivedi has handed over the cheques for 2005 & 2006. He also informed that the amount of Baroda Traveling Fellowship is in fixed deposit in the bank up to 2008 after which it will be passed to the IASO. It was also decided to award the fellowship to Dr. Mithelender Kumar for the year 2006.

7. Minimal Invasive Surgery Fellowship – Money.

Dr. Kiran Kothari & Dr. Dave once again assured the members to send the amount of Rs. 75,000/- for the fellowship which will be sent shortly to IASO. The amount will be kept in the fixed deposit, which will generate annual interest of Rs. 6000/- He also requested that Rs. 1500/- to be given by the IASO so that total amount will be Rs. 7500/- (6000/- + 1500/-), which was turned down.

8. Association of IASO with Societies of other countries.

Dr. Raghu Pillarsette appraised the members about the progress and future plans to associate other European and Canadian surgical oncology societies. The efforts were appreciated and approved.

All the members congratulated Dr. H.S. Shukla for becoming President of WFSOS and then meeting ended after vote of thanks by the chair.

Prof. R K Karwasra,
Secretary IASO

IASO: GENERAL BODY MEETING

23rd September, 2006, Varanasi

Minutes:

1. ***Meeting*** called to order by President
2. ***Quorum*** was complete and all the members signed the attendance.
3. ***Condolence*** was held for untimely demise of the Prof NC Misra, Lucknow and Dr I. P. Elhence of Agra. 1 minute silence was observed
4. ***Minutes of last GBM -*** No objection received against the minutes of last GBM held on September 24, 2005 at Kodaikanal, which were circulated to all the members in the December 2005 News Letter. Dr H S Shukla proposed to approve the minutes, which were seconded by Dr L S Vohra, and the minutes passed unanimously.
5. ***Decisions taken by the Executive committee*** in the meeting held on 29.12.05 at Jaipur, (minutes of which were circulated to all the members in the August 2006 News Letter and approved in the EC meeting held at Varanasi on 22.09.06 with minor corrections), were placed before the General body. Dr Sandeep Kumar proposed to accept them and Dr Manoj Pandey seconded the proposal. The decisions of EC were approved unanimously.
6. ***Secretary report*** as circulated in the August 2006 Newsletter was placed in the meeting. Dr Sarangi proposed and Dr Thomas seconded and the agenda was passed unanimously.
7. ***Change of nomenclature of Senior Vice President to President elect***. All the members agreed to this proposal, which has already been approved by the EC.
8. ***Codification of inaugural ceremony.*** Though members were divided on the issue of whether President elect should also be on the dais or not during inaugural function, however, it was agreed that place of President on the dais should be next to the chief guest as already decided in earlier meetings. A committee of Dr N Kanan, Dr Sameer Bhatacharya and Dr was constituted to suggest the sitting arrangement during the inaugural function after going through the protocols of various organizations.
9. ***Scientific committee of IASO*** was approved unanimously as decided by EC, which include President, President Elect, Immediate Past president, Vice President, Present Secretary, Immediate Past Secretary, Editorial Secretary and Organising Secretary. It was decided that all the proposals regarding Symposia, Panel discussions and Orations etc. should be sent to this committee, which will take further decision. It was also decided that all the short papers/posters should be send to Secretary who will send them after finalizing to Organising secretary.

10. ***Executive members of IASO*** should represent whole country and therefore, one member each from North, East, West and South zone of the country should be elected every year.(There are 4 posts of EC member every year which can be distributed according to NEWS: geographic location of executive member).

11. **Eligibility for Vice President**- shall be ten years as life member and one term as Executive member.

12. **Protocol for IASO elections** – Most of the members feel that elections should be held. It was decided that, vacant posts will be advertised in the News letter and nominations for vacant posts shall be invited by the secretary well in advance. Voting should be held by secret ballots by the IASO Secretariat and result shall be declared in the GBM. Only one name should be proposed or seconded per post by a life member.

13. **NATCON IASO 2005 – Kodaikanal** - Dr B K C Mohanprasad handed over the audited accounts and cheque of Rs. 25000/- to the secretary towards the secretarial charges of Rs. 100/- per registration during the conference, which was accepted.

    Some members from Eastern region pointed out that they sent the in house registration to the organizing secretary but could not attend the meeting due to flood in the region at the time of the conference and therefore demanded that, their money should be refunded. Dr Mohanprasad explained that he received this request from some members and already taken up the matter with the management of the resort at Kodaikanal where the conference was held but they refused for refund since as per the contract no money would be refunded after 31st August 2005. In view of this it was decided to drop this matter.

14. ASICON 2006, Varanasi - scientific program – Secretary Dr R K Karwasra informed that this time the IASO will probably get a separate hall from the afternoon of 28th to 30th December 2006 for its sectional activities as intimated by Dr K S Gopinath, President ASI, and requested the members to send the proposals for this within a week so that they can be included in the final program. He also informed about the IASO sectional scientific program already sent to the ASI headquarter.

15. **NATCON IASO 2007 Ludhiana** – Organising Secretary Dr Satish Jain informed that the date for the conference will be 21, 22 & 23 September 2007 and it will be held at a resort near Ludhiana where AC halls are available. The registration fee will be same as was this year and all types of accommodation are available in plenty at Ludhiana.

    Following proposals were received from members for the Symposia / Panel discussion;

    a) What not to do in cancer surgery?
    b) D2 Gastrectomy
    c) PET Scan
    d) Oncoplastic Breast Surgery
    e) Controversies in Cancer Surgery
    f) Bone tumors

g) Liver SOLs
h) Old & New
i) Surgical management of Metastatic cancers
j) Thyroid cancers
k) Ovarian Cancer
l) Lasers in oncology
m) Renal tumors

Since "What not to do in Cancer Surgery?" is more relevant to General Surgeons and therefore it was decided to hold symposium on this topic during ASICON – 2007 by Dr. S.V.S. Deo who proposed this topic. Scientific Committee will take decision about the remaining topics and some additional topics proposed by others members.

16. **ASICON 2007 Scientific program -** The symposium will be on "What not to do in Cancer Surgery?" by Dr. S.V.S. Deo. The Scientific committee will take decision on the proposal received from the members on UICC Silver Jubilee – IASO - Dr. P.B Desai oration & Invited/ guest Lectures.

17. **NATCON IASO 2008 – Venue** - Following Proposals received to hold the 2008 Annual Conference

a) Hyderabad - By Raghu Pillersetti
b) Mount Abu - Dr. Kiran Kothari
c) Chennai - Dr. Hemant Raj
d) Delhi - Dr. Sanjay Kapoor & Dr. Chitamani
e) Kolkatta - Dr. Sameer Bhattacharya
f) Jamshedpur - Dr.
g) Mahableshwar - Dr.Sharad Desai
h) Kathmandu - Dr. Sharma

After presentation of the proposals to hold the meeting by the representatives of these places and discussion, voting was held. It was decided to hold the 2008 Annual Meeting at Hyderabad by Dr. Raghu Pillersetti.

18. ***Baroda Traveling fellowship* –** The Secretary informed that Dr. P.M. Trivedi handed over the cheque for 2005 & 2006 since Dr. G.N. Shukla could not come because of his illness. Dr.P M Trivedi intimated that the seed money for this fellowship is in fixed deposit up to 2008 after which this will be transferred to IASO. Dr. Mithlender Kumar was selected for Baroda traveling fellowships for the year 2006.

19. ***Minimal Invasive Surgery Fellowship* –** Secretary intimated that IASO yet to receive money for MIS fellowship promised by GCRI group. Dr. R.I. Dave & Dr. Kiran Kothari informed that GCRI decided to give cheque of Rs. 75,000/- to IASO to be kept in fixed deposit to start the ***GCRI – IASO MIS fellowship*** at GEM Hospital, Coimbatore. Rs. 6000/- will be available to the candidate out the interest of Rs. 75,000/- and Dr. Palanivelu will wave the registration charges. Dr. Kothari & Dr. Dave proposed that the IASO Secretariat should make Rs. 1500/-

available to the candidate so that the fellow can get Rs. 7500/- (6000 + 1500 = 7500). This proposal was rejected and it was decided that no money would be provided for this fellowship from the corpus fund of the IASO.

20. ***Association of IASO with Societies of other countries***. – Dr. Raghu Pillersethi informed the General body about the progress made regarding association of IASO with Surgical Oncology Societies of other countries. The dialogue is in final stage with European Society of Surgical Oncology & Canadian Society of Surgical Oncology. It is likely that more number of societies will like to associate with IASO after this integrated International meeting of IASO with WFSOS.

21. ***Election*** - Nominations were invited for following vacant posts of IASO up to 01.00 pm on 23rd September 2006 and elections were held;

a) Vice President
b) Secretary
c) Editorial Secretary
d) Associate Editorial Secretary
e) Executive member from NEWS- (one each from four zones)

A. Vice – President - Following 5 nominations received

1.	Dr. Hemant Raj	-	Chennai
2.	Dr. L.Sarangi	-	Varanasi
3.	Dr. M. Ganguly	-	Chandigarh
4.	Dr. Raj Govind Sharma	-	Jaipur
5.	Dr. R.K. Karwasra	-	Rohtak

Dr. R.K. Karwasra & Raj Govind Sharma withdrew their nominations. The voting was held for remaining 3 candidates by rising of the hands and Dr. L. Sarangi was declared elected for the post of Vice – President for the year 2007 by the president.

B. Secretary - Following 2 nominations received

1.	Dr. Sanjeev Misra	-	Lucknow
2.	Dr. M. Ganguly	-	Chandigarh

Since nobody withdrew, voting was held by rising of the hands & Dr. Sanjeev Misra was declared elected for the post of Secretary for the year 2007 -08 by the President.

C. Editorial Secretary - Following 2 nominations received

1.	Dr. Sanjay Kapoor	-	Delhi
2.	Dr. Manoj Pandey	-	Varanasi

Since nobody withdrawn, voting was held by raising of the hands & Dr. Manoj Pandey declared elected for the post of Editorial Secretary for the year 2007-08 by the President.

D. Associate Editor - Following 3 nominations received

1. Dr. Sanjay Kapoor - Delhi
2. Dr. S.V.S Deo - Delhi
3. Dr. Jahar Majumdar - Kolkatta

Dr. S.V.S. Deo withdraw his nomination & election was held by raising was hands between Dr. Sanjay Kapoor & Dr. Jahar Majumdar in which Dr. Jahar Majumdar declared elected for the post of Associate Editor for the year 2007-08 by the President.

E. Member Executive Committee

- Only 1 nomination of Dr. Jacob Kurian of Manipal was received from South zone & he was declared elected as E.C Member by the President.
- Similarly only one nomination of Dr. Mukul Trivedi of Ahemdabad was received from West Zone & he also declared elected as E.C. Member for the year 2007-08 by the president.
- 3 nominations received from East Zone. Dr. Deeptendar Sarkar (Kolkatta), Dr. Ajay Kumar (Jamshedpur) & Dr. Amit Verma (Bilaspur). Dr. Amit Verma & Dr. Ajay Kumar withdraw their nominations & Dr. Deeptender Sarkar declared elected as E.C. Member for the year 2007-08.
- For North Zone again 3 nominations received. Dr. Malika Tiwari from Varanasi, Dr. Vimal Bhandari & Dr. Chinatamani both from Delhi. Nomination of Dr. Malika Tiwari was found invalid since she has not completed 5 yrs as life member of IASO and Dr. Chintamani withdrew his nomination. Dr. Vimal Bhandari was declared elected for the post of E.C. Member for the year 2007-08 by the president.

All the members congratulated Prof. H.S. Shukla for being President of WFSOS and meeting ended after thanks by the Chair.

Prof. R K Karwasra,
Secretary IASO

PAST PRESIDENT OF IASO CONFERRED WITH HONORARY MEMBERSHIP OF BASO

Honorary membership of the British Association of Surgical Oncology (BASO) was conferred on Dr. Devendra D Patel during annual conference of British Association of Surgical Oncology in November 2006.

Dr. Devendra D. Patel was born in Bhadran, Dist. Kaira. He had initial education at Bhadran followed by higher education at Gujarat College and Medical Education at B. J. Medical College and K. M. School of Postgraduate Medicine and Research at Ahmedabad. He obtained MBBS in 1956 with highest marks in surgery and obtained University Gold Medal and MS in 1959 from Gujarat University. He then proceeded to England for obtaining FRCS of England and Edinburgh. He proceeded to USA and worked as Senior Surgical Fellow at Lahey Clinic, Boston, USA and obtained experience in Cancer Surgery. On his return from USA, he was appointed as Chief Surgeon at M P Shah Cancer Hospital, Ahmedabad in 1966. Since, then he has been associated with this institute and has played a major role in development of Cancer Hospital. He was secretary of Gujarat Cancer Society for one year. He was Hon. Deputy Director of Gujarat Cancer & Research Institute 1990-93 and Hon. Director February 1993 to January 2003.

He is past Member of the Executive Committee of the Association of Surgeons of India, Past President of Indian Society of Oncology and Indian Association of Surgical Oncology. He is Past Executive Committee Member of the World Federation of Surgical Oncology Society. Many prestigious orations have been delivered by Dr. Patel. Smt. Bimla Saha Cancer Award 1993 of Banaras Hindu University, Varanasi, U.P. and Col. Pandalai Oration of Association of Surgeons of India are most outstanding. He also delivered Sir Dorab Tata Oration of Indian Society of Oncology, November 2002. He received Life Time Achievement Award September 2003 at Lucknow from the hands of H.E. Governor of Uttar Pradesh (India) during Silver Jubilee Celebration of Indian Association of Surgical Oncology. He was Guest of Honor at Banquet of Inner Temple London during 30th year Celebration of British Association of Surgical Oncology Royal Challenge of Surgeons of England November 2003. Dr. Patel has been awarded Dr. B. C. Roy National Award as eminent Medical Teacher by Medical Council of India for the year 1998. He also an active Rotarian since 1971 and was awarded Award for Professional Excellence by Rotary International for Dist. 3050.

The executive committee of BASO short listed two Surgical Oncologists for conferring honorary membership, Dr. Patel was one of them. In its general body meetings both the names were unanimously approved. Dr. Patel has been awarded this membership for his contribution to surgical Oncology, long association with BASO, and for promoting relations between BASO and Indian Association of Surgical Oncology (IASO). After announcement of the fellowship, Dr. Patel was felicitated at a banquet held at Hall of Chancery lane. Prof. Ravikant, the president of IASO was also present at this occasion.

PROF. H S SHUKLA ELECTED AS WFSOS PRESIDENT

World Federation of Surgical Oncology Societies (WFSOS) in September 2006 elected Professor Hari Shankar Shukla, former Dean, Institute of Medical Sciences, Banaras Hindu University, Varanasi and Professor of Surgical Oncology as its President acknowledging his contribution to the field of Surgical Oncology. He becomes the first ever Indian to hold the prestigious post.

Peri-pasu pare with his efforts to develop Surgical Oncology in the country, Prof. Shukla has persevered in helping to bring out World Surgical Oncologists on one forum. World Federation of Surgical Oncology Societies (WFSOS) has 52 member countries and Prof. Shukla is the founding member. He held the position of Member Executive Committee of WFSOS since 1992. He invited this forum to come to Banaras Hindu University in September 2006 for 4 days conclave on evidence based treatment of cancer, an event jointly organized by the Indian Association of Surgical Oncologists. Prof. Shukla was unanimously elected the President of WFSOS by the Executive Committee of WFSOS in the meeting held at B.H.U., Varanasi in September 2006.

Born at Allahabad, Dr. Shukla graduated from MLN Medical College, University of Allahabad in 1968 In the final year MBBS he joined Indian Army Medical Corps for 5 years serving the country by active participation during the Bangladesh liberation war of 1971. He rejoined his alma mater in 1973 and qualified for MS (General Surgery) in 1974 under Prof. Pretam Das, at MLN Medical College, Allahabad. He joined the Department of Prof. LE Hughes at Cardiff, University of Wales, where he completed FRCSEd in 1976 and returned to India in 1977. In 1979 he was appointed Lecturer in General Surgery at Banaras Hindu University. There he passed Immunology of Cancer, earning him PhD in 1984. He was appointed as Chair, Division of Surgical Oncology at IMS, BHU in 1990. Division was upgraded to a full department in 2004 and a MCh program was started in 2006.

Prof. HS Shukla is a person of great academic stature. He has contributed 170+ research paper publications in national and international journals, chapter contribution in books, besides presentation of papers in national & international meetings, orations and workshops. He steered IASO as a Secretary to full maturity during his two terms of 3 years each. He was crowned president of IASO at a young age. He served as a member of the Institute body, All India Institute of Medical Sciences where as the Chairman of Selection Committee (1 year) and subsequently Chairman of Academic Committee (4 years). He was appointed the Associate Editor of Journal of Surgical Oncology, and after six years, he is now Asia Region representative of the Journal. His contribution in the Social Sector is immense. He visits his village on every Sunday (if not on duty or overseas) since 1978 and has helped innumerable patients to recover.

Members of the Indian Association of Surgical Oncology join hands in congratulating Prof. Hari Shankar Shukla on his achievement.

NATCON-IASO-2007

Annual Conference of Indian Association of Surgical Oncology (IASO)
Pre-Conference Workshop
20th September 2007

Venue:
College of Nursing – Mohan Dai Oswal Cancer Hospital - Ludhiana

Video Workshop:
Registration 8'O Clock onwards & Breakfast

OPERATIVE PROCEDURES:
9:00 a.m. to 9.30 a.m. – Inauguration

SESSION – 1 (9.30 to 10.30 a.m.)

GI Oncology		***Chairperson***
Radical Cholecystectomy	Dr. Munemasa Ryu – Japan	Dr. H. Ramesh
D2 Gastrectomy	Dr. Taira Kinoshita – Japan	Dr. Satpal Virk
Whipple's Operation	Dr. Kanemoto H – Japan	Dr. Vinod Tiku
		Dr. Mrs. J.P.K. Shergill

TEA/COFFEE

SESSION – 2 (11.30 to 1.00 p.m.)

Thoracic Oncology

Lung Resection	Dr. R.S. Dhaliwal – PGI Chandigarh	Dr. Mohan Vergees
Thoracoscopic Minimal Invasive Surgery in Oncology	Dr. Arvind Kumar	Dr. I.J.S. Shergill Dr. Sanjeev Misra
Role of Mediastinoscopy and thoracoscopy		
Thymecotmy	Dr. Arvind Kumar – AIIMS New Delhi	Dr. R.K.Karwasara

LUNCH

SESSION – 3 (2.00 to 4.00 p.m.)

Minimal Invasive Surgery GIT Oncology

Laproscopic APR	Dr.G.R. Verma – PGI Chandigarh	Dr. Kuldip Singh
Lap. Assisted Distal Gastrectomy	Dr. Kiran Kothari – Ahmedabad	Dr. Gurdip Sidhu
Laparoscopic Colorectal Surgery	Dr. Subodh Kumar – New Delhi	Dr. Mohinder Singh
Laparoscopic Onco-Surgery	Dr. C. Planivelu – Coimbatore	Dr. P.S. Bakshi
Laparoscopy Assisted Colectomy	Dr. Kiran Kothari – Ahmedabad (Stand By)	

SESSION – 4 (4.00 to 5.00 p.m.)

		Chairperson
Laparoscopic Radical Prostectomy	Dr. A.K. Hemal – New Delhi	Dr. Amrik Singh
Groin Dissection	Dr. Anurag Srivastava	Dr. V.K. Bansal - AIIMS
Radical Nephrectomy	Dr. Karwasara – Rohtak	Dr. Gurpreet Singh - PGI
High frequency Ablative procedures in oncology	Dr. Sameer Kaul – New Delhi	

SESSION – 5 (5.00 to 6.00 p.m.)

Pancreatico Gastrostomy - How we do it	Dr. V.K. Bansal – New Delhi	Dr. Arindam Ghosh
Anterior Resection	Dr. H. Ramesh – Kochin	Dr. Jaspal Singh
Radical neck dissection	Dr. R.K.Karwasa	Dr. Praful Arya
Stand by Procedures:		
Conservative Breast Surgery	Dr. Satish Jain – Ludhiana	
Retro Sternal Thyroid Mass	Dr. Satish Jain - Ludhiana	

NATCON-IASO 2007

Venue:
Punjab Agricultural University – Paul Auditorium

TENTATIVE SCIENTIFIC PROGRAMME

21st September (Friday)- 2007

Time	Hall – A	Hall – B
08.00 A.M. Onwards	**Registration & Breakfast**	**Display of Posters**
Session – I 08.30 –10.00 A.M	**PLENARY LECTURES** *Dr. H.S. Shukla* – Varanasi • Topic: Global Cancer Control *Dr. P.B. Desai* – Mumbai • Topic: "Review of Surgical Oncology & Its Perspectives in Future"	
10.00 to 10.30 A.M.	**ORATION** Sh. Vidya Sagar Oswal Memorial Oration Speaker: *Dr. C Palanivelu* – Coimbatore Topic: Minimal Access Surgery a Viable standard Approach in Surgical Oncology	
10.30 to 10.45 A.M.	**TEA / COFFEE**	
Session – II 10.45 to 11.30 A.M.	**ORATION** Smt. Radha Devi Oration Speaker - Dr. Ravi Kant – New Delhi Topic – Lasers	
11.30 to 13.00 P.M.	**PLENARY LECTURES** *Dr. H. Kanimoto* - Japan • Topic: "Hilar Cholangio Carcinoma in MDCT Era" *Dr. Donald Weaver* – USA • Topic: "Changing Face of Surgical Oncology" *Dr. KS Gopinath* – Bangalore • Topic: "Cancer Breast Beyond Surgeons Perspective"	
13:00 to 14:00 P.M.	**LUNCH AND EXECUTIVE MEETING**	
Session - III 14:00 to 15:30 P.M	**PANEL DISCUSSION** Surgical Management of Metastatic Cancer Moderator: *Dr. Sanjay Kapoor* – New Delhi	**SYMPOSIUM** Symposium on Bone Tumours Moderator: *Dr. M. Ganguly* – New Delhi

Time	Hall – A	Hall – B
Session – IV 15:30 to 17:30 P.M.	**GUEST LECTURE** *Dr. Sanjay Sharma* – Mumbai • Topic: Current Trends in the Management of Lung Cancer" *Dr. Ajay Mehta* – Nagpur • Topic" Gene Expression Signature – Clinical Implications for Breast Cancer Therapy *Dr. K.C. Kothari* - Ahmedabad • Topic: Minimal Invasive Surgery for Cancer of Oesophagus and Post cricoid *Prof. B.K.C. Mohan Prashad* - Madurai • Topic: Tumor Markers" – Current Clinical Relevence	**GUEST LECTURE** *Dr. Sandeep Kumar* – Lucknow • Topic: Oncoplastic Breast Surgery – The Indian public perspective" *Dr. P Raghu Ram* - UK • Topic: The Art & Science of Onco-plastic Breast Surgery – The Royal Marsden Experience. *Dr. Madan Arora* – USA • Topic: Advances in Adjuvant chemotherapy for breast cancer" *Dr. Sameer Kaul* – New Delhi • Topic: Role of Hormonal Therapy in the management of Breast Cancer
	TEA/COFFEE	
	Inauguration Function at 6:00 PM (Venue: Paul Auditorium – PAU)	
	Musical Night – 8:00 PM Onward (Venue: Paul Auditorium – PAU)	
	Dinner at 9:30 PM to 10:30 PM (Lawns near Paul Auditorium)	

22nd September (Saturday)- 2007

Time	Hall – A	Hall – B
08.00 A.M. Onwards	**Registration & Breakfast**	**Display of Posters**
Session – V 8.30 -10.00 AM	**GUEST LECTURES –3** *Prof. R. Rajaraman* • Topic: Regional Lymphadenectomy" Where do we stand? *Hemant Raj* – Chennai • Topic: "Peritoneal Surface Malignancies" A Promising Future *Dr. Arun Chaturvedi* – Lucknow • Topic: Statistics for Surgical Oncology – A Necessary Evil?"	**FREE PAPER SESSION – I** 8.30 to 10.00 A..M.

Time	Hall – A	Hall – B
10.00-10.40	**ORATION** Prof. N.C. Misra Oration Speaker - Dr. Munemasa Ryu, Japan Topic – "Hepatic Resection"	
10.40 to 11.00 A.M.	**TEA / COFFEE**	
Session – VI 11.00 to 11.40 A.M.	**ORATION** Moti Bhai Oration Topic- Fertility sparing surgery for Carcinoma Cervix and Trachelectomy Speaker – *Dr. John Shephered, U.K.*	
11.40 to 1:00 P.M.	**GUEST LECTURE** *Dr. Shaleen Kumar* – Lucknow • Topic: Facts or Fiction – Concurrent chemo-radiotherapy for Head and Neck cancer in Indian patients – Is it Feasible *Dr. A.D. Cruz* - Mumbai • Topic "Post Chemo-radiotherapy Salvage surgery for head and neck cancers – Problems and Issues. • Targeted treatment in Head and Neck Cancer – Speaker –To be announced	**GUEST LECTURE** *Dr. Madan Arora* – USA • Topic: "Advances in Chemotherapy in Colorectal Cancer" *Dr. Taira Kinoshita* – Japan • Topic: D 2 Gastrectomy *Prof. M.C. Misra* – N. Delhi • Topic: Multi Modality Management of Soft Tissue Sarcomas
13:00 to 14:00 P.M.	**LUNCH**	
Session - VII 14:00 to 15:30 P.M	**SYMPOSIUM** Topic: Renal Cell Carcinoma Moderators: *Dr. Kim Mammen, Dr. Satish Jain*	**PANEL DISCUSSION** Management of Periampullary Carcinoma Moderator: *Dr. L. Sarangi*
Session – VIII 15:30 to 17:00 P.M.	**Detroit Fellowship Award Papers**	**Free Paper Session – II**
17:00 to 17:45	*Dr. KS Gopinath & Dr. K Panda* - Onco-quiz Moderator: *Dr. L. Vohra*	
17:45 to 18:00 P.M.	**TEA/ COFFEE**	
	General Body Meeting at 6:00 PM (Venue: Paul Auditorium)	
	Banquet Dinner: 8:00 PM Onwards (Venue: Silver Oak Resort- Pakhowal Road – Ludhiana)	

23rd September (Sunday) 2007

Time	Hall – A	Hall – B
08.00 A.M. Onwards	**Registration & Breakfast**	**Display of Posters**
Session – IX 08.45 –10.45 A.M	**GUEST LECTURES** *Dr. Santosh Abraham* – Cochin • Topic: Locally advanced thyroid cancer - Our Experience *Dr. Chintamani* – N. Delhi • Topic: "Neck Dissection Head & Neck Cancer – How much is Optimum ? *Dr. Sandeep Guleria* – N. Delhi • Topic: Diagnosis & Management of Post Transplant Tumours *Dr. Gurpreet Singh* - Chandigarh • Topic: "Predictions and Prognostic factors in breast cancer	**VIDEO AND FREE PAPERS PRESENTATION** • Video • Free Paper Session- I 9.00 to 10.00 A.M. Session – II 10.00 to 11.00 A.M. Session – III 11.00 to 12.00 A.M.
10:45 to 11.00 A.M.	**TEA / COFFEE**	
Session –X 11.00 to 12.30 P.M.	**SYMPOSIUM** Carcinoma Cervix Moderators – Dr. R.K. Karwasara & Dr. Mrs. Veena Jain	
12:30 to 13:00 P.M	**VALEDICTORY FUNCTION**	
13.00 – 14.30 P.M.	**LUNCH**	

Hereditary Breast Cancer: Genetics, Pathology, Clinical Features

Gurpreet Singh*

Introduction

When Paul Broca, a French surgeon, described his wife's pedigree of four generations of breast cancer in 1865, he started the process of establishing hereditary breast cancer. Almost a century later Henry Lynch described 34 families with two or more first-degree relatives with breast cancer, including a description of hereditary breast and ovarian cancer. In 1990, Hall *et al* [1] noted a linkage between chromosome 17q and early-onset breast cancer. Narod *et al* [2] demonstrated a linkage to this same site in the hereditary breast and ovarian cancer syndrome. The site was soon cloned and named BRCA1. In 1994, a second breast cancer–susceptibility gene, BRCA2, was linked to chromosome 13q. The description of these genes firmly established the existence of hereditary breast cancer.

Genetics

Approximately 45% breast cancer susceptibility syndromes are induced by BRCA1 and BRCA2 and are transmitted as a dominant autosomal trait, accounting for about 40% cases of families with both early onset breast cancer and ovarian cancer. Rarely, other genes, such as CHK2, ATM, p53, PTEN and others, may be implicated in familial cancer syndromes, but still a large chunk of familial breast cancer cases remain unexplained [3]. The current understanding of genetic predisposition to breast cancer is that a small number of highly penetrant mutations in single genes, such as BRCA1 and BRCA2, cause a high risk of breast cancer and account for a small proportion of patients with breast cancer (probably 2–3%). The identification of other highly penetrant breast cancer susceptibility genes has so far been largely unsuccessful. Combinations of many minor genetic variants conferring small rises in risk probably account for much of the genetically determined rise in breast cancer risk, but at present this risk is difficult to quantify in any given individual. The prevalence of germline BRCA1 or BRCA2 mutations in the general population is 0.1–0.2%[4] but it may be much higher in certain ethnic groups (e.g. 2.5% in the Ashkenazi Jewish population).

The BRCA1 gene is located on 17q21 and has a total length of about 100 kb. The BRCA2 gene is located on 13q12.3 and has a total length of 70 kb. Both genes are large and encode for large proteins (1863 amino acids BRCA1 and 3418 amino acids BRCA2). They also share a complex genomic structure encompassing 24 and 27 exons in the case of BRCA1 and BRCA2, respectively. They are also characterized by the presence of the extremely large exon 11 that accounts for about half of the coding region in both genes [3]. Small deletions, insertions,

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nonsense mutations and splicing aberrations account for 87% of all pathogenic mutations of the BRCA1 gene, resulting in the generation of truncated BRCA1 protein. The types of mutation in the BRCA2 gene are generally similar to those in the BRCA1 gene [5]. It is important to note that about 80% of patients with familial breast cancer do not have detectable mutations in any known genes.

Two categories of mutations are described - founder mutations and private mutations. Founder mutations are discrete genetic abnormalities that are particularly prevalent among certain ethnic population subsets that have a relatively homogenous ancestry. Founder mutations within the BRCA1 and BRCA2 genes have been studied most extensively among the Ashkenazi Jewish community. The BRCA1–185delAG, 5382insC, and BRCA2–6174delT mutations appear to be present in at least 2% of this population. Other founder mutations have been identified in association with Icelandic, Dutch, Norwegian, Swedish, Russian, and Japanese population subsets [6]. More than 5000 different BRCA1 and BRCA2 mutations have been described to date and each is essentially unique or "private" to a given family. These private mutations are characterized by highly heterogeneous pattern scattered throughout the entire coding regions. Thus, when presented clinically with a family in which a BRCA1 or BRCA2 mutation is suspected, that family's specific mutation could be anywhere within either gene. More than half of these private mutations have been reported only once, i.e. each has been identified in just one family. No strong phenotypic correlation seems to exist between the sites of mutation and the phenotype and thus clinical data cannot give any indication of the region where the alteration is likely to be found.

A clear genotype-phenotype correlation exists for some BRCA2 mutations, where the central part of the gene is named the ovarian cancer cluster region (OCCR) because mutations within it are associated with an increased ovarian: breast cancer ratio. Compared to other BRCA2 mutations, OCCR mutations are associated with higher ovarian cancer risk and lower breast cancer risk [7]. Similar studies on BRCA1 mutations are less conclusive, but suggest that mutations in the central part of the gene are associated with lower breast cancer risk, and that mutations in the 3 end could be associated with lower ovarian cancer risk. The phenotypic expression of these mutations can vary widely even between individuals with the same disease-causing mutations, as a result of nongenetic variation and polymorphisms / mutations in other genes, known as genetic modifiers.

The mutational spectra of BRCA1 and BRCA2 include many high penetrance, individually rare genomic rearrangements. Among patients with breast cancer and suggestive family histories of cancer who test negative for BRCA1 and BRCA2, approximately 12% can be expected to carry a large genomic deletion or duplication in one of these genes, and approximately 5% can be expected to carry a mutation in *CHEK2* or *TP53*. Effective methods for identifying these mutations are being developed and should be made available to women at high risk [8].

A recent meta-analysis has combined the data derived from 22 studies based on unselected series of familial breast cancer. Using a modified segregation analysis, it has been estimated that BRCA1 mutation carriers have a 65% average cumulative risk of developing breast cancer of by age 70 years and a 39% average cumulative risk of developing ovarian cancer, while for BRCA2

mutation carriers, the corresponding values are 45% and 11% [9]. Besides the life-span risk of developing cancer, BRCA1 gene mutations particularly increase the risk of early onset breast carcinoma, while the risk to develop a contralateral breast cancer is estimated to be 40% within 10 years from the initial diagnosis [10]. BRCA1 and BRCA2 families are also exposed to the risk of developing other malignancies. Recent data demonstrate that BRCA1 mutations are associated with an increased risk of cervical, endometrial, and pancreatic cancers. BRCA2 mutation carriers also have an increased risk of pancreatic, prostate, melanoma, stomach, and gallbladder cancers. The presence of other cancers, particularly pancreatic, early-onset prostate, or a second primary in an individual with breast cancer, should heighten the clinical suspicion for the presence of a BRCA1 or BRCA2 mutation in a family with breast cancer. Male breast cancer is a characteristic of the BRCA2 associated cancer syndrome. Cumulative risk for this malignancy is estimated at 2.8% by age 70 years, rising to 6.9% by age 80 years [7]. Male breast cancer risk in BRCA1 carriers is lower and has been estimated at 5.8% over the entire lifetime.

Ductal carcinoma in situ (DCIS) is a part of the breast/ovarian cancer syndrome defined by BRCA1 and BRCA2, with mutation rates similar to those found for invasive breast cancer. These findings suggest that patients with breast cancer with an appropriate personal or family history of breast and/or ovarian cancer should be screened and followed according to high-risk protocols, regardless of whether they are diagnosed with in situ or invasive breast cancer.

While the penetrance (chance of developing cancer) for BRCA1 or BRCA2 carriers is substantially elevated, it does not reach 100%. That is, not every carrier will develop cancer. Moreover, the cancer risk rises with age. Members of the same family – who each carry the same mutation - develop different types of cancer at different ages (along with the occasional carrier who never develops cancer at all). The reasons for the variable risks and the unpredictable age of onset of cancer in BRCA1 and BRCA2 carriers are not fully understood at present.

Genetic Testing

Repeated occurrence of a specific cancer within a family suggests two possibilities. First, the family members share a genetically related predisposition or increased susceptibility to a specific cancer. The second possibility involves increased risk for a specific cancer due to common exposure to an environmental agent, including factors related to habits and lifestyle. In this sense, “familial” is not necessarily synonymous with “hereditary”, but many cases of familial breast cancer are attributable to genetic factors. This reflects the difficulty a clinician faces in precisely identifying the population of patients that might really benefit from the genetic testing. The high cost of the testing due to the large dimensions of the genes and to the large number of mutations identified in them, makes it mandatory for the clinician to apply reliable selection criteria. A triage tool to identify those families most likely to benefit from genetic testing would, therefore, be very useful.

Several criteria have been identified that might predict the probability to be a mutant BRCA1/2 individual. Probability models based on these criteria have been developed to estimate the likelihood that an individual or family has a mutation in BRCA1 or BRCA2. Although many

models exist, the BRCAPRO model (http://astor.som.jhmi.edu/brcapro/) and the Myriad mutation prevalence tables (http://www.myriadtests.com/provider/brca-mutation-prevalence.htm) are the most widely used. A discussion on the pros and cons of various models is beyond the scope of this article. Genetic testing for cancer risk assessment should be considered in women whose mutation probability is greater than 10%. Clinical judgment remains a key component in estimating prior probabilities, particularly in families with non breast-ovarian cancers (e.g., male breast cancer, pancreatic cancer, and early-onset prostate cancer) or individuals with multiple primary cancers.

The NCCN guidelines (National Comprehensive Cancer Network; http://www.nccn.org/) define these criteria as:

- Early age onset breast cancer
- Two breast primaries or breast and ovarian cancer in a single individual,

  OR
- Two breast primaries or breast and ovarian cancers in close relative(s) from the same side of family (maternal or paternal)
- Clustering of breast cancer with male breast cancer, thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, dermatologic manifestations or leukemia/lymphoma on the same side of family
- Member of a family with a known mutation in a breast cancer susceptibility gene
- Populations at risk *(For populations at risk, requirements for inclusion may be lessened e.g., women of Ashkenazi Jewish descent with breast or ovarian cancer at any age.)*
- Any male breast cancer
- Ovarian cancer: One or more on same side of family.

The NCCN guidelines also give the testing criteria for hereditary breast and ovarian cancer.

- Member of family with a known BRCA1/BRCA2 mutation
- Personal history of breast cancer + one or more of the following:
  - Diagnosed age 40 years, with or without family history
  - Diagnosed age 50 years, or two breast primaries, with 1 close blood relative with breast cancer 50 years and/or 1 close blood relative with epithelial ovarian cancer
  - Diagnosed at any age, with 2 close blood relatives with breast and/or epithelial ovarian cancer at any age
  - Close male blood relative with breast cancer
  - Personal history of epithelial ovarian cancer
  - For an individual of ethnicity associated with deleterious mutations (e.g., founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other) no additional family history may be required

- Personal history of epithelial ovarian cancer
- Personal history of male breast cancer particularly if
  - 1 close male blood relative with breast cancer
  - 1 close female blood relative with breast or epithelial ovarian cancer
- Family history only—Close family member meeting any of the above criteria

For an individual of ethnicity associated with deleterious mutations (eg, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other) no additional family history may be required.

When a hereditary cancer syndrome is suspected in a family, the most important person to test is the relative affected with early breast or ovarian cancer. Once a mutation is identified in an affected family member, the test is considered informative in that family and suitable for testing at-risk individuals. The incidence of BRCA1 and BRCA2 mutations in different segments of population is shown in Table 1. Unfortunately, data on Indian patients is not available.

Table 1: Risk of harboring a *BRCA* mutation based on personal and family history

• General population prevalence	0.2%
• Women with breast cancer at age 60	1%
• Women with breast cancer at any age	5%
• Women with breast cancer ≤ 35	10%
• At least 2 breast cancer < 50 in a family	12%
• Women with ovarian cancer at any age	12%
• Men with breast cancer	14%
• Bilateral breast cancer	25%
• Breast and ovarian cancer in one woman	33%
• Men with breast cancer and a relative with breast or ovarian cancer	36%

Adapted from: Evans JP, Skrzynia C, Susswein L, Harlan M. Genetics and the Young Woman with Breast Cancer. Breast Disease 2005,2006; 23:17–29

The results of genetic testing can be classified as:

- True-positive: The person is a carrier of an alteration in a known cancer-predisposing gene. The person is at an increased risk of developing breast or ovarian cancer throughout her life.
- True-negative: The person is not a carrier of a known cancer-predisposing gene that has been positively identified in another family member. The risk of breast cancer developing in this individual is the same as the women without a family history of breast cancer.

- Inconclusive: The person is a carrier of an alteration in a gene that currently has no known significance. These are called "variants of uncertain significance" and are typically missense mutations in which one amino acid had been substituted for another. Information about these mutations is insufficient to determine whether they are associated with an increased risk for breast cancer or are normal variations (polymorphisms). To investigate whether a variant might be harmful, one must consider family structure and cancer history, whether the variant tracks with the cancer in the family and the type of amino acid substitution. In addition, certain specialized laboratory techniques can sometimes be employed to define the meaning of such a variant.

Any woman who seeks this testing must be well informed about the risks and benefits of the testing. A positive BRCA genetic test result in one person may mean that an entire at-risk family has been identified. Issues related to communicating the results with other family members who may or may not wish to have this information need to be considered when making a testing decision. Receiving BRCA test results, either positive or negative, may affect emotional health and self esteem. Finally, before referring the person for testing the clinician himself should be clear on what he has to offer to the individual in case she tests positive.

Pathology of BRCA 1 & 2 Related Breast Cancer

Invasive ductal adenocarcinoma is the most frequent histological type (74%) in BRCA1-associated tumors. However, these patients showed a higher proportion of medullary carcinomas than patients with sporadic tumors (13% vs. 3%). A proportion of BRCA1 tumors also have characteristics of atypical medullary carcinomas. In this, BRCA1 tumors are characterized by a prominent lymphocytic infiltrate and pushing margins occupying a high proportion (>75%) of the tumor perimeter (found in 13 and 21%, respectively). In addition, a high proportion of BRCA1 carcinomas (48%) show extensive areas of necrosis [11]. BRCA1-related breast cancer is associated with a high frequency of solid tubular carcinoma (corresponding to invasive ductal carcinoma and invasive ductal carcinoma with a predominant intraductal component in the WHO classification). The size of the primary lesion is not strictly correlated with the number of positive loco-regional lymph nodes

A study by the Breast Cancer Linkage Consortium showed that in a cohort of 440 patients, including 118 carriers of *BRCA1* mutation, there was a higher proportion of high-grade tumors in the *BRCA1* patients [12]. These findings were confirmed by a second study that examined 182 tumors, of which 119 carried *BRCA1*-mutations. Results showed that *BRCA1* tumors were less likely to express ER (10% *BRCA1* vs. 65% of sporadic controls), PgR (21% vs. 59%), and HER2/neu (3% vs. 15%) [13]. In this study, *BRCA1* tumors were more likely to express p53.

ER negativity is characteristic of BRCA1 tumors. Between 63 and 90% of BRCA1 carcinomas have been reported to be ER-negative in different series. Although it has been suggested that this relationship might be explained by the higher grade of tumors and the younger age of patients, BRCA1 tumors are more likely to be ER-negative than sporadic ones, when tumors from patients of the same age are compared. In addition, the likelihood of ER negativity is

four to eight times higher in BRCA1 grade 3 tumors than in grade 3 sporadic cases. Taken together, these results suggest that BRCA1 tumors tend to be ER, PgR, and HER2 negative (triple negative). They are more likely to express high levels of myoepithelialcell- type cytokeratins and therefore share similarities with tumors that are classified as basal-like in origin. BRCA2-related tumors are usually medium to high grade ductal carcinomas, ER receptor expression is usually positive, and HER2 expression negative [12].

While such histological associations hold true in a population, it should be emphasized that they are not precise enough to offer significant guidance in an individual's case.

Clinical Features and Prognosis of BRCA 1 & 2 Associated Breast Cancer

As compared with sporadic breast cancers, breast cancers developing in carriers of BRCA1/2 mutations are characterized by early onset (average age of onset, BRCA1/2-related cancers, 46 years; sporadic cancers, 54 years) and a high frequency of bilateral involvement (BRCA1, 44%; BRCA2, 28% vs. sporadic, 6%) [14].

Several reports have documented the high incidence of contralateral breast cancer that is seen in BRCA mutation carriers diagnosed with their first unilateral breast cancer. Cases of sporadic breast cancer have the expected nearly 1% per year risk of contralateral disease. However, these rates approximately quadruple for BRCA mutation carriers, ranging from 14% to 31% at 5 years [6].

Despite these poor prognostic features, survival studies of BRCA1/2 mutation carriers have provided conflicting results. The reasons for this are many. Most available data, derived from retrospective or indirect data, are based on small numbers and are confounded by different biases and by lack of appropriate controls. For example, in most studies of breast cancer prognosis, molecular genetic testing was not performed in the control group and controls were not matched to cases for stage at diagnosis.

In one study, 49 Dutch patients with BRCA1 mutations were compared with 196 patients with sporadic cancer. Disease-free survival at five years was 49% for BRCA1 and 51% for sporadic patients. The overall survival at five years was 63% and 69% respectively for BRCA1 and sporadic cancer patients respectively [15]. A study of 278 women over 10 years demonstrated a trend toward a worse prognosis for BRCA1 mutation carriers [16]. In contrast, a retrospective analysis of 92 women (including 30 women with breast cancer and *BRCA1/2* mutations) who developed breast cancer before age 42 found no difference between *BRCA* and non-*BRCA* associated cancers in five-year relapse-free survival or overall survival. The overall consensus is that there is not much difference in the prognosis of BRCA associated breast cancer as compared to sporadic breast cancer.

The poor prognosis associated with *BRCA1* mutation status may be mitigated by adjuvant chemotherapy. This is further explained in the next section.

BRCA 1 as a Predictive Factor

Experimental models suggest that *BRCA1* can regulate differential sensitivity to different classes of chemotherapy agents *in vitro*. The absence of *BRCA1* results in increased sensitivity to

DNA damage-based chemotherapy, whereas the presence of *BRCA1* promotes an increase in sensitivity to antimicrotubule agents. These observations could have a significant impact on the clinical management of breast cancer because these different types of chemotherapy agents are used in various treatment regimens in both early and metastatic breast cancer

A small study in Ashkenazi Jews evaluated 38 patients with locally advanced breast cancer [18]. Seven of these patients had germline mutations in *BRCA1* and a further four had *BRCA2* mutations. All patients received anthracycline based neoadjuvant chemotherapy, and 10 of 11 patients with *BRCA* mutations had a clinical complete response compared with only 8 of 27 non carrier patients with sporadic breast tumors. Four of nine breast cancer patients had a complete pathological response compared with only one non carrier. From this study, it was inferred that tumors with BRCA1 mutation were highly sensitive to anthracycline-based chemotherapy regimens.

A more recent study confirmed that tumors arising in *BRCA1*-mutation carriers are more chemosensitive [19]. This study investigated response to neoadjuvant anthracycline- based chemotherapy in 15 BRCA1, 5 BRCA2, and 57 sporadic breast tumors. A clinical response was observed in 100% of BRCA1 tumors compared with 80% and 63% of BRCA2 and control tumors, respectively. A pathological complete response was observed in 53% of BRCA1 patients, whereas no *BRCA2* patients and only 14% of sporadic controls had a similar response. This study suggests that tumors with BRCA1 mutations are more chemosensitive than both *BRCA2*-mutated and sporadic breast tumors.

Initial indications are that the predictive value of BRCA1 and response to different chemotherapy agents in preclinical models can be transferred into a clinically useful prognostic and predictive tool.

References

1. Hall JM, Lee MK, Newman B, et al. Linkage of early-onset breast cancer to chromosome 17q21. Science 1990; 250:1684–9.
2. Narod SA, Feunteun J, Lynch HT, et al. Familial breast ovarian cancer locus on chromosome 17q12-q23. Lancet 1991; 338:82–3.
3. Palma M, Ristori E, Ricevuto E, Giannini G, Gulino A. BRCA1 and BRCA2: The genetic testing and the current management options for mutation carriers. Crit Rev Oncol/Hematol 2006; 57:1–23.
4. Ford D, Easton DF, Peto J. Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet 1995; 57:1457–62.
5. Couch FJ, Weber BL. Mutations and polymorphisms in the familial early-onset breast cancer (BRCA1) gene. Breast Cancer Information Core. Hum Mutat 1996; 8:8–18.
6. Newman LA, Kuerer HM, Hunt KK, Vlastos G, Ames FC, Ross MI, Singletary SE. Role of the Surgeon in Hereditary Breast Cancer. Ann Surg Oncol 2001; 8:368–378.
7. Thompson D, Easton D. Variation in cancer risks, by mutation position in BRCA2 mutation carriers. Am J Hum Genet 2001; 68: 410–419.

8. Walsh T, Casadei S, KH Coats, et al. BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer. JAMA 2006; 295:1379-1388.
9. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003; 72:1117–30.
10. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004; 22:2328–35.
11. Honrado E, Ben´ıtez J, Palacios J. Histopathology of BRCA1- and BRCA2-associated breast cancer. Crit Rev Oncol/Hematol 2006; 59:27–39.
12. Breast Cancer Linkage Consortium. Pathology of familial breast cancer: Differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Lancet 1997; 349:1505–1510.
13. Lakhani SR, Van De Vijver MJ, Jacquemier J et al. The pathology of familial breast cancer: Predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol 2002; 20:2310 –2318.
14. Arai M, Utsunomiya J, Miki Y. Familial breast and ovarian cancers. Int J Clin Oncol 2004; 9:270–282.
15. Verhoog LC, Brekelmans CTM, Seynaeve C, et al. Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. Lancet 1998; 351:316-21.
16. Goffin JR, Chappuis PO, Bégin LR, et al. Impact of germline BRCA1 mutations and overexpression of p53 on prognosis and response to treatment following breast carcinoma: 10-year follow up data. Cancer 2003; 97:527- 36.
17. Robson M, Gilewski T, Haas B, Levin D, Borgen P, Rajan P, et al. BRCA-associated breast cancer in young women. J Clin Oncol 1998; 16:1642-9.
18. Chappuis PO, Goffin J, Wong N, et al. A significant response to neoadjuvant chemotherapy in BRCA1/2 related breast cancer. J Med Genet 2002; 39:608–610.
19. Delaloge S, Pautier P, Kloos I, et al. BRCA1-linked breast cancer (BC) is highly more chemosensitive than its BRCA2-linked or sporadic counterparts. Paper presented at: 27th Congress of the European Society for Medical Oncology; October 18–22, 2002; Nice, France. Abstract 120.

DETROIT VISITING FELLOWSHIP

A fellowship to visit Wayne State University, Detroit will have local hospitality included by the host institution, excluding the travel cost of to and fro travel to USA. The candidate should be less than 40 years of age (on 31 -12-2008), and permanently employed. He should be a Full member of IASO. Selection based on CV and paper presentation during NATCON meeting. The paper must be on the work done in India only. Application must reach Secretary IASO by 15 August 2008

Human Pappiloma Virus Vaccine for Prevention of Carcinoma Cervix: A Major Breakthrough

Mudit Agarwal*

Abstract

The human papilloma virus family of viruses causes a variety of benign, premalignant and malignant lesions of which cervical cancers. It is the leading cause of death from cancer in women in developing countries; every year approximately 493,000 women develop cervical cancer and 230,000 die every year from this disease. The vaccine against HPV includes virus-like particles, composed of the major viral capsid protein of HPV without the carcinogenic genetic core. A number of randomized controlled trials have shown that the vaccine is tolerated well, leads to high antibody levels in both men and women, and prevents chronic HPV infection and its associated diseases. For the vaccine to be effective it should be given before a lady becomes sexually active. The only prohibitive factor for its world wide implementation is the prohibitive cost of the vaccine.

Introduction

Worldwide, about 500,000 new cases of cervical cancer are diagnosed each year of which nearly 80% occurs in the developing countries; resulting in more than 250,000 deaths each year [1,2]. Cervical cancer is one of the commonest cancer amongst women in India. Approximately 132,000 new cases of cervical cancer are estimated to occur in India in 2002 (i.e., nearly one-fourth of all new cervical cancer cases worldwide)[3]. The incidence rates in the country vary between 11 per 100,000 in Trivandrum and 30 per 100,000 in Chennai, both in southern India [4]. In Delhi, it is the second most common cancer among women after breast cancer, the incidence is estimated to be 26.6% of cancers [5] As in other developing countries, squamous cell carcinoma predominates, whereas adenocarcinoma of the cervix accounts for a small percent of cervical cancer, even in urban areas (e.g., Mumbai, 7%, Delhi 4%) [6, 7].

Mechanism of Human Papilloma Virus (HPV) Carcinogenesis

HPV is a non-enveloped DNA virus and is a member of the papillomaviridae family. Its double-stranded DNA is circular and comprises approximately 7900 nucleotide base pairs [8]. The genome is composed of two regions: the "early" region that contains six open reading frames encoding for early proteins (E1, E2, E4, E5, E6 and E7) that control viral replication, transcription and cellular transformation; while the late region encodes for a large nucleocapsid protein L1 and a small L2 of the capsid.

More than 100 types of papillomaviruses are known to infect humans. Approximately 35 types are known to infect the genitalia. These types are divided into groups based on the frequency

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of association with malignant tumors and their oncogenic potential. A high risk genital type is an HPV that may be associated with advanced precancer or cancer. The high risk HPV types are: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 [8]. The low risk types are 6, 11, 26, 42, 44, 54, 70 and 73. They are associated with *Condylomata acuminata* of the genital tract. The HPV virus reaches the basal layer of the epithelium, where they bind to and enter into the cells through small breaks. It has been suggested that for the maintenance of infection, the virus has to infect the stem cell .[9] Infection by HPV results in the maintenance of the genome as a viral episome in the nucleus of the infected cell, independent of the host cell genome. Infrequently, the circular episome genome breaks at the region of the E1-E2 region, leading to integration of the viral DNA into the host genome. The break of the E2 gene is significant because the E2 gene product regulates transcription of the HPV genome. Its disruption leads to an increase in the production of E6 and E7 gene products [9]. The critical molecules in the process of virus replication are the viral proteins E6 and E7, which interact with a number of cellular proteins. In experimental studies these interaction have been shown to induce proliferation and eventually immortalization and malignant transformation of cells [10]. This excess production of E6 and E7 proteins initiates the carcinogenic process. Binding of E7 to pRb activates the E2F transcription factor, which triggers the expression of proteins necessary for DNA replication [11]. Unscheduled S-phase would normally lead to apoptosis by the action of p53 however, in HPV infected cells, this process is counteracted by the viral protein E6, which targets p53 for proteolytic degradation [12]. This results in loss of cell-cycle control and normal keratinocyte differentiations retarded. The persistence of HPV 16 infection and its induction of progression of malignancy may be explained by constant activity of viral proteins and leads to genomic instability, accumulation of oncogene mutation, further loss of cell-growth control, and ultimately cancer [13]. During tumor progression, the viral genome integrate into the host chromosome, which results in a constant level of E6/E7 proteins via stabilization of the mRNA, by the influence of modified chromatin structure or by loss of he negative regulation of transcription mediated by the viral E2 protein [14].

Epidemiological evidence for the causal link between HPV and cervical, anogenital cancer and other anogenital diseases

HPV is sexually transmitted; it is acquired by young women soon after initiation of sexual activity, with a cumulative incidence of 40% within 16 months [15]. Although most HPV infections are cleared without clinical sequel, persistent infection can cause abnormalities in the cervical epithelium that may progress to cancer. For a lesion to progress to neoplasia, the HPV infection must be persistent. The initial significant consequence of persistent HPV infection is usually a low grade cervical premalignant cervical lesion– cervical intraepithelial neoplasia grade 1. Each year, 30 million women develop CIN-1. In up to 33% it may progress to a high grade lesion – CIN-2 or CIN-3. Ten million women are diagnosed yearly with CIN-2 and CIN-3 [16]. The transit time of an untreated high-grade lesion to cervical cancer is variable, ranging from a few months to a few decades.

The largest series of cases of invasive cervical cancer investigated with a standard protocol has been put together by the International Agency for Research on Cancer (IARC). Thousand

women with histological proof of invasive cervical cancer were analyzed for the detection of HPV-DNA, for the presence of malignant cells in sections adjacent to the sections used for PCR-based assays. The patients which were initially HPV negative were found to have HPV-DNA in 99.7% of tumors, leading to the conclusion that HPV is a necessary cause of cervical cancer [17,18].

The eight most common HPV types detected in one of the IARC studies, in descending order of frequency, were HPV-16, 18, 45, 31, 33, 52, 58and 35 and these are responsible for about 90% of all cervical cancer world wide [19]. In the pooled analysis of 11 case-controlled studies of invasive cervical cancer conducted by IARC in 11 countries, HPV-16 and -18 were most common types in both squamous cell carcinoma and adenocarcinoma but fraction of squamous cell carcinoma due to HPV-16 and -18 were 70% while that for adenocarcinoma was 86% [20,21]. In India, Bhatla *et al*., in hospital-based study in New Delhi, North India evaluated the prevalence of HPV in cases of invasive cervical carcinoma. They had found HPV 16 was the commonest type, seen in 73.6% cases, followed by HPV 18 (14.2%) and 45 (11.3%) [23]. We have enough epidemiological evidence to say that certain types of HPV have central and causal role in development of carcinoma cervix.

There is role of HPV in development of other anogenital cancer, there is a strong evidence of HPV-16 causing carcinoma of vulva, anus and penis and there is limited evidence of HPV-18,-6 and -11 in carcinogenesis of these cancers [24]. The majority of HPV-associated diseases are caused by HPV types 6, 11, 16, and 18. HPV types 6 (HPV-6) and 11 (HPV-11) cause most anogenital warts, a portion of the cases of low-grade neoplasia [25, 26]. This was the basis of quadrivalent HPV vaccine for type -16, -18, -6 and -11.

Rationale for HPV vaccine

HPV vaccine commercially was developed in 1993 and after a decade and half of research proving the causal relationship between HPV and cervical cancer and better understanding of natural history of HPV infection has become commercially available. The vaccine development programs were based on the discovery that L1 coat protein could assemble into virus like particles (VLP) when expressed as a recombinant protein in a heterologous eukaryotic system. This is capable of inducing immunogenic response in animal models [27]. The HPV vaccine was developed by isolating the gene encoding for HPV envelope protein L1. This gene was then inserted into the DNA of the yeast *Saccharomyces cerevisiae* to create a recombinant DNA. The yeast then expressed the L1 capsid protein [28] and produced the L1 protein that spontaneously assembles into a virus-like particle (VLP). The VLP resembles the native HPV virus, but lacks the DNA core. Vaccination with L1 VLP derived from species-specific papilloma viruses neutralizes virus [29]. The commercial vaccine contains the 97% purified VLP adsorbed onto an aluminum adjuvant, which varies among the pharmaceutical companies. The human immune system recognizes the VLP as if it were HPV itself, thus producing a neutralizing antibody response. Presently two types of vaccine are produced bivalent (HPV16/18) and quadrivalent (HPV16/18/6/11) i.e. immunizing against 2 types or 4 types of HPV infection. This incorporation of more than one type of HPV in vaccine was based on the observation that there is very limited cross neutralization against other genotypes [30].

Composition of vaccine

Each 0.5-mL dose of Quadrivalent HPV vaccine (GARDASIL™, produced by Merck and Co, Inc.) contains 20 μg HPV 6 L1 protein, 40 μg HPV 11 L1 protein, 40 μg HPV 16 L1 protein, and 20 μg HPV 18 L1 protein. VLPs are adsorbed on an aluminum-containing adjuvant. Each 0.5 ml dose contains 225 μg amorphous aluminum hydroxyphosphate sulfate. The formulation also includes sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection [31]. This vaccine is FDA approved [32].

The bivalent HPV-16/18vaccine (Cervarix™, GlaxoSmithKline Biologicals) contains 20 μg of HPV-16and 20 μg of HPV-18 in adjuvant of 500 μg of aluminium hydroxide with 50 μg of 3-deacylated monophosphoryl lipid A(ASO4)[33].

Dose and administration

Quadrivalent HPV vaccine is administered intramuscularly as three separate 0.5 mL doses. The second dose should be administered 2 months after the first dose and the third dose 6 months after the first dose.

Clinical evidence of efficacy of HPV vaccine

The studies used prespecified endpoints to evaluate the impact of the bivalent/quadrivalent vaccine in preventing HPV-related infection and disease. Phase II studies evaluated the efficacy of vaccine using a persistent infection endpoint. Phase III studies evaluated the efficacy of vaccine on clinical lesions. Predefined combinations of phase II and III studies were used to improve the precision of the efficacy findings. Various endpoints were assessed in the different studies, including vaccine type-related persistent HPV infection, CIN, VIN and VaIN, and genital warts. The primary endpoint and the basis for approval was the combined incidence of HPV 16- and 18-related CIN 2/3 or AIS. These endpoints served as surrogate markers for cervical cancer. Studies using an invasive cervical cancer endpoint were not feasible because the standard of care is to screen for and treat CIN 2/3 and AIS lesions to prevent invasive cervical cancer. Furthermore, the time from acquisition of infection to the development of cancer can exceed 20 years.

Table 1.Relevant Clinical trials

	Type of Vaccine	HPV type	No. of patients	Age (yrs)	Duration	Efficacy prevention CIN-2 3 (%)
Koutsky *et al*., 2002 [34]	Monovalent	16	1533	16–23	17 months	100
Harper *et al*., 2004 [37]	Bivalent	16/18	1113	15-25	36 months	91.60
Villa *et al*., 2005 [36]	Quadrivalent	16/18/6/11	481	16-23	2yrs	90
FUTURE II 2007 [38]	Quadrivalent	16/18/6/11	12,167	15-26	3yrs	98
Garland *et al* 2007 [41] FUTURE 1	Quadrivalent	16/18/6/11	5455	16-23	3yrs	100

HPV 16 is common in young women and is difficult to clear. A randomized, placebo-controlled trial evaluated a prototype HPV 16 vaccine in 1533 women, 16–23 years old with no evidence of HPV infection at enrollment. At follow-up a median of 17 months after the third vaccine dose, 41 cases of persistent HPV 16 infection and 9 cases of CIN grade 1/2 were found in the placebo group, compared to no cases of either one among those who were vaccinated [34]. A further follow-up at 48 months found no cases of HPV 16- related CIN grade 2/3 among women who were vaccinated, compared to 12 in the placebo group [35]. Harper *et al*., evaluated the efficacy of Bivalent HPV vaccine16/18 randomized 1113 women between 15-25 years of age in North America and Brazil [37]. On assessment at 27 months vaccine efficacy was 91.6% (95% CI 64.5-98.0) against incident infection and 100% against persistent infection (47.0-100) with HPV-16/18. This vaccine preparation was well tolerated, and is expected to be approved for routine use within the next year.

Quadrivalent HPV vaccine (equivalent to *Gardasil*) was evaluated in a randomized, double-blind, 3-year trial in women 16–23 years old; women with previous HPV infection were not excluded. The primary endpoint, persistent infection with HPV 6, 11, 16 or 18, or cervical or external genital HPV-associated disease, occurred in 4 of 235 women who received the vaccine and in 36 of 233 who received placebo, a 90% reduction [36]. A randomized double blind study by FUTURE group involving 12 000 women aged 15–26 years showed that after an average of 3 years' follow-up, vaccination was 98% effective in preventing high-grade cervical lesions due to HPV16 or HPV18, compared with placebo [38]. The same group confirmed the effect of this vaccine preparation in reducing the development of CIN grades 2 and 3 and cervical adenocarcinoma *in-situ* lesions in a combined analysis of four placebo controlled randomized trials [39]. The quadrivalent HPV vaccine has also been shown to be almost 100% effective in preventing other anogenital lesions related to HPV types 6, 11, 16, and 18, including vulvar and vaginal intraepithelial neoplasia [40, 41]. Vaccination appeared less effective in women who did not complete the planned vaccination regimen. The principal side effect associated with vaccination was discomfort at the injection site, and occasional mild fever; extended follow-up of immunized women will be needed to identify any long-term toxic effects associated with HPV vaccine. No clinical data are available in girls younger than 16 years. The FDA apparently inferred efficacy in this age group from immunogenicity studies in girls.

Cost and cost effectiveness of HPV vaccination

The average wholesale cost is $119.75 per dose and 3 doses cost 360$ in USA. Several cost-benefit analyses have been conducted which suggest a positive overall effect from routine HPV vaccination [42,43]. Using a mathematical model with a cost-effectiveness ratio of less than $60,000 per quality-adjusted year of life saved, Goldie and colleagues suggested a program to immunize adolescent girls at age 12 and begin screening (Pap tests) every three years starting at age 25 to provide an estimated overall lifetime reduction in cervical cancer risk of 94% compared to no intervention [43].

Recommendations

Although HPV vaccine would ideally be administered before the onset of sexual activity, girls and women who are already sexually active should also be vaccinated. The US Advisory Committee on Immunization Practices (ACIP) recommends vaccination in all girls and women who are 11–26 years old. Girls 11 and 12 years old can begin the vaccine series during their routine young adolescent visit where they are already scheduled to receive 2 other vaccinations (Tdap and meningococcal vaccine). The ACIP has suggested that vaccination could be started as early as age 9 at the discretion of the healthcare provider [44]. HPV vaccine should not be given to women who are pregnant.

The vaccine contains VLPs of HPV genotypes that account for approximately 70% of cervical cancers. Thus, women must understand that they should continue to participate in pap screening even after vaccination.

Conclusion

HPV vaccination can prevent development of cervical cancer and other anogenital diseases thus decreasing the mortality, morbidity and cost involved in the treatment. There are certain question which needs to be answered by ongoing studies about HPV vaccination. First how long will adequate protection from HPV infection last after immunization? Second, should boys and young men also receive the vaccine? Third the cost US$360 for the required series of three immunizations with the quadrivalent vaccine will certainly be a substantial barrier to widespread use, especially in the developing world. HPV vaccination is indeed a major breakthrough in prevention of cervical cancer and other anogenital diseases thus decreasing the mortality, morbidity and cost involved in the treatment.

References:

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA-A Cancer J Clinicians* 2005; 55: 74–108.
2. Waggoner SE. Cervical cancer. *Lancet* 2003; 361: 2217–25.
3. International Agency for Research on Cancer. GLOBOCAN 2002 database. http://www-dep.iarc.fr/globocan/database.html.
4. Parkin DM, Whelan SL, Ferlay J, et al. Cancer Incidence in Five Continents, Vol. VIII. IARC Scientific Publications No. 155. Lyon: International Agency for Research on Cancer, 2002.
5. National Cancer Registry Programme (NCRP). Indian Council of Medical Research (ICMR). Population based cancer registries. Consolidated report (1990Y96).
6. Krishnamurthy S, Yecole BB, Jussawalla DJ. Uterine cervical adenocarcinomas and squamous carcinomas in Bombay: 1965Y1990. J Obstet Gynaecol Res 1997; 23:521-7.
7. Anonymous. Consolidated Report of the Population Based Cancer Registries 1990-1996, Indian Council of Medical Research, New Delhi.
8. De Villiers EM, Fauquet C, Broker TR, et al. Classification of papillomaviruses. *Virology* 2004; 324:17–27.

9. Door Bar J. The papilloma virus life cycle. JClin Virol 2005;32(Supppl1):S7-S15

10. Munger K, Howley PM. Human papilloma virus immortalization and transformation functions. *Virus Res* 2002;89:213–28

11. Munger K, BaldwinA, Edward KM, Hayakawa H, Nguyen CL, OwensM et al. Mechanism of human papilloma virus induced oncogenesis. J Virol 2004;78:11451-60

12. Thomas M, Pim D, Banks L. The role of the E6-p53 interaction in the molecular pathogenesis of HPV. Oncogene1999;18:7690-700

13. Duensing S, Munger K. Mechanisms of genomic instability in human cancer: insights from studies with human papillomavirus oncoproteins. Int J Cancer 2004;109:157-62.

14. Bernard HU. Gene expression of genital human papillomaviruses and considerations on potential antiviral approaches. Antivir Ther 2002; 7:219-37.

15. Wright TC Jr, Cox JT, Massad LS, et al. ASCCP-sponsored consensus conference. 2001 Consensus Guidelines for the Management of Women with Cervical Cytological Abnormalities. JAMA 2002; 287:2120–9.

16. Lowy DR, Frazer IH. Prophylactic human papilloma virus vaccines. Chapter 16. *J Natl Cancer Inst* 2003; 31:111–16.

17. Bosch FX, Manos MM, Munoz N, Sherman M, Jansen AM, Peto J, Schiffman MH, Moreno V, Kurman R, Shah KV. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst 1995; 87:796-802.

18. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Munoz N. Human papilloma virus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999; 189:12-19.

19. Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papilloma virus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer 2003; 88:63-73.

20. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, Snijders PJ, Meijer CJ. International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papilloma virus types associated with cervical concern. Engl J Med 2003; 348:518-27.

21. Castellsague X, Diaz M, de Sanjose S, Munoz N, Herrero R, Franceschi S, Peeling RW, Ashley R, Smith JS, Snijders PJ, Meijer CJ, Bosch FX; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst. 2006 Mar 1;98(5):303-15

22. Peeling RW, Ashley R, Smith JS, Snijders PJ, Meijer CJ, Bosch FX; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Worldwide human papilloma virus etiology of cervical adeno carcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst 2006; 98:303-15.

23. Bhatla N, Dar L, Patro AR, Kriplani A, Gulati A, Verma K, Broor S, Shah KV, Gravitt PE. Human papilloma virus type distribution in cervical cancer in Delhi, India. Int J Gynecol Pathol 2006; 25:398-402

24. IARC Monographs on the evaluation of carcinogenic risks to humans. Human Papillomaviruses. Vol.90. Lyon: International Agency for Research on Cancer.

25. Gissmann L, zur Hausen H. Partial characterization of viral DNA from human genital warts (condylomata acuminata). Int J Cancer 1980; 25:605-9.

26. Koutsky L. Epidemiology of genital human papilloma virus infection. Am J Med 1997; 102:3-8.

27. Inglis S, Shaw A, Koenig S. Chapter 11: HPV vaccines: Commercial Research & Development. Vaccine. 2006 Aug 21; 24 Suppl 3:S99-S105.

28. Hagensee ME, Yaegashi N, Galloway DA. Self-assembly of human papillomavirus type 1 capsids by expression of the L1 protein alone or by coexpression of the L1 and L2 capsid proteins *Virol* 1993; 67:315–22.

29. Brown DR, Bryan JT, Schroeder JM, et al. Neutralization of human papilloma virus type 11 (HPV-11) by serum from women vaccinated with yeast-derived HPV-11 L1 virus-like particles: correlation with competitive radioimmunoassay titer. J Infect Dis 2001; 184:1183-6.

30. Roden RB, Greenstone HL, Kirnbauer R, Booy FP, Jessie J, Lowy DR, Schiller JT. In vitro generation and type-specific neutralization of a human papilloma virus type 16 virion pseudo type Virol. 1996;70:5875-83

31. Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papilloma virus types 16 and 18 in young women: a randomized controlled trial. *Lancet* 2004; 364:1757–65.

32. HPV and HPV Vaccine – Information for Healthcare Providers. Available at www.cdc.gov/std/HPV/STDFact-HPV-vaccine-hcp.htm

33. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papilloma virus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005; 6:271–8.

34. LA Koutsky, Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, Chiacchierini LM, Jansen KU; Proof of Principle Study Investigators. A controlled trial of a human papilloma virus type 16 vaccine. N Engl J Med 2002;347:1645

35. C Mao, Koutsky LA, Ault KA, Wheeler CM, Brown DR, Wiley DJ, Alvarez FB, Bautista OM, Jansen KU, Barr E. Efficacy of human papilloma virus- 16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. Obstet Gynecol 2006; 107:18-27.

36. Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, Wheeler CM, Koutsky LA, Malm C, Lehtinen M, Skjeldestad FE, Olsson SE, Steinwall M, Brown DR, Kurman RJ, Ronnett BM, Stoler MH, Ferenczy A, Harper DM, Tamms GM, Yu J, Lupinacci L, Railkar R, Taddeo FJ, Jansen KU, Esser MT, Sings HL, Saah AJ, Barr E. Prophylactic quadrivalent human papilloma virus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomized double blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005; 6:271-278.

37. Harper DM, Franco EL, Wheeler CM, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papilloma virus types 16 and 18 in young women: a randomized controlled trial. *Lancet* 2004; 364: 1757–65.

38. The FUTURE II Study Group. Quadrivalent vaccine against human papilloma virus to prevent high-grade cervical lesions. *N Engl J Med* 2007; 356: 1915–27.

39. The Future II Study Group. Effect of prophylactic human papilloma virus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomized clinical trials. *Lancet* 2007; 369: 1861–68.

40. Joura EA, Leodolter S, Hernandez-Avila M, et al. Efficacy of a quadrivalent prophylactic human papilloma virus (types 6, 11, 16, and 18) L1 virus-like particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomized clinical trials. *Lancet* 2007; 369: 1693–702.

41. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papilloma virus to prevent anogenital diseases *Engl J Med* 2007; 356: 1928–43.

42. Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papilloma virus vaccine to screening programs. JAMA 2003;290:781-9

43. Goldie SJ, Hohli M, Grima D, et al. Projected clinical benefits and cost-effectiveness of a human papilloma virus 16/18 vaccine. J Nat Cancer Inst 2004;96:604-15

44. CDC's advisory committee recommends human papilloma virus vaccination. June 29, 2006. Available at: www.cdc.gov/od/oc/

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Applications are invited for Baroda traveling fellowship for the year 2008-09. A sum of Rs 5000 will be awarded to a young surgeon for visiting to a research or therapy oriented cancer center. No person can be awarded the prize again.

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ONCOLOGY: Future Trends

Manoj Pandey*

Abstract

*Oncology is a fast changing branch. The last decade has seen a sea change in cancer diagnosis and treatment leading to increased survival from cancer. Developments in information technology, gene imprinting and inoculation and biological response modification are all going to help in future developments in Oncology. The slogan of last century "**cancer is curable if detected early**" is all set to change to **"Stop cancer in its track**".*

Introduction

The last century saw a sea change in diagnosis and treatment. These were influenced by discovery of X-Rays, radium, blood groups, antibiotics, anaesthesia and exfoliative cytological techniques. These coupled with discoveries in the electronic, communication and computing has changed the face of medicine. Discovery of DNA by Watson and Crick was the most important discovery by far which has helped in not only understanding the biological basis of cancer but has also helped in waging a war on cancer by adding another treatment modality "Gene therapy" to the existing armamentarium of treating oncologists. This century will see oncologist capitalising on these past discoveries and the newer ones to fight the battle on cancer. The specific issues, which will be targeted in the coming century, are discussed in this chapter.

Screening

Effective screening programs exist for number of cancers like breast, cervix and oral cancer. The screening is carried out religiously in developed countries, however, in developing countries like India, even though the concept exist on paper, it is barely implemented. The coming century will see a change in attitude of treating physians thereby people will understand the importance of screening. Countries like Japan has shown what screening can do. By use of routine use of endoscopy the incidence of oesophagus and stomach cancer has been brought down, along with down staging of the disease which has led to improved survival. World over there is great interest in starting the screening for other cancers like lung, prostate and ovarian cancer, however, the screening programs are still in evolution.

Aetiology

Enormous efforts by scientific community have led to identification of same of the genetic and biological factors that causes cancer. The stage has shifted from "curse of god" to 'chemical carcinogenesis' to 'genetic changes' to "gene-environment interaction" at present. For almost all cancers the genetic and molecular defects has been identified. These will help scientists tailor the treatment for each individual defect, opening the doors for gene therapy and cancer vaccines.

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Prevention

Identification of some other aetiological factors like smoking and tobacco chewing, sunlight exposure, sexual practices, viral infections and association of diet and cancers have opened the portals for cancer prevention. Majority of these factors are avoidable hence primary cancer prevention efforts are on to prevent exposure. Anti-tobacco lobbies, prevent sun exposure campaigns are on and in future will gain in strength. It is presumed that these efforts will bring down the cancer incidence by almost 50%.

Evidence based medicine

The treatment in the beginning of last century was based on personal experience (read past experience) of treating physicians or their peers. This practice is fast changing to what is called as evidence based medicine. More and more emphasis is being placed on conducting clinical trials. It is mandatory to conduct clinical trials before a treatment can be accepted. The trials are conducted in stepladder fashion with first step testing for efficacy and toxicity. Second for specific efficacy and third the randomised controlled trials to compare the new modality with established ones.

The best examples of these are trials comparing breast conservation with mastectomy, neoadjuvant chemotherapy etc. In this century no treatment option will be accepted without the evidence from prospective randomised clinical trials. However, there are situations where RCT may not provide evidence or may take a long time to do so. In such situation a meta analysis may prove useful. Meta-analysis is carried out by using special statistical techniques comparing previously reported series and finding out what is the best treatment options. Best examples of meta-analysis are studies in breast cancer showing the effect of adjuvant chemo and hormonal therapies.

Diagnosis

Past century has seen the sea change in diagnosis of cancer with newer imaging modalities being developed, ultrasonography, CT scanning, Magnetic Resonance Imaging, PET and PET-CT, Elisa and flow cytometry are examples of this.

The future will see the further development of these modalities and refinement in technology for others like position emission tomography, molecular essays like western, and southern blotting and gene clip technologies. It is estimated that with these developments it will be possible to identify the cancers early even before any morphological alternation has taken place and treatment at that stage will improve the survival.

Treatment

Treatment of cancer in the last decade of 20^{th} century underwent a sea change. This was seen in all established form of treatment i.e. surgery, radiotherapy, chemotherapy, hormonal therapy and immunotherapy. Gene therapy was added to the armamentarium of treating surgeons with development of B-cell specific antibodies for lymphoma and HER-2 neu antibodies for breast cancer.

Surgical oncology

The past century saw the surgical oncologists move from radical Halstead type of surgeries to conservative therapies. Organ preservation will continue to be the keyword in the next century as

well with scope of surgeons getting redefined. The stage has shifted from surgery being the only treatment of cancer to multimodality treatment. This has led to breast conservation, limb preservation and organ preservation (specially larynx) being possible.

Technology too has come to aid of surgeons with development of staplers, hand held gamma probes, CUSA, hand held PET probe and gamma knife. Making it possible to avoid colostomy, iliostomy, wet colostomy, debilitating surgeries etc. It also speeded up the surgery and helped to reduce the blood loss. Future developments will see surgeons becoming more conservative and organ preservation will be the key word for all cancer at all sites. This will also make surgical oncology more specialized and only those who are trained will be able to perform many of these procedures.

Radiotherapy

Discovery of Radium and X-Rays in last century were the key to development of radiotherapy (RT). Starting with ortho voltage radiotherapy and cobalt 60 the radiotherapy saw a change with development of linear accelerator, brachy therapy and now low, medium and high-energy electron therapy along with particle therapy with neutron and positron is possible without much side effects. The future developments will be in 3-D radiotherapy delivering technique and at avoiding side effects of RT. Stereotactic RT for brain tumours is now possible and further refinement are expected. IMRT and GMRT are already here and techniques are being modified quite fast.

Chemotherapy

Chemotherapy for cancer was developed in last century and has seen multitude of change with discovery of many chemotherapeutic agents. Last decade has seen development of compounds like colony stimulating factors for reducing chemotherapy toxicity. Further development in chemotherapy in this century will see development of compounds with least toxicity to normal cells, development of compound to reduce chemotherapy toxicity and stem cell rescue. Tailoring of drug delivery system and genetically delivered drugs. Many of these are already here and many more are in pipeline. At present cost is a prohibited factor for patients in India but as their availability increase cost will be came reasonable.

Health education

Probably the most important aspect of cancer management is awareness and health education. Last decade saw a sea change in attitude of people, awareness campaigns and a great effort to educate people. With increasing literacy rates, availability of internet and shrinkage of distance has led to increase in knowledge of people and change in their attitudes. These will be stretched in this century due to development in information technology and concentrated efforts of physicians to educate the masses. More patients are reaching oncologists and referral has increased.

Conclusion

Oncology has made tremendous progress in last century and specifically in the last decade. However, the most hope is from the developments in gene therapy, molecular markers and cancer vaccines beside health education and cancer prevention. The day is not for when we will succeed in “stopping cancer in its track”.

HIV Infection: Crossing the Surgeon's Path

Col LS Vohra*

Introduction

Human Immunodeficiency Virus (HIV) infection is currently receiving worldwide attention and not without sufficient reasons. The disease impacts almost all health care professionals and also several strata of society. The health care givers need to be as much sensitized to the plethora of issues involved in HIV infection as the rest of society. Unfortunately, cocooned as we are in our own specialty practices and in the busy lives we lead, there is little opportunity or incentive to educate ourselves of the ramifications of this disease. The need to acquire this knowledge cannot be over-emphasized. What follows is an attempt in the same direction.

The Surgeon's Path Crossed

Among the various categories of Health Care Workers (HCW), it is the surgeons (including dentists and gynecologists) who come into the closest contact with an HIV positive patient and are therefore the most vulnerable. While surgeons are indeed vulnerable, a possibility also exists for an HIV infected surgeon to pass on the virus to a patient under his care. In both events, the surgeon's career, health and social standing are at stake.

Several questions arise in this context and in this paper an attempt is made to answer them based on current evidence. These are:

(a) What is the mechanism of spread?

(b) What is the degree of risk?

(c) Should all patients and surgeons undergo HIV screening?

(d) Should the HIV status of surgeons be disclosed to individual patients?

(e) Should the practice of HIV-positive surgeons be restricted?

(f) Is routine elective surgery safe in the HIV positive patient?

(g) What are the measures to be taken in the event of an exposure?

(a) Mechanism of Spread:

Transmission of HIV and other blood-borne pathogens in the health care setting may occur through percutaneous exposure, mucous membrane exposure, or contact with non-intact skin [1, 2, 3]. HIV infection through contact with intact skin has not been documented [4]. Body fluids considered infectious or potentially infectious include blood, semen, CSF, vaginal, synovial, pleural, pericardial, peritoneal, or amniotic fluid and saliva in dental procedures [5].

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(b) Risk of Infection

(i) ***Patient to HCW risk:*** For a given exposure, the risk of subsequent infection or seroconversion depends on several factors. These include the type of exposure (cutaneous, mucous membrane, or percutaneous) and its severity (depth of penetration), the type and amount of fluid in the inoculum, the viral titer in the patient's blood and whether or not he/she is receiving antiviral medication [6, 7, 8]. For sharp injuries, the type of instrument is important: hollow needles pose a higher risk than other sharps as they introduce a larger amount of blood. The risk of seroconversion after a single percutaneous or mucous membrane exposure to HIV has been estimated at 0.3%– 0.4% [9, 10, 11].

(ii) ***HCW to patient risk:*** The first case of transmission of HIV from a doctor to a patient was reported in 1990 [12]. Subsequent investigations [13] showed that five other persons were infected by this HCW, a dentist in Florida with AIDS. Another case of transmission from an orthopedic surgeon to a patient was reported in 1998 and this was backed by compelling molecular evidence [14]. These seven cases are the only ones reported of HIV transmission from a HCW to patients so far in medical literature. Serologic surveys of patients of HIV-positive dentists and surgeons have failed to uncover any further cases of HIV transmission [15]. The risk of HIV being transmitted from surgeon to patient depends on how frequently the patient is exposed to the surgeon's blood and the risk of seroconversion after exposure [16]. It is estimated that at an average 8.4 procedures per week, during a 30-year career, an HIV-positive surgeon would infect 0.7 patients in his or her entire professional career [17]. Recently another estimate has been made of this risk to be less than 1 in 1,000,000 procedures [18]. Reasons for the low risk of HIV transmission from the surgical team include routine utilization of sterile surgical technique and universal precautions. The surgical team is continually aware of the dangers of transmission of infections, which is inclusive of HIV infection. It is known that the blood concentration of viral particles in healthy carriers is low.

(c) Patient and Surgeon screening for HIV:

The overall risk of transmission of HIV from infected surgeons to patients and vice versa is so low that costly measures, such as testing and limiting of work, are not justified. These screening tests cannot be enforced across the board for several reasons: they need informed consent, they are not completely reliable, they are not financially viable and are not feasible in the emergency setting [20,21,22].

Finally, testing for HIV will not identify patients who pose other hazards to health care workers: in one study, testing for HIV alone would have failed to identify 87% of patients infected with HBV and 80% of those infected with HCV [23]. The only logical course, then, is to treat every patient as a potential source of infection, and observe universal precautions scrupulously in all cases.

(d) Should HIV-positive surgeons disclose their status to individual patients?

As detailed above the risk of HIV transmission from surgeon to patient is extremely low and this risk may be well below the level of other sources of risk during surgery. It is therefore logical to state that if surgeons are required to disclose their HIV status, then patients deserve to be informed of all the risks of surgery above this threshold [24]. Hence the knowledge of a surgeon's seropositivity is a confidential one, limited to select authorities of the hospital and is not to be communicated to individual patients.

(e) Should the practice of HIV-positive surgeons be restricted?

There is evidence from several studies that if standard universal precautions are routinely taken, there is no significant risk of transmission of HIV from HCW to patients. Therefore from a public health perspective, restricting the practice of HIV-positive surgeons would be unfair, wasteful and unnecessary. Surgeons should know their HIV serologic status in the same way that they would want to have knowledge of any other disease about which they may have personal concerns. This personal and confidential information about HIV infection would allow the surgeon to obtain important treatment and counseling for his or her own personal health, and should not be used for any determinations of credentialing or privileging for surgical practice [25].

(f) Is routine elective surgery safe in a known HIV positive patient?

Published data supports the safety of routine surgery in the HIV positive individual in the modern era of Highly Active Anti- Retroviral Therapy (HAART). However, optimizing the CD4 count and getting the viral load as low possible before surgery is best. A high viral load (> 30,000 copies/mL) and a low CD4 T-cell count (< 50/L) may be associated with a higher complication rate [26]. There is sufficient experience that indicates that most HIV-infected patients who require anorectal surgery [27] or laparotomy [28] showed no increase in wound complications.

(g) What are the measures to be taken in the event of an exposure?

When a high-risk exposure event has occurred to a surgeon during the performance of a surgical procedure, the Centers for Disease Control, Atlanta, USA recommends postexposure antiretroviral chemoprophylaxis. Because HIV status of a patient is often not known at the time of exposure, prophylaxis should be initiated as quickly as possible, preferably within hours. A rapid HIV assay carried out on the patient's blood, which can also provide a result within hours, is recommended in order to minimize the amount of medication taken by individuals exposed to HIV-negative patients. Once the source patient is established to be HIV-negative, prophylaxis should be discontinued.

Individuals exposed to HIV-positive source patients and prescribed antiretrovirals should be monitored for specific side effects, and prophylaxis should be administered for a 4-week period. Serological follow-up to determine whether HIV seroconversion has taken place should be carried out at 6 weeks, 3 months, and 6 months following exposure.

Conclusion

Surgeons have the same ethical obligations to render care to HIV-infected patients as they have to care for other patients and they can continue to deliver safe care without hesitation even when carrying the virus. Surgeons should utilize the highest standards of infection control, involving the most effective known sterile barriers, universal precautions, and scientifically accepted infection control practices.

References

1. Centers for Disease Control. Update: human immunodeficiency virus infections in health-care workers exposed to blood of infected patients. MMWR 1987; 36:285–289.
2. Henderson DK, Fahey BJ, Willy M, et al. Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures: a prospective evaluation. Ann Intern Med 1990; 113:740–746.
3. Marcus R, and the CDC Cooperative Needlestick Surveillance Group. Surveillance of health care workers exposed to blood from patients infected with the human immunodeficiency virus. N Engl J Med 1988; 319:1118–1123.
4. Occupational Safety and Health Administration. Occupational exposure to bloodborne pathogens; final rule. Fed Register 12/6/91; 56:64003–64182.)
5. Guidelines Regarding HIV and Other Bloodborne Pathogens in Vascular/Interventional Radiology Hansen, ME, Curtis W. B Dixon, D Eschelman, DJ, Horton, KM, Katz, M, Olcott, EW, Sacks, D, J Vasc Interv Radiol 2003; 14:S375–S384)
6. Henderson DK, Fahey BJ, Willy M, et al. Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures: a prospective evaluation. Ann Intern Med 1990; 113:740–746.
7. Mast ST, Gerberding JL. Factors predicting infectivity following needle-stick exposure to HIV: an in vitro model. Clin Res 1991; 39:58A.
8. Goudsmit J, DeWolf F, Paul DA, et al. Expression of human immunodeficiency virus antigen (HV-Ag) in serum and cerebrospinal fluid during acute and chronic infection. Lancet 1986; 2:177–180.
9. Henderson DK, Fahey BJ, Willy M, et al. Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures: a prospective evaluation. Ann Intern Med 1990; 113:740–746.
10. Marcus R, and the CDC Cooperative Needlestick Surveillance Group. Surveillance of health care workers exposed to blood from patients infected with the human immunodeficiency virus. N Engl J Med 1988; 319:1118–1123.
11. Beekmann SE, Fahey BJ, Gerberding JL, Henderson DK. Risky business: using necessarily imprecise casualty counts to estimate occupational risks for HIV-1 infection. Infect Control Hosp Epidemiol 1990; 11:371–379.
12. Centers for Disease Control. Possible transmission of human immunodeficiency virus to a patient during an invasive dental procedure. MMWR Morb Mortal Wkly Rep. 1990; 39:489-93.

13. Update: transmission of HIV infection during an invasive dental procedure-Florida. JAMA 1991;265:563-568.

14. Blanchard A et al. Molecular evidence for nosocomial transmission of human immunodeficiency virus from a surgeon to one of his patients. J Virol 1998 May 72 4537-4540.

15. Armstrong F, Miner J, Wolfe W: Investigation of a health care worker with symptomatic human immunodeficiency virus: an epidemiologic approach. Mil Med 1988; 152: 414-418.

16. Owens DK, Nease RF Jr. Transmission of human immunodeficiency virus (HIV) infection between physicians and patients: a model-based analysis of risk. In:Kaplan EH, Brandeau ML, eds. Modeling the AIDS epidemic: Planning, Policy, and Prediction. New York: Raven; 1994:153-77.

17. Mishu B. HIV-infected surgeons and dentists: looking back and looking forward.JAMA 1993 Apr 14 269 1843-1844.

18. Schulman KA, McDonald RC, Lynn LA, Frank I, Christakis NA, Schwartz JS. Screening surgeons for HIV infection: assessment of a potential public health program. Infect Control Hosp Epidemiol 1994; 15:147–155.

19. Petersen LR, Satten GA, Dodd R, et al. Duration of time from onset of human immunodeficiency virus type 1 infectiousness to development of detectable antibody. Transfusion 1994; 34:283– 289.

20. Sloand EM, Pitt E, Chiarello RJ, Nemo GJ. HIV testing: state of the art. JAMA 1991; 266:2861–2866.

21. Simonds RJ, Holmberg SD, Hurwitz RL, et al. Transmission of human immunodeficiency virus type 1 from a seronegative organ and tissue donor. N Engl J Med 1992; 326:726–732.

22. Screening Surgeons for HIV Infection: A Cost-effectiveness Analysis Owens DK; Harris RA; Scott PM; Nease RF Annals of Internal Medicine 1995 |Vol 122 (9) pg 641-652.

23. Kelen GD, Green GB, Purcell RH, et al. Hepatitis B and hepatitis C in emergency department patients. N Engl J Med 1992; 326:1399–1404.)

24. EDITORIAL HIV-seropositive surgeons: informed consent and public-health policy James G. Wright, Peter A. Singer, Bulletin of the American College of Surgeons Vol.89, No. 5, May 2004.

25. Horberg et al .Arch Surg 2006;141:1238-1245.

26. Burke EC, Orloff SL, Freise CE, Macho JR, Schecter WP. Wound healing after anorectal surgery in human immunodeficiency virus-infected patients. Arch Surg. 1991 Oct;126(10):1267-70; discussion 1270-1.

27. Buehrer JL, Weber DJ, Meyer AA, Becherer PR, Rutala WA, Wilson B, Smiley ML, White GC 2nd. Wound infection rates after invasive procedures in HIV-1 seropositive versus HIV-1 seronegative hemophiliacs. Ann Surg. 1990 Apr;211(4):492-8.56.

WFSOS - Academy for Quality in Oncology (WFSOS-AquiO) was founded *to approve treatment guidelines and trial proposals, to give opinion in contentious issues arising out of differences in the perception of treatment in a given case and more; WFSOS will organize the board of experts by invitation in both items.*

Management of Neck in Oral Cancer - What dissection and when?

L. Sarangi *

In oral cancer management of neck is closely tied to management of primary site. Death due to failure to control the disease in neck, with the primary tumor controlled, should be an uncommon event if surgery and radiation therapy are used optimally [1]. Modern trends in cancer management lay emphasis on organ preservation. So the standard RND has given way to modified neck dissections where the non lymphatic structures like accessory nerve, internal jugular vein, stemocleidomastoid muscle are not unnecessarily sacrificed. With the advancement of radiation techniques, there has been perceptible shift from surgery to radiation with comparable results. The controversial issues in neck node management in oral cancer center around management of N0 and N1 nodal diseases.

Oral cavity tumors disseminate to lymph nodes in a predictable and sequential fashion. Hence specific regional lymph node groups should be appropriately addressed in treatment planning for a given primary site. The first nodal station for buccal mucosa, gingivo-alveolar complex, retromolar trigone is either level I or II, where as in oral tongue there may be skip metastasis in level III or IV. Classical radical neck dissection devised by George Crile in 1906 involved sacrifice of non lymphatic structures like accessory nerve, internal jugular vein, stemocleidomastoid muscle. This has been modified by Suarez and Bocca where these structures are preserved (MND type I, II, III) with comparable survival but profound increase in the quality of life. Subsequently various types of selective neck dissections like supraomohyoid, lateral, posterolateral, central were added to address NO neck to further improve the quality of life [2]. A comprehensive classification of various types of neck dissections has been enumerated in Table 1.

Management of N0 neck node-

The neck must be evaluated clinically and various imaging studies like USG or CT. Various options available are observation, selective neck dissection (SOHD), comprehensive neck dissection (MND), and elective nodal irradiation. Before deciding the line of treatment one must understand the risk of metastasis in such situations. This has been analyzed by Mendenhall in 1986 [3] as per the table 2.

The disease which has a risk of less than 20% metastasis in neck nodes may be a candidate for observation. However studies have shown that disease free survival (DFS) in T1 and T2 lesions drops from 72% to 49% where neck is not addressed during initial treatment (Kligerman 1994) [4]. The local recurrence rate increases from 8% to 14% between the two groups (resection with SOHD vs. resection alone). Similarly Haddadin in 1999 reported a 5 year DFS of 80.5% in patients where nodal dissection were added as compared to 59.7% in resection of primary alone [5].

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Sentinel node biopsy is still under investigation in oral cancer through preliminary studies have shown encouraging results with 90 to 97% positive correlation and 100% negative predictive value. Technical problems like shine through effect of radioactivity from the primary tumor, being close to the neck and identification of actual sentinel nodes located at different levels limit the application of this procedure. Once these technical problems are solved sentinel node biopsy may instill power and confidence to observation group in T1 oral cancers [6]. So the current recommendations of surgical management of N0 neck are:

1) Neck must be addressed where risk is >20%
2) The modality should be same as that employed for the primary.
3) Where cheek flaps are raised to resect the primary, neck dissection should be performed. Usually selective dissection. SOHD (Level I, II, III) for buccal mucosa, gingivo alveolar complex, RMT. Level IV may be added for oral tongue, floor of mouth primaries.
4) Standard radical neck dissection has no place in N0 status.
5) Accessory nerve sparing is mandatory.
6) Comprehensive neck dissection should be performed if FS of node is positive on selective neck dissection.
7) Observation only, is advisable in very early, superficial lesions in elderly, unfit patients and patients who can comply with the observation protocol.

Management of N1 disease:

The standard teaching is when regional metastasis is clinically palpable, comprehensive clearance of all the regional nodes which are at risk is mandatory. The underlying principle is, once metastasis have occurred to one node, then it is likely that subclinical deposits may be found in other nodes. A modified neck dissection of all the five levels is indicated. However the accessory nerve is almost always preserved. A standard RND must be avoided unless there is direct infiltration of the nerve. The failure rate of RND in N1 neck is 8 to 15% as compared to 0 to 16% in modified neck dissection [7].

Recently few workers have performed selective dissection like SOHD in N1 neck with comparable results. Researchers like Traynor, Gourin, Bradley tried to avoid MND in solitary neck node metastasis by performing SOHD to further improve the quality of life [8,9]. In their series there were no significant differences in both the groups. Traynor in 1996 reported a failure rate of 0%, Gourin in 2004 reported 4-10%, Bradley in 2005 reported a failure rate of 11% as compared to 5% in MND arm. But all have warned to exercise a fair amount of caution in subjecting these potentially curable patients to selective dissection. The staging must be accurate and this procedure is applicable where there is minimal neck disease. So, as on date, the whole issue of SND in N1 neck is a matter of debate and should be undertaken under clinically controlled situation. Current recommendations in N1 neck are -

- Neck must be addressed. The modality should be same as that employed for the primary.
- Where cheek flaps are raised to resect the primary, a modified neck dissection of all 5 levels should be performed. Accessory nerve must be preserved unless directly infiltrated by the disease.

- Modified neck dissection has least recurrence.
- Selective dissection needs further confirmation & may be suitable for single, positive node, <3cm, without extracapsular spread.

Indication of classical radical neck dissection -

The underlying principle is, where the non lymphatic structure can be preserved without compromising the nodal dissection then the classical RND is to be avoided. The most important non lymphatic structure is the accessory nerve. The indications of RND are [10] -

- N3 disease especially in upper neck
- Bulky metastasis near XI nerve or directly infiltrating the nerve
- Clinically palpable multiple nodes (N2), more so near XI nerve
- Post RT recurrence or post surgery recurrence
- Salvage surgery after CT+RT

Tumors located near the midline such as lip, middle third of mandible where bilateral neck dissection is required, particular attention must be paid to preserve at least one internal jugular vein. So dissection may be started on the side having less nodal burden. SOHD may be done in N0 status and MND where nodes are clinically palpable.

Management of neck is an integral part in the treatment of head & neck cancer. From the above discussion one must not carry the impression that surgery is the only option available. Various combinations of surgery, radiation and chemotherapy have achieved better local control over single modality. Though cure is supreme, the issue of surgery versus radiation lies on the quality of life each modality offers. Each patient needs to be individualized keeping in view of the various factors discussed.

Table 1: Classification of neck dissection

Classification	Level of LN removal
Radical neck	I, II, III, IV, V +XI N, JV, SCM
Modified neck	
Type I	I, II, III, IV, V, XI preserved
Type II	I, II, III, IV, V, XI, N & JV preserved
Type III	I, II, III, IV, V, XI, JV, SCM preserved
Selective neck	
Supraomohyoid	I, II, III
Lateral type	II, III, IV
Posterolateral	II, III, IV, V
Central	VI, VII
Extended neck dissection	

Table 2: Risk group of neck node metastasis (Cancer-Principle &Practice of Oncology-De Vita7th edition 2005)

Group Risk	(%)	T	Site
• I Low risk	<20	T1	fl. of mouth, oral tongue, RMT, gingiva, hard palate, BM
• II Intermediate risk	20-30	T1	Soft palate, pharyngeal wall, supraglottic larynx, tonsil
		T2	Fl of mouth, oral tongue, RMT, gingiva, hard palate, BM
• III High risk	>30	T1-4	Nasopharynx, pyriform sinus, base tongue
		T2-4	Soft palate, pharyngeal wall, supraglottic larynx, tonsil
		T3-4	Fl of mouth, oral tongue, RMT, gingiva, hard palate, BM

References

1. Cancer - Principle & Practice of Oncology - De Vita 7th edition 2005
2. Shaha AR. Neck dissection : an operation in evolution. World J Surg Oncol 2005, 3:22 doi:10.1186/1477-7819-3-22
3. Mendenhall WM, Million RR. Elective neck irradiation for squamous cell carcinoma of the head and neck: analysis of time-dose factors and causes of failure. Int J Radiat Oncol Biol Phys 1986; 12:741-746
4. Kligerman J, Lima RA, Soares JR, Prado L, Dias FL, Freitas EQ, Olivatto LO. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of the oral cavity. Am J Surg 1994;168:391-94
5. Haddain KJ. Soutar D. Oliver R, et al. Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. Head neck 1999;21:517-25
6. Wemer J A. Dunne AA, Ramaswamy A. et al. The sentinel node concept in head and neck cancer: solution for the controversies in the N0 neck?; Head neck 2004, 26: 603-611
7. Harish K. Neck dissections: Radical to conservative. World J Surg Oncol 2005, 3:21 doi; 10.1186/1477-7819-3-21
8. Traynor SJ. Cohen JI. Grey J. et al. Selective neck dissection and the management of the node positive neck. Am J Surg 1996; 172;654-657
9. Gourin CG. Is selective neck dissection adequate treatment for node positive disease? Arch Otolarynngol Head Neck Surg 2004, 130: 1431-1434.
10. Shaha AR. Radical neck dissection. Operative Techniques in General Surgery 2004, 6:72-82

Biological Response Modifiers in Cancer

Manoj Pandey *

Many different biological response modifiers have been evaluated in pre-clinical and clinical trials. Contact allergens, bacteria and bacterial products, some cytotoxic drugs like 6 mercaptopurine (6-MP), cyclophosphamide, doxyrubicine and cisplatin and cytokines etc. Some of them have been found useful while others not. This chapter will focus on Interferon, Interleukin and other cytokines and the studies carried out using them as immunomodulator.

Interferons

The Interferons (IFN) are a group of protein, first identified by Isaacs and Lindeman in 1957. They are so named due to their ability to mediate the phenomenon of viral interference. There are two broad types including at least 20 classes of IFN. Type I IFN includes Alpha (α), Beta (β), tau (τ) and Omega (ω) while type II includes IFN gamma (γ). These are closely related and are derived from genes located on chromosome 9 except IFN γ that is expressed from chromosome 12. IFN are expressed by exposure of cell to virus or double stranded RNA.

IFN are now licensed worldwide as therapeutic agents against cancer, as antiviral and against as agents multiple sclerosis. The cellular action follows binding to relatively small number (<2000/cell) of high affinity receptors. Positive and negative regulatory proteins controlling its expression are also identified. Cellular protein induced by IFN underlie plethora of biological actions like virus inhibition, immunomodulation, slowing of cell proliferation, oncogene suppression, angiogenesis inhibition, and alterations in differentiation. Nonetheless, which cellular protein result in various biological activities including tumor suppression still remains undefined. IFN result in regression or control of more than a dozen cancers. Either single agent, or part of combination, IFN are now establishing their role in cancer therapeutics. Like many other chemotherapeutic agents IFN are more active in hematological malignancies than solid tumors.

Both IFN α and β are 166 amino acid in length with an additional 20 amino acid secretary peptide present on the amino terminal end. They show about 45% homology of nucleotides and 30% homology of amino acids gene for both are situated at chromosome 9. IFN γ on the other hand is 143 amino acid in length and the gene is located on chromosome 12. This too contains a 20 amino acid secretary peptide at amino end.

Induction

Conceptually, viruses remain the prototype inducers of IFN, in almost all body cells, except IFN γ. IFN γ was first identified after exposure of lymphocytes to mitogens or sensitized lymphocytes to specific antigens. Interleukin-2 (IL-2), tumor necrosis factor (TNF) and IL-12 protein

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induced by IFNα and β are also potent inducers of IFN γ. Production of IFN is part of host defense response to pathogens and neoplasia.

Molecular mechanisms of cellular production of IFN are partly understood. The codon sequence for production of IFN-β consists of two separable positive domains and an overlapping negative sequence. In an uninduced cell this expression is suppressed by a protein repressor, which blocks one of the two positive IFN regulatory elements. Virus exposure results in displacement of this repressor leading to IFN expression. Low molecular weight organic inducers of IFN include tilorone halopyrimidinones, acridines, substituted quinolines and flavone acetic acid. In addition to production of IFN these molecules too are Immunomodulators.

Receptors

The cellular response to IFN requires interaction of a small number of molecules with high affinity, species-specific numeric cell surface receptors. These receptors are found on most cells. IFN-α and β share and compete for the same receptor, however, IFN β binds with higher affinity. Binding has also been observed with nuclear membrane. The gene for receptor is on chromosome 21.

Signal transduction

After receptor binding to specific tyrosine kinase, tyk2 together with one or more additional tyrosine kinase, JAK-1 and JAK-2, is phosphorylated. These activated tyrosine kinase activate the signal transducting peptides. This induces the formation of a complex, ISGF (Interferon stimulated Growth factor), that consist of 3 protein subunits (STAT- Signed transducers and activators of transcription) 1 α, 1β and STAT-2. The proteins 1 α and 1 β are alternatively spliced products of the same gene. One phosphorylated the ISGF - 3α complex is translated to nucleus and forms a DNA binding complex specific for the IFN stimulated response element (ISRE) resulting in activation IFN specific gene. The STAT 1α component of IFN signal transduction pathway is a component in the activation of other cytokine genes, epidermal growth factors (EGF) and IL-6.

Antitumour action

IFN are cellular modulators, the antitumor effect is produced by either direct effect on functional capacity or antigenic composition of tumor cell populations. They regulate gene expression, modulate expression of proteins on the cell surface and induce synthesis of new enzymes. Other actions are detail on table 1.

Biological Response Modulation

IFN augment the effectiveness of all immune effecter cell types that have potential to kill tumor target cells, including cytotoxic T-cells, non-major histocompatibility complex (MHC) restricted cytotoxic cells and monocytes.

IFN enhances cell surface expression of MHC antigens, tumor associated antigens (TAA) and Fc receptors. All IFN's enhances MHC class I expression while IFN-γ also expresses MHC-II expression on tumor cells and monocytes. Increased expression of MHC enhance monocyte / macrophage antigen presenting function. The genes modulated by IFN are detailed in Table 2.

Table 1: Biological effects of interferons

Immunomodulation	**Cell modulation**
Cytotoxicity	Oncogene Suppression
T-cell stimulation	Slow mitotic cycles
NK / LAK cell stimulation	Differentiation
Monocytes stimulation	Trophoblastic implantations
Antibody dependent killing	**Microbial inhibition**
Vascular	RNA virus
Angiogenesis inhibition	DNA virus
Lipoprotein reduction	Intracellular pathogens.
Protein induction	
Adhesion protein	
Enzyme induction	
Cytokines induction	

IFN besides being a modulator of genetic expression also have antiproliferative and differentiation effect. They retard growth and proliferation of tumour cells and normal cells by prolonging cell cycle. Diploid cells are less sensitive to the action of IFN.

Clinical trials

IFN-α as a single agent has been found to have caused regression in various malignancies like leukaemia lymphoma, melanoma, carcinoids, gliomas, Kaposi's sarcoma, ovarian cancer and urinary bladder cancer. The drug is approved by US FDA United States – Federal Drug Administrator as antitumor agent.

In trials on haematological malignancies, especially hairy cell leukaemia resulted in its approval by FDA. More than 85% of the patients had either partial or complete response with gradual decrease in tumor cell infiltration of bone marrow and normalisation of peripheral haematological parameters. In CML a sustained therapeutic response had been observed in over 75% patients, with continuing treatment 25% patients will develop cytogenetic complete response in approximate 6 years and 90% in about 10 years. It has been demonstrated that IFN is equivalent or superior to Busulfan and hydrox urea.

In some solid tumors IFN-α has resulted in response rates in metastatic disease equivalent to best chemotherapeutic approach. Response in melanoma has ranged from 2 to 29%. Responses have been correlated with better performance status and no prior chemotherapy, low volume disease and lung metastasis.

Table 2: Modulation of gene expression by Interferons

Tumour associated antigens
- TAB 72
- CEA

Adhesion proteins
- ICAM – 1
- P16
- P56

Cell surface protein
- Antigen processing
- Ring 4
- Ring 12
- HLA complex
  - Class I
  - Class II
  - β_2 microglobulin
  - Invariant chain

Depressed functional activities
- Oncocgenes
- c-myc, CHa-ras, c-fos, c-mos
- P-450 microsomal enzymes

Enzymes and other proteins
- 2-5 A synthetase
- Protein kinase R
- Indoleamine dioxygenease
- Guanylate – binding proteins
- Mx protein
- GTP cyclohydrolase
- Metallothionein II
- IL – 16
- P 56

Transcriptional factors
- I R F – 1
- I R F – 2
- I C S B P

Similarly metastatic renal carcinoma shows a response rate of 4-26% compared to 10% with chemotherapy. High dose regimens have better response rates. The clinical use of IFN as antitumor agent is detailed in Table 3.

Table 3: Clinical use of IFN as antitumor agents

Lymphoproliferative disease
- Hairy cell leukemia
- CML

Solid tumors
- Melanoma
- Renal cell carcinoma
- Ovarian tumor
- Colo-rectal carcinoma

Combinations

To achieve better response combinations with other cytokines and chemotherapy has been tried. The immunomodulatory effects are better if tumor cell mass is reduced. IFN is being used as an adjuvant to surgery in renal cell carcinoma and melanoma. 2-year disease free survival (DFS) of 46% was observed with high doses of IFN-α. An improvement in Quality of life was also observed. Side effects are detailed in table 4.

Table 4: Side effect of Interferons

Acute	Chronic
Fever	Fatigue
Malaise	Anorexia
Chills	Weight loss
Myelgia	Mild neutropenia
Nausea	Elevation of transaminase
Headache	Diarrhea
	Depression
	Mental slowing
	Confusion
	Thrombocytopaenia
	Nausea vomiting

Cytokines

The term Interleukin has been used to designate any soluble protein or glycoprotein product of leukocyte that regulates the response of other leukocytes. It is difficult to differentiate interleukins from the growth factors as most interleukins are growth factors and vise versa. They produce their effect through endocrine, autocrine and paracrine interactions. The cascade of Interleukin that are generated by both pathogen exposure and antigen interaction are primarily secreted and act locally. Function of individual Interleukin is mediated by interaction with specific receptor expressed differentially on different cell type. The paracrine effect includes the initiation, amplification, maintenance and termination of various phases of immune response.

Interleukin – 2

Interleukin (IL) – 2 was first described in 1976 as "T-cell growth factor" for its ability to support growth of T-Lymphocytes. IL-2 with IFN-γ represents the major cytokine products of Th 1 helper cells induced by antigen and counter regulated by cytokines IL-4 and IL-10. IL-2 is a 133 amino acid glycoprotein of 15 kd molecular weight and contains an interchain disulfide bond.

Through its interaction with T-cell, B-cell, macrophages and natural Killer cells, IL-2 plays an important role in maturation and development of T-cells. IL-2 receptor complex is composed of three subunits, an α chain, a β chain and a γ chain. γ Chain is common component of numerous other cytokine

receptors. α Chain is responsible for rapid association with IL-2, the β-γ complex is responsible for long dissociation time. This results in a highly specific trimeric receptor of very high affinity.

Following interaction of this trimeric receptor with IL-2 the internalisation occurs and cell cycle progression form G1 to S phase is induced. A second response that occurs through IL-2, β-γ interaction allows differentiation of several subclass of lymphocytes into "lymphokine- activated Killer" (LAK) cells. This response occurs in patients who receive IL-2. Recently IL-2 induced secondary cytokine elaboration and monocyte tumouricidal activity has also been defined.

In short IL-2 response on immune cell include proliferation of antigen-stimulated T-cells, induction of cytotoxicity in MHC-restricted antigen-specific T-lymphocytes, non MHC-restricted LAK activity and induction of other cytokines.

Rationale for use as anticancer drug

Numerous studies have demonstrated the therapeutic benefit of IL-2 activated effecter cells. The models tested suggest that the degree of intrinsic immunogenicity of the tumor, host's immune status and the tumor burden all may effect IL-2 response. It is also suggested that beside activated cells, increased expression of other cytokines may also help in enhancing tumor response.

IL-2 in melanoma

Although still investigational, IL-2 has shown clear antitumor activity against melanoma cells. Large phase II trials using high dose regimens have reported 5(4%) complete, 22(16%) partial response among 134 patients treated. Despite a clear activity the response is short lived and hence, this has lead to exploration of use of IL-2 in combination with other chemotherapeutic agents. A lower dose regimen has been used with cyclophosphamide has been investigated however; this too produced a similar response.

On the other hand the high dose regimens using chemotherapeutic agents or IFNα has been reported to produce response ranging from 45 to 55% with complete response rate as high as 20%. The phase III trials are still underway and results are awaited. Till then despite a clear activity, use of IL-2 in melanoma is investigational.

IL-2 in Renal cell carcinoma (RCC)

IL-2 has been approved by US FDA (food and Drug Administration) and by regulatory authorities in Canada and Europe for treatment of RCC in patients with good performance status and metastatic disease. 255 patients have been treated in 7 Clinical trials using a regimen developed by National Cancer Institute (NCI). Here recombinant IL-2 was administered in dose of 600,000 or 720,000 IU/kg by 15 min bolus infusion every 8 hours to tolerance every 1 to 5 days and repeated on day 15-19. An overall response rate of 14% was observed with 4% patients achieving complete regression. Even though the response rate is moderate the prolongation of median duration of response (20 month) and apparent permanence of all complete response in patients with advanced progressive RCC shows significant clinical benefit. Response occurred at all sites, however, maximum response was observed in lung or lymph node metastatic disease.

In the 56 patients who received IL-2 after excision of the bulky primary disease the response was 27%, a number of patients went in for long progression free response. A number of studies have also combined IL-2 with other cytotoxic drugs. Most commonly studied is a combination with IFN α the results of phase II trial suggest dramatic increase in response rates with combination compared with IL-2 alone. However, it is not recommended to use these drugs outside the settings of a clinical trial.

Other cancer

Response to IL-2 has been reported in isolated cases with ovarian cancer, non-small cell lung cancer, head and neck cancer, colon cancer, breast cancer and bladder cancer. However, there had been no definite attempt and the data from phase II trials is limited. In this light best strategy perhaps would be to integrate IL-2 with conventional cytotoxic regimens for each cancer. However, without the evidence of randomized clinical trials it's hard to say.

There have been number of reports of the use of IL-2 with LAK cells in patients with malignant Glioma. This has involved resection of recurrent tumor and direct instillation of IL-2 at the time of surgery. Although Clinical response is reported there is no evidence of benefit from such treatment strategy.

Another area where IL-2 looks promising in patients undergoing bone marrow transplant for hematological malignancies. Several studies have reported an objective response in this settings. It is suggested that following BMT the IL-2 may amplify the graft versus leukemia effect. Phase III investigations are underway and their results are awaited.

Adoptive cellular immunotherapy and IL-2

Pre-clinical studies suggest that IL-2 together with *ex-vivo* activated and expended antitumor lymphocytes shows enhanced antitumor activity. The first response was noted in patients receiving IL-2 with LAK cells prepared through *in vitro* activation of autologus peripheral blood lymphocytes that were harvested by lymphopheresis. The results of Randomized controlled trial showed no definite benefit of the combination of IL-2 with LAK cells over IL-2 alone.

In another study on 136 patients of melanoma treated with high dose bolus IL-2 with adoptive transfer of LAK cells, in three separate trials, showed a complete response in 8(6%) and 14 partial (10%) response however, this response too was not better then IL-2 alone.

In another study the IL-2 was used in combination with tumor infiltrating lymphocytes (TIL) produced by placing digested, fresh tumor biopsies into an *in vitro* culture with IL-2. Over 3-4 weeks expanded population of antigen-specific, MHC restricted T cells can be generated for administration together with IL-2. Response rate in this study ranged from 30-40% however, no comparative data is available. It appears from above studies that IL-2 may prove useful as an vaccine adjuvant or in *in vitro* culture of antigen specific T-cell harvesting.

Interleukin-1

IL-1 is produced by activated monocytes and macrophages. It is a cytokine with diverse immunologic, physiologic and hematopoietic effects. The two forms of IL-I α and β are two diverse gene products with about 26% homology; however, they bind to the same receptor and hence, have similar biologic activities.

IL-1 is primarily involved in inflammation having direct effect on endothelial cells, B-cell and T-cells. It activates a cascade of biological events through activation of other cytokines. IL-1 has direct antitumor activity both *in vivo* and *in vitro*. These effects are acute hemorrhagic necrosis associated with microvascular injury, decreased tumor blood flow and tumor cell kill.

The hematopoietic effects of IL-I are induction of bone marrow stromal cells to produce IL-6 and colony stimulating factors. With these factors it synergies to produce differentiation and proliferation of hematopoietic progenitor cells. Hence, it accelerates recovery of both neutrophils and platelets after chemotherapy.

IL-1 has been studied for its myelorestorative functions. Platelet count increase 1 to 2 week after administration. Phase I trials of IL-I β and α also showed increase bone marrow megakaryocytes and increased serum levels of IL-6. It also has been shown to reduce the duration of carboplatin-induced thrombocytopenia.

IL-4

IL-4 is produced by a subset of activated T-helper cells characterized for its ability to stimulate the proliferation of activated B-cells. Its other biologic activities include expression of MHC class II on B-cells, regulation of IgE and IgG and specific receptor of IgE. It also stimulates as well as inhibits various subclass of T cell. Its other functions include activation of connective tissue type mast cells, inhibition of lymphocyte response to IL-2 while promoting antigen specific interactions.

IL-4 is expressed in single form with a molecular weight of 12-15 kd. The biological activity is produced through a single type of receptor found on both hematopoietic and non-hematopoietic lineage cells. IL-4 is a pleiotropic B and T-cell growth and differentiation factor. Unlike IL-2 but similar to TNF, it is species specific. IL-4 can augment antigen specific cytolytic T-cells and induce differentiation of B-lymphocytes.

Phase I and II studies using IL-4 injections through subcutaneous and IV route in patients with renal cell carcinoma and melanoma resulted in a single response. The side effect included diarrhea, gastric ulceration, headache, nasal congestion, fluid retention, arthralgia fatigue, anorexia, nausea and vomiting.

Interleukin – 6

IL-6, IL-3 and IL-11 are important regulatory proteins for hematopoiesis and their relevance to clinical oncology relates to their use as growth factor for chemotherapy associated myelosupression. IL-6, in addition to being a thrombopoietin has other functions with variety of biological effects.

IL-6 is secreted by T-cells, monocytes, macrophages, fibroblasts, keratinocytes and endothelial cells. It is also characterize as B-cell growth factor, T-cell differentiation factor and plasmocytoma growth factor.

Biological effects of IL-6 include synthesis of acute phase reactants in liver, hypothalamic pituitary axis, bone resorption and stimulation both cellular and immune system. Phase I trials of IL-6 in patients with advanced cancer has been conducted and symptoms including fever, chills, and fatigue has been noted. Significant increase in C-reactive protein, fibrinogen platelet counts and soluble lymphocyte IL-2 receptor levels were observed at doses greater than 3 mg /kg. This was accompanied by fall in serum albumin and hemoglobin levels.

Interleukin-7

IL-7 was first described as a bone marrow stromal cell derived growth factor involved in early B-Lymphocyte development. It has been produced by fetal liver, thymus, keratinocytes and number of lymphoid tumor cell lines. In addition to its effect on B-cells it is a thymocyte growth factor, pro T-cell differentiation factor and activation factor for NK cells, cytotoxic T-lymphocytes, monocytes and macrophages. Both myeloid and lymphoid series are accelerated after IL-7 administration. Pre-clinical studies suggest its use either as antitumor agent or as an adjuvant with cytoreductive surgery or a growth factor. This has however, not been used in clinical settings yet.

Interleukin-10

IL-10 is an tumor regulatory cytokine with principal function appears to involve the suppression of cytokine synthesis in the Th 1 subset of $CD4^+$ T helper cells. It is also called by cytokine synthesis inhibiting factor. It is produced by Th 1 and Th 2 T-cells, monocytes, B-lymphocytes and kerationcytes. The suppressive effect of IL-10 on cell-mediated immunity suggest a possible role in transplant rejection or treatment of graft versus host reaction. There are no clinical trials of this cytokine on cancer available yet, however, it is also a promising factor in treatment.

Interleukin-12

IL-12 was originally described as natural killer stimulatory factor and cytotoxic lymphocyte maturation factor. IL-12 is a 70kd product of activated monocytes. This is composed of 2 unrelated glycoproteins linked covalently by a disulphide bond. Because of this IL-12 has a complex characteristics of cytokine and cytokine receptor. A receptor for IL-12 has been described on activated T-cells, NK cells and bone marrow progenitors. IL-12 is a powerful inducer of IFN-γ from both T and NK cells, and other cytokines like TNF and granulocyte macrophage colony stimulating factors. It enhances the NK cell activity, generate LAK cell activity and facilitate both proliferation and cytolytic activity of $CD8^+$ T lymphocytes. It exhibits a dose dependent increase in NK cell number and activity and enhances $CD8^+$ MHC- restricted T-lymphocyte activity.

Another important activity is promotion of differentiation of progenitor T-cells into Th 1 cells, which produces IL-12 and IFN-γ. In short key biological function is to boost innate immunity through stimulation of IFN production and stimulation of NK cell activity.

The IL-12 has been studied in pre-clinical study in various tumor models like melanoma, reticular cell sarcoma, renal cell carcinoma, and has been found to have potent antitumor activity. Although this activity was dose dependent and mediated partly though $CD8^+$ T-cell mechanism. Its antimetastasis effect was mediated by suppression of angiogenesis. The toxicities include mucositis and transient hepatotoxicity.

IL-12 may have an apparent clinical application in differentiation of Th 1 helper cells and Induction of IFN-γ phase I and II clinical trials in renal cell carcinoma using IL-12 with other cancer vaccines are underway and their results awaited.

Interleukin-13

IL-13, like IL 4 and IL-10 is produced by activated-T cells that shares the capacity to inhibit cytokine synthesis by activated monocytes and modulated B-cell responses thought its effects on activation, proliferation and differentiation of B-cells. There are no clinical studies involving IL-13.

Interleukin-15

IL-15 is a recently defined cytokine that binds to β and γ component of IL-2 receptor. IL-15 is expressed by wide variety of tissues including activated monocytes, macrophages and skeletal muscles, kidney and placenta. IL-15 also potentates NK-cell cytokine production and cytokine activity. It suggests a possible role of IL-15 in normal host immunity. There are no clinical trials for this cytokine.

Tumor Necrosis factor-α

TNF-α is a 17 kd non-glycosylated polypeptide, with secreted form being monotrimer. Its actions are brought about by binding of TNF to 55 or 75 kd molecular weight receptors present on cell membrane. The important activities are cytolytic activity, antiviral activity, IL-6 induction etc.

There is another related cytokine known as TNF-β or '*lymphotoxin'*. This is produced by distinct gene closely linked to MHC complex on short arm of chromosome 6. TNF α is produced by activated T and NK cells. The production is stimulated by a number of signals including lipopolysacchrides, anti CD-3 monoclonal antibody and cytokines including IL-2, IL-4 and Il-6.

TNF has a direct, *in vitro*, anti tumor cytotoxicity on almost 50% of tumor cell lines, and *in vivo* activity against murine tumors and human tumor xenograft. The tumors undergo hemorrhagic necrosis after TNF injection. TNF acts on endothelial cells directly activating procoagulant activity and leading to fibrin formation, leukocyte infiltration, defective perfusion, and hemorrhagic necrosis. Response is best in immunogenic tumor. Enhanced cell killing is noted when TNF combined with chemotherapeutic agents in injected. The apparent mechanism involves TNF mediated increased DNA stand breakage.

Clinical trials

The maximum tolerated dose of bolus TNF is in the range of 200-400mg/m^2. Rigors, tachycardia and hypertension develops shortly after administration of TNF α, followed a few hours later with fever and hypotension, which responds to IV fluids and vassopressors. Other side effects include thrombocytopenia, leucopoenia and hepatotoxicity.

Minimal antitumor activity is observed in phase I and II trials including common solid tumor. Other trials of TNF -α were carried out in combination with chemotherapeutic agents and other cytokines showed minimal tumor response. There results have been disappointing considering minimal benefit and life threatening toxicity. Further studies are on and results awaited.

Conclusions

The pre-clinical and clinical studies in past few decades have contributed greatly to our knowledge of biological response modifiers only two families of these compounds namely interferons and cytokines are described here. Beside these there are plenty of other drugs, growth factors etc, which can enhance and modulate immunity. Due to limitation on space those are not dealt with in this chapter. However it is very clear form the studies that biological response modifiers are very effective modulators and will find increasing clinical application as adjuvant to gene therapy in future.

Web site of Indian Association of Surgical Oncology: *http://www.iasoindia.in/*

This website is now functioning and is maintained by the IASO. The web site is maintained with a generous educational grant from Pfizer India. The site has not been updated for last one year. Contributions and suggestions are welcome for regular updating of the website.

Dr KS Panda Dr Gopinath Quiz Award

During NATCON meeting winner will be awarded Rs. 700 and runners up to Rs. 300. Dr K Panda & Dr Gopinath donated Rs. 10,000 each towards the seed money for the Quiz award.

Eligibility:

All the delegates of NATCON. In case of prize being won by a person who is not a member, the winner will get an additional Rs. 300 from the IASO towards his life membership dues, and cash award will be adjusted towards the life membership of IASO.

ANNUAL CONFERENCE OF

INDIAN ASSOCIATION OF SURGICAL ONCOLOGY (IASO)

in association with

BRITISH ASSOCIATION OF SURGICAL ONCOLOGY (BASO)

NATCON 2008

19 – 21 September 2008

From the desk of the Organising Secretary

A WARM WELCOME TO HYDERABAD

Dear Colleague,

It gives me great pleasure to inform you that I have been successful in my bid to host NATCON 2008 in HYDERABAD at the General Body Meeting of IASO in September 2006. I wrote to Mr Greame Poston, President, British Association of Surgical Oncology (BASO) in October 2006 with a proposal to host NATCON 2008 in association with BASO. I am delighted to inform you that the Executive Committee of British Association of Surgical Oncology has unanimously agreed to my proposal to hold this Joint Meeting in 2008. This proposal has since been endorsed by the Executive Committee of IASO at its Meeting held in December 2006 at ASICON 2006.

The Conference would indeed be a landmark event in the calendar of IASO in that this would be the very FIRST National Conference of IASO to be held in the state of Andhra Pradesh since IASO was formed in 1977 and the Second Official Joint meeting of IASO with BASO to be held in India.

In view of the fact that Hyderabad is a 'hot destination' for International Conferences with popular venues booked up well in advance and also because this would be an International Congress, plans are well underway to host this mega event. Quotations have been requested from various Conference Venues & negotiations are underway to obtain the best deal for delegates. A final decision on the Conference Venue would be taken in due course before the end of the year.

This letter is merely to inform you of this International Conference well in advance. Furthermore, I shall be most grateful if you would kindly bring this Event to the notice of your Colleagues, Juniors & postgraduates. I very much look foreword to the participation from many of you in what promises to be an intellectual extravaganza coupled with an 'away from it all' Fellowship & Relaxation in the historic and most beautiful city of Hyderabad.

With warm personal regards.

Yours sincerely,

Dr. P. Raghu Ram
MS, FRCS (Edin), FRCS (Glasg), FRCS (Irel)
Organising secretary, NATCON IASO 2008
Overseas Co-ordinator & Member, Executive Committee
Indian Association of Surgical Oncology

AGENDA FOR ANNUAL GENERAL BODY MEETING AT LUDHIANA ON 22 SEPTEMBER 2007

- Annual report
- Minutes of the last GBM at Varanasi
- Audited account 2006
- Audited account NATCON IASO 2006
- IASO Sectional programme ASICON 2007
- Proposed budget and programme for 2008
- Oration, symposia etc 2008
- Confirmation of venue for NATCON 2008
- Venue for NATCON 2009
- Amendments
- IASO news letter
- Election of office bearers
- Any other matter with permission of chair
- Vote of thanks to Organisers of NATCON IASO-2007
- Vote of thanks

The WFSOS-Cairo Statement 2007: *WFSOS agrees to deposit the position of the surgeon/surgical oncologist as case manager in the multidisciplinary team for diagnosis and treatment of cancer. WFSOS supports all activities to ensure education and quality management in Oncology (QM) on a high level.*

The WFSOS-Trials: *WFSOS agrees to organize an internet based registration in special topics. As first proposal we will organize and collect older breast cancer patients 70 years over. The registration will be possible in due time over www.WFSOS.com. The form of registration will be standardized by QM-guidelines. If you have a proposal for a WFSOS registered trial, don`t hesitate to contact us.*

IASO BYE LAWS

IASO has been registered under society of registration at Varanasi (UP) in the year 2004-05 bearing registration number 627. The income tax PAN number is AAA14187N issued on 27th August 2004.

The bye-laws of the IASO have been adopted at one of the general body meetings held in December 1997, Mumbai and amended time to time.

These bye-laws supercede all previous bye-laws of the IASO.

1. In the byes-laws, unless there is anything repugnant in the subject or context.

a) **IASO** means "Indian Association of Surgical Oncology".-this will remain a section of the ASI

b) **ASI** means "Association of Surgeons of India."

c) **Memorandum and Rules and Regulations** mean Memorandum of the Association and Rules and Regulations of the ASI which came in to force in 1985.

2. **Name:** The name of the association is Indian Association of Surgical Oncology: -A section of ASI.

3. **Address:** The office of IASO is the place from where the secretary functions.

4. **Objectives:** IASO is formed as per guidelines set in schedule II of memorandum of ASI and was approved as a section in 1997. The objectives of IASO are same as stated in schedule III of memorandum of ASI. Further to that, IASO will encourage and advance the study and practice of the science and art of surgical oncology and allied organizations concerned with cancer problems.

5. **Membership:**

a) *Life Membership:* A life member should be a full member (Annual/life) of the parent body The Association of Surgeons of India. All persons, being surgeons with sufficient interest in cancer surgery/practicing cancer surgeons /completed an acceptable training in cancer surgery/pursuing research in cancer surgery or related subjects, are eligible for becoming life member.

b) *Associate Membership:* Those who are under training in cancer surgery or those who are interested in surgery but belong to other specialties, such as Radiology, Pathology, Biochemistry and who may not be in the member of the ASI.

Subscription of membership will be decided from time to time by the general body of the IASO. Generally all members will be inducted as life members.

6. **Termination of Membership:**

a) If a member of IASO ceases to be a member of ASI, he/she will cease to be member of IASO.

b) If a member fails to pay subscription by due date or resigns, he/ she will cease to be a member of IASO.

7. **Year:** The year of IASO will be same as of ASI-lst January to 31st December.

8. **Management:**

   a) IASO will be managed by an Executive Committee consisting of following office bearers, members and ex- officio members:

      - President
      - President elect
      - Vice President
      - Secretary
      - Editorial Secretary
      - Associate Editor

      Members: usually 8 members will constitute the executive committee. The executive committee will have a representative from each from North, East, West and South zones (NEWS). (Resolution 10, GBM 23/9/2006, Varanasi).

   b) All past Presidents will be invitees to Executive committee meetings.

   c) Organizing Secretaries of both immediate past and future NATCON will be co-opted members of Executive Committee of IASO for the year.

   d) Only those members and life members who have put in minimum 5 years of membership are eligible for election to Executive Committee.

   e) Save and except President, President elect and Vice President the tenure of all office bearers and members will be for two years. (Resolution 7 GBM, 23/9/2006, Varanasi)

   f) The President shall hold office for one year. President elect will be the President and Vice President will be President Elect after expiry of his term unless he/ she has resigned, indisposed or disqualified otherwise. (Resolution 7 GBM, 23/9/2006, Varanasi)

9. **Election**

   a) Election of the vacant posts as notified by the Secretary of IASO will be conducted in the Annual General Body Meeting of IASO to be held during the annual conference of IASO in NATCON every year.

   b) Every eligible member shall be proposed and seconded by two full members of IASO in the meeting after the proposed member has consented for the election.

   c) If there is no contest, the President shall declare the member elected for the post. Otherwise the election shall be by show of hands or secret ballot as decided by the President.

   d) A full member of IASO who has completed 10 years as full member and has served at least one term as executive member is eligible to contest for the post of Vice-President. (Resolution 11, GBM 23/09/06 Varanasi)

   e) If a poll is demanded by at least 25% of the members of IASO present in the meeting and President are satisfied that such demand has been carried out by majority of members present in the meeting the vote shall be taken by ballot.

10. **Power of Executive committee** shall be same as power of governing council of ASI

11. The function and responsibility of different office bearers of IASO will be same as that of ASI. The secretary will present and maintain the audited accounts each year at the annual conference.

12. **Meeting and Conference:**
    a) IASO shall hold Annual General Body Meeting every year during the Annual Conference of NACTON and transact the business stated in bye -law 15(b). Other meetings, be it of Scientific, Social/Executive Committee/General Body in nature, may be held as per the requirements of IASO.
    b) IASO shall endeavor to organize annual conference at least once every year and appoint an organizing secretary for the conference in its annual General Body Meeting. The dates of the conference will be fourth weekend of September.

13. **Annual Report:** An Annual report stating the activities of the year shall be prepared by the secretary for Annual General Body Meeting, a copy of which is to be sent to headquarters of ASI.

14. **Accounts of the year:** Accounts of the year of IASO shall be prepared by secretary and audited by an auditor appointed by general body within six months of the closing of the year. This should be placed in the general Body Meeting and after adoption, a copy sent to Headquarters of ASI.

15. **Annual General Body Meeting:**
    a) Annual General Body Meeting (AGM) shall be held once every year as stated in Bye -Laws.
    b) The following business will be transacted in the AGM.
        - Annual report
        - Audited accounts of the previous year
        - Program and budget of the next year
        - Recipients of various orations for the next year
        - The venue of annual conference and appointment of Organizing Secretary
        - Election of the office bearers and members of the executive committee

    Any other business with the permission of the President. Topics of the symposia and their conveners, theme of CME, workshops and program outline should be discussed in the General Body Meeting.

16. **Journal:** IASO shall publish its own Newsletter and shall elect Editorial secretary for the same. He will be sectional editor of the Indian Journal Surgery.

17. **Income:** Income of the IASO shall be derived from:
    a) Admission fees and subscription from members, life members and associate members.
    b) Excess of income over expenditure in annual conference and zonal CME's.
    c) Donations.

18. **Investment:** IASO shall have account with nationalized or reputed bank to be operated by persons authorized by General Body Meeting. The surplus fund after meeting statutory annual expenditure shall be invested in fixed deposits of such banks and approved securities or any other manner to be decided in the General Body Meeting.

19. **Utilization of Funds:** IASO shall have account with nationalized or reputed bank and shall invest funds not required for its regular day to day activities in fixed deposits of such banks or approved securities as had been decided by the General Body Meeting. The accounts will be operated as per provisions of memorandum of ASI. The proceeds of income from various deposits and investments shall be strictly spent for specific purpose for which such fund/funds are created.

20. **Representation:** IASO shall be represented as per Memorandum of ASI.

21. **Amendment of Bye-Laws:** Any of the bye-laws of IASO may be altered or rescinded to or new bye-laws may be made at General Body Meeting by majority vote. The amendment shall come into force after it is circulated to all members and provided objection to such amendment of IASO is not received from ASI and 50% of valid members of IASO within three months from the date of circulation. A copy of such amendment is to be sent to Headquarters of ASI.

22. **Schedule:** IASO secretariat shall maintain a schedule comprising the various orations, fellowship research grant or any other grant for scientific works with rules and regulations for these awards and management.

23. **Orations, Fellowship & Awards:** Will be decided by a scientific committee consisting of President, President Elect, Immediate Past President, Vice President, Secretary, Immediate Past Secretary, Editorial Secretary and Organizing Secretary of NATCON. (Resolution no 9, GBM 23/9/06, Varanasi)

    a) *Radha Devi Oration* will be delivered by the outgoing President at the annual meeting of ASI. Rs. 5000/- have been donated for the oration by the family of Dr. S. Jain. The orator will get a plaque, a cheque for Rs. 2000, certificate and a medal.

    b) *Motibhai Oration* will be delivered by an orator selected by the executive Scientific committee, and endorsed Presented to the GBM. The oration will be delivered at the Annual Meeting of IASO- NATCON. Rs. 50,000/ -have been donated for the cause by Dr. D.D. Patel and family.

    Only interest to be used. 50% of interest to be reinvested to generate same amount of money even in the era of falling interest rates. Thus, only 50% of interest should be available in the year to award the orator a plaque, a cheque for Rs.2000, a certificate and a medal. Local hospitality by the organizing secretary NATCON. (Amended as per Resolution no 9, GBM 23/9/06, Varanasi)

    c) *Dr. N.C.Misra Oration:* Will be delivered preferably by an eminent foreign speaker selected by a panel consisting of the President IASO, Secretary IASO and the Organizing

Secretary of the NATCON Scientific Committee. In case of selection of eminent speaker from India, consultation will be held with the nominee of "The Student of Dr. N.C Misra", who have donated Rs. three lakhs as endowment. Only interest is to be used. 50% of interest is to be reinvested to generate same amount of money even in the era of falling interest rate Thus, only 50% or less of interest should be available in a year to award the orator a plaque, a cheque for Rs. 5000 or more/less (subject to calculation of interest),a certificate and a medal. Local hospitality by the organizing secretary NATCON. (Resolution no 9, GBM 23/9/06, Varanasi)

d) *Silver Jubilee oration in ASICON*- Will be delivered by national or international faculty. The orator shall receive a medallion, citation and Rs.2000.

e) *Detroit Visiting Fellowship*- A Fellowship to visit Detroit will have local hospitality included by the host institution, excluding the travel cost to and from USA. The candidate should be less than 40 years of age (the cut off date is 31st of December of the year of application),a full member of IASO, and permanently employed. Selection is based on CV and paper presentation during NATCON meeting .The paper must be on the work done in India only. Selection panel includes Dr.K K Moudar, President and Secretary of IASO. In case Dr. KK moudar is not available than a person nominated by him or in case nominee is not available, then President Elect will be member of the panel. (Resolution no 7, GBM 23/9/06, Varanasi)

f) *Baroda Traveling fellowship:* Rs.5000/- will be awarded to a young surgeon for visiting to a research or therapy oriented cancer center. No person can be awarded the prize again. Frequency of award-Once a year. Selection Panel: President, Secretary IASO & Dr. G. N. Shukla, Eligibility of applicant-young surgeon, full member of IASO, selection based on CV.

g) *Best paper presentation* will be awarded TRs.1000 towards complimentary Associate Membership of IASO. Eligibility: Post-graduate student.

h) *Best poster presentation* will be awardedRs.1000 towards complimentary Associate Membership of IASO. Eligibility: Post-graduate student.

i) *WFSOS:* The official representative of IASO in WFSOS will be immediate past president of his nominee. It will be the responsibility of President to generate$500 for yearly membership of WFSOS.

j) *DR. K. S. Panda-Dr. Gopinath Quiz award:* During NATCON meeting winner will be awarded Rs.700 and runners up Rs: 300. Dr. K. Panda &Dr. Gopinath donated Rs. 10,000 each towards the seed money for the Quiz award. Eligibility- all the delegates of NATCON. In case of prize being won by a person who is not a member, the winner will gate an additional Rs. 300 from the IASO towards his life membership dues, and cash awards will be adjusted towards the life membership of IASO.

k) *Free papers and posters:* All the short papers / posters should be send to Secretary who will send them after finalizing to Organizing secretary (Resolution no 9, GBM 23/9/06, Varanasi)

24. Guidelines of invitation for NATCON

a) Organizing secretary or his representative must be present in AGM to present his proposal.

b) Rs.100 per delegate must be deposited in IASO account. Besides this a part of the savings may be denoted to IASO.

c) Audited accounts to be presented by next NATCON or circulated in the Newsletter.

d) It has been decided that on request, a loan of Rs. 25000 may be given to the organizing secretary of NATCON as seed money to start preparation, repayable within 6 months of the conference.

25. Use of IASO banner in CME programs, Workshops, & Conference - It was decided that in CME where delegation fee was charged, a token amount of Rs. 5000 or Rs. 50 per delegate for one day event of rs.75 for two days event which ever was more must be deposited to use IASO banner.

OBITUARIES

The unexpected demise of **Dr. Amitabh Singh** at the early age of 41 has come as a shock to his friends and colleagues. Dr. Amitabh singh did his MS in general surgery from Institute of Medical Sciences, Banaras Hindu University, Varanasi in 1994 and was working as Associate Professor of Surgical Oncology at Indira Gandhi Institute Patna. Dr. Amitabh Singh was a very active member of the IASO and also served a term as Executive member of IASO.

The Association also lost a Doyen of Surgery, **Prof. I P Elhence**. Prof. Elhence has retired as Professor of Surgery from Agra Medical College and was practicing there in Sarkar Nursing Home at Delhi Gate, Agra.

It was ironic that one of the person who was involved in the fight with cancer succumbed to it at a very young age. **Dr. Shubha Sharma**, Assistant Professor of Surgical Oncology at Gujarat Cancer and Research Institute, Asarwa, Ahmadabad, succumbed to a very rare form of primary peritoneal cancer at the age of 36 loosing a battle that was on for last 8 years. During which she continued to operate and contribute to the growth of Surgical Oncology. Dr. Sharma, a graduate and postgraduate of Institute of Medical Sciences, Banaras Hindu University and was working at GCRI since 1996.

The member of Indian Association of Surgical Oncology pass their love and condolences to the families

LIST OF NEW MEMBER OF IASO IN THE YEAR – 2007

Dr. Sanjay Kisanrao Khopde
25, Garud Colony,
Behind Jai Hind Mangal Karyalaya,
Deopur, Dhule,
Maharashtra – 424001

Dr. Puneet Takkar
C/o Military Hospital, Cantonment
Shahibaug
Ahmedabad 380003

Dr. Arvind Krishnamurthy
94, Durai Arasan Street
Kaverirangan Nagar
Saligramam, Chennai-93

Dr. Ramakrishnan Ayloor Seshadri
Dept. of Surgical Oncology
Cancer Institute (WIA)
Annexe Campus, No. 18,
Sardar Patel Road, Guindy
Chennai-600 036

Dr. S.G. Balamurugan
Surgical Oncologist
94, T.P.K. Road, Pykara, Madurai-4
Tamilnadu

CHANGE IN ADDRESSES

IASO No. P 0027
Dr. Manoj Pandey
Department of Surgical Oncology
Institute of Medical Sciences
Banaras Hindu University
Varanasi 221 005 (UP), India

IASO No. S0097
Dr. Kamal Singh
25, Parivartan Apartment
Thorn Hill Road
Allahabad-211002

IASO No. V-0008
Dr. Ajay Vidyarthi
Type IV/10, New Doctor's Colony
Jagjivan Nagar, Saraidhela
Dhanbad – 826003

IASO Number B 0008
Dr. Debashis Banerjee
6A, Elgin Road
Calcutta 700 020

IASO Number D 0005
Dr. Shashank Sharad Date
"Sahwas" 34, Samratnagar
Jamnagiri Road, Dhule,
Maharashtra 424001

IASO No. R0013
Dr. S.Vijaya. Mohan Rao
Sri Vijaya Bhavan,
Panuganti Vari Street,
Ramachandera Rao Pet
Eluru, A.P. 534002 (AP)

IASO No. K0015
Dr A K Khanna
M8/180-AU1, Rajendra Vihar
Mevana, Sunderpur
Varanasi 221005

IASO No. S0053
Dr. Chandra Mohan Singhal
603, Eldorado Apt.
7/88 Tilak Nagar
Kanpur-208002

IASO No. T0016
Dr. Leo Francis Tauro
Department of Surgery,
Fr. Muller Medical College Hospital, Kankanady
Mangalore-575002 (D.K.)

Dr. Arvind Krishnamurthy
94, Durai Arasan Street
Kaverirangan Nagar
Saligramam, Chennai-93

CITATION OF PROF. N.C. MISRA

MS, FICS, FACS, FAMS, FRCS
Prof. & Head of the Department of Surgery (Ex.)
King George's Medical College, Lucknow &
Director, Lucknow Cancer Centre, Lucknow

Prof. N.C. Misra, MS, FICS, FACS, FAMS, FRCS did his MBBS and MS (Surgery) in 1958 and 1961 respectively from King George's Medical College, Lucknow. He joined the Department of Surgery, King George's Medical College, Lucknow as Lecturer in 1963 and retired as Head, Department of Surgery in 1996. He, however, continued as Professor till 1998 because of his National & International recognition.

Prof. Misra had been the recipient of the highest Medical Honours and Awards of India and had received International acclaim. Dr. B.C. Roy Award (1986) and Silver Jubilee Research Award of Medical Council of India (1997) were awarded to Prof. Misra for his outstanding and pioneering Research work in Oncology. He was recipient of 24 other National and International awards, a few notable are ICMR Sandoz Cancer Research

Award 1985, Sir Shri Ram Memorial Oration of National Academy of Medical Sciences, Dr. Kinni Memorial Oration Award 1995, Sir Dorabji Tata Oration Award of Indian Society of Oncology 2000 and the most prestigious award of Association of Surgeons of India – PANDALAI ORATION AWARD 2001. Prof. Misra was awarded the Fellowship of the Royal College of Surgeons (Glasgow) and was Fellow of the International College of Surgeons, American College of Surgeons and the National Academy of Medical Sciences. Prof. Misra was Honorary Consultant to Army Medical Corps and Cromwell Hospital, London. Dr. Misra had been President of Indian Association of Surgical Oncology, Indian Society of Oncology, Indian Association of Cancer Chemotherapists, U.P. Chapter of Association of Surgeons of India (ASI), Member of important bodies like World Summit Against Cancer, Paris, Teaching Faculty of U.I.C.C., Geneva, Sole Signatory from India on the Paris Charter Global Crusade Against Cancer and member steering Committee of National Cancer Registry Programme of ICMR and Governing Council of ASI. Dr. Misra had lectured and presented his work all over the world and had been visiting Professor to Institutions in Japan, USA and U.K. He had published over 156 scientific papers in National and International Journals, and his research interest were Carcinoma Gallbladder, Breast, Oral Cavity, Soft Tissue Tumour, Carcinoma Penis and Ovarian Cancer.

His research work has been cited in more than 250 research publications, Journals, and books like Devita's book of Cancer –"Principles and Practice of Oncology 1999" and The Year Book of Cancer etc. The State of the art research work on Cancer Gallbladder and Oral cancer is published in the Recent Advances in Surgery Vol. 20 and 25 UK. His work on gallbladder, breast, penile cancer and oral cancer has also been published in Lancet Oncology, Cancer, Anticancer Research etc.

Prof. Misra was a teacher par excellence and had trained innumerable postgraduates in Surgery and Oncology and had been a role model to several of his students and colleagues. The A.S.I. has published his biography in their book "Extra Ordinary Surgeons of Ordinary People". The title of "Modern Leader of Oncology of India-2000" was conferred upon him by the "Indian Society of Oncology" – Premier body of Oncologists in India.

Prof. Misra had pioneered the development of Oncology at King George's Medical College, Lucknow. He started the Oncology Unit in the Department three decades back. This later became the independent Department of Surgical Oncology in 1998 and this department is now one of the few centers recognized by Medical Council of India for imparting M.Ch Surgical Oncology training in the country.

Prof. N.C. Misra was a skilled surgeon, excellent teacher and a charming personality. His poise and affection was applauded by everybody who came in his contact including patients and relatives. He was a guiding force for his students as a teacher and his pupils held him in a very high esteem. Prof Misra left for his heavenly abode on 15 Sept 2006. He is survived by his wife Prof PK Misra, Former Principal, Dean and Head of the Department of Paediatrics, King George's Medical College, Lucknow and children - son Professor Sanjeev Misra, Prof of Surgical Oncology at King George's Medical University, Lucknow and daughter Mrs Sumita Misra, IAS, a senior IAS officer in Haryana. Dr Misra will always be remembered with love and respect by the medical fraternity, his students, patients friends and relatives for his humane behaviour, unparallel virtues and several contributions to society.

WFSOS –Egypt Congress 27-30 March 2007, Ain el Shouknan: *A common meeting was held between the executive of the Egyptian Society of Surgical Oncology and the representatives of WFSOS. There was a warm welcome and different topics were discussed. It was decided to have scientific exchange and mentorship for residents, communication, common discussion about guidelines and participation in further congresses and education (WFSOS - log book).*

WFSOS – International board of experts — tumor board (conference): *WFSOS plans to organize a panel of experts along the different tumor sites on an international high level — to answer management issues for specific cancers, to support individual countries management issues, to interact on larger management issues with the members of different countries. In the next days there will be a call to nominate candidates.*

FORM FOR MEMBERSHIP / CHANGE OF ADDRESS OF INDIAN ASSOCIATION OF SURGICAL ONCOLOGY(IASO)

To
Dr. Sanjeev Misra
Professor of Surgical Oncology
Department of Surgical Oncology
King George's Medical University
Lucknow-226 003
Email: misralko@satyam.net.in

Phone :
0522-2255346 (O)
0522-3240428 (O)
0522-2324656 (R)
0522-2386829 (R)

Sir,

1. I wish to become a member of Indian Association of Surgical Oncology (IASO)(a section of ASI).I enclose Rs. 2000.00 (two thousand only) or Rs. 2100.00 (two thousand one hundred only for outstation cheque) by Cash/Cheque/Draft/ no.....dated.....drawn on.....payable at Allahabad bank KGMU branch Lucknow.
2. Cheques & Drafts should be made in favour of Secretary Indian Association Of Surgical Oncology(IASO) Enclosed details as per para1 to 6.
3. Or I am an existing member of IASO. My address details have changed as para 1 to 4.

Signature of Applicant :.....Date of Application.....

DETAILS :

1.1 First Name.....1.2 Middle Name.....
1.3 Last Name.....1.4 Date of Birth.....
2.1 ASI Number.....
2.2 IASO Number (to be filled by the office).....
3.1 Present address, including pin code: .....
.....
.....
3.2 Present Institution /Place of Work : .....
.....
.....
3.3 Institutional address, including pin code : .....

.....
.....
3.4 Preferred mailing address : .....
.....
.....
3.5 Permanent address, including pin code: .....
.....
.....
4.1 Mobile :.....4.2 Telephone (R) please write STD code.....
4.3 Telephone(W) :.....4.4 Fax :.....
4.5 E-mail :..... 4.6 Personal Website :.....
5.1 Percentage of Oncology Work : .....
5.2 Research in Oncology : .....
5.3 Educational Qualifications : .....
5.4 MCI Number : .....
5.5 Experience-details attached : .....
5.6 Papers published : ..... and presented (List only the number of publications and presentations above and attach a separate sheet with details.)
6.1 Name of Proposer :.....ASI Number.....
Signature of Proposer .....
6.2 Name of Seconder .....ASI Number.....
Signature of Seconder .....

Comments by Secretary :.....Accepted/Not Accepted.....Signature of Secretary

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RECEIPT

Received Rs.2000.00(outstation cheque Rs.2100.00) cash/draft/cheque no.....
from Dr.....towards IASO membership on date :.....

Glimpses of IASO NATCON 2006