

International  
Society of  
Cryosurgery

# CRYOSURGERY



[www.societyofcryosurgery.org](http://www.societyofcryosurgery.org)

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**Issue 11**

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# Contact

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# I.S.C. Committee

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# Welcome

*We have great pleasure in bringing to you the eleventh issue of Cryosurgery.*

*The Society has been extremely busy during 2004 with its autumn activities. "Cryosurgery in the Americas" took place on 24<sup>th</sup> and 25<sup>th</sup> September in Montreal, the 4<sup>th</sup> Annual Meeting of the Association of British and Irish Cryosurgery (ABIC) was held in Crewe, U.K. on 1<sup>st</sup> October and the I.S.C. symposium "Cryosurgery in the Treatment of Cancer" on 26<sup>th</sup> October in Corfu, Greece. All three meetings went well. Congratulations to Rita Jean-Francois for her excellent organisation of the Montreal meeting, despite lack of manpower and limited resources, to Arthur Jackson for his planning and superb choice of Crewe Hall as the venue for ABIC's annual meeting which was very well attended by doctors and nurses from Britain and Ireland and finally to Odysseas Zoras for his initiation of the I.S.C. symposium in Corfu. I recently attended "Cryomedicine 2004", the 31<sup>st</sup> annual meeting of the Japan Society of Low Temperature Medicine in Tokyo, held with the collaboration of the International Society of Cryosurgery and International Institute of Refrigeration. I was very pleased to see many I.S.C. members present. Full reports of all the above meetings are given in this issue. On behalf of the Society, our sincere thanks and gratitude to all organisers and participants of the above meetings.*

*Preparations for the I.S.C.'s 2005 congress in Crete, Greece are progressing well and Professor Odysseas Zoras, I.S.C.'s Meeting President, is finalising the programme which will be available shortly. Crete is a popular holiday destination and an excellent social programme is being organised to accommodate accompanying persons and families. I hope that you will take advantage of this and combine your trip with a family holiday.*

*In this issue, we are including abstracts from the I.S.C. Symposium held in Corfu. We also have a News section, Articles, Future Events and further details on I.S.C. Crete 2005. As usual, my thanks to all contributors and supporters of the Society. I would appreciate anyone who is interested in writing for the next issue to contact me.*

*I look forward, once again, to your support and participation at our forthcoming meetings.*

**Omar Maiwand**

# News

## Members

A plea to all members to update their registration by sending in a completed I.S.C application form. Forms can be downloaded from the Society website and are also included in this issue. Paid-up members are eligible for reduced registration charges for ISC meetings. Members also receive a free copy of the I.S.C.'s biannual journal "CRYOSURGERY".

## Website

Do look at the I.S.C. website regularly for updates as the Society has been involved in a lot of activities in the last year. We have meeting reports, photographs and news.

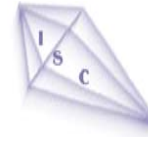
## Cryotechnology companies

As always, we need your support and sponsorship. We hope to see many of you at the I.S.C.'s 2005 congress in Crete. Please contact the Society if you wish to book an exhibition booth or sponsor a specific event.

## July 2005 issue

In addition to all the normal features, the next issue of CRYOSURGERY will publish an interesting article by Dr Andrew A. Gage (I.S.C. Honorary member) on the history of cryosurgical societies and the I.S.C.

# Forms



## APPLICATION TO JOIN I.S.C.

Please complete and return this form with your payment to:  
Ann Dudhia, International Society of Cryosurgery  
Harefield Hospital, Harefield, Middlesex UB9 6JH, U.K.  
Emails: A.Dudhia@rbh.nthames.nhs.uk  
cryotherapy.rbh.nthames.nhs.uk

Membership charges: 50 US\$ per annum

Cheques should be made payable to "Society of Cryosurgery"

Surname: .....Dr/Prof/Mr/Mrs

First Name: .....

Position: .....

Email: .....

Telephone: .....

Fax: .....

Affiliation: .....

Address: .....

..... Postcode: .....

Applicants Signature: ..... Date:.....

# Forms



13<sup>th</sup> Congress of  
**INTERNATIONAL SOCIETY OF CRYOSURGERY**  
 12-14 May 2005, Univ. of Crete, Heraklion, Crete,  
 Greece

## Registration Form

### Registration fees

#### ISC Members

Before 15.03.05: \$ 300

After 15.03.05: \$ 350

#### Non Members

Before 15.03.05: \$ 350

After 15.03.05: \$ 400

Accomp.persons:\$ 100

#### Medical Companies:

1 Rep \$1000

2 Reps \$1300

Please return this form  
 by **15<sup>th</sup> March 2005** to

**International Society  
 of Cryosurgery**  
 Harefield Hospital  
 Harefield  
 Middlesex UB9 6JH  
 U.K.

Title: .....Surname: .....

First Name:.....

Position: .....

Affiliation: .....

Postal Address: .....

Tel: .....Fax: .....

Email: .....Website: .....

I am sending an abstract for oral/poster\*  
 presentation *(\*delete as appropriate)*

I am bringing .....*(insert no. of people)*  
 accompanied person(s):

Name(s): 1).....2).....

Company Registration *\*(1 Rep / 2 Reps ) \*(delete as appropriate)*

Fee enclosed: US\$ .....member/non-member  
 Cheque/Bank transfer

Title of presentation: .....

.....

# 13<sup>th</sup> Congress of the **INTERNATIONAL SOCIETY OF CRYOSURGERY**

12 - 14 May 2005

Faculty of Medicine  
 University of Crete  
 Heraklion, Crete  
 Greece  
 www.med.uoc.gr

Meeting President: Assoc. Prof. Odysseas Zoras  
 1st Vice President: Dr Franco Lugnani  
 2nd Vice President: Assist. Prof. Manolis Chrysos

Meeting held under the auspices of

University of Crete  
 Municipality of Heraklion  
 International Society of Regional Cancer Treatment (ISRCT)  
 Mediterranean Society of Coloproctology (MSCP)  
 Italian Society of Colorectal Surgery (ISCRS)  
 Hellenic Sarcoma Society (HSS)  
 International Institute of Refrigeration (IIR)  
 Hellenic Society of Dermatological Surgery (HSDS)




# Crete 2005

## SCIENTIFIC COMMITTEE AWARDS COMMITTEE

Alessandro Delbello	Jose Carlos Almeida Gonçalves
Ahmed Gad	Jean-Paul Homasson
Gloria Graham	Nikolai Korpan
Arthur Jackson	Omar Maiwand
Rita Jean-Francois	Sajio Sumida
Marcial Peralta	Odysseas Zoras
Jean-Michel Vergnon	
Fengrui Zhao	
Odysseas Zoras	

## STUDENTS ORGANISING COMMITTEE

Stamatiou Dimitris	 Feretos Konstantinos
Kastrinakis Haralambos	Kontostanou Lea
Marantos Georgios	Tambakaki Zoe

## CONTACTS

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Website: www.societyofcryosurgery.org

# Future Events



7<sup>th</sup> edition

## Intensive "Hands on" course on Models and Pigs

Dates: 19-23 June 2005  
Venue: Hospital Notre-Dame du CHUM, Montreal  
Supported by: The Committee of Continuing Medical Education of "L'Association des pneumologues de la province de Québec"  
Accredited activity of: The Royal College of Physicians and Surgeons of Canada.  
Course Director: Rita Jean-François (Email: rjfm@d@hotmail.com)

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5<sup>th</sup> Meeting of the

## St George Peritoneal & Liver Oncology Group

Date: 8-9 September 2005  
Venue: St George Hospital, Sydney, Australia  
Chairperson: Prof. David L Morris  
Speakers: Prof. D.Elias, Gustav Roussy Institute, France  
Dr V.Verwaal, Netherlands Cancer Institute  
Contact: Ceri Walker Tel: +61 2 9350 2070  
Email: slog@unsw.edu.au

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4<sup>th</sup> Congress of the

## French Vietnamese Association of Pulmonology (AFVP)

Date: 9-11 November 2005  
Venue: Ho Chi Minh City, Vietnam  
Contact: Dr Jean-Paul Homasson  
24 Rue Albert Thuret, 94550 Chevilly-Larue, France  
Email: jeanpaulhomasson@chsp.asso.fr  
Tel: +33 1 49082020. Fax: +33 1 49082000

# Future Events



## 1st International Symposium of Cryosurgery

Date: 30 April 2005  
Venue: Korea University International School, Seoul, Korea  
Chairman: Prof. Kwang Tak Kim  
Contact: Prof. Kwang Tak Kim  
Korea University Medical Centre  
Thoracic Cardiovascular Dept.  
Korea University, Seoul, Korea  
Tel: +02 920 5309. Fax: +02 924 5536  
Email: [ktkim@korea.ac.kr](mailto:ktkim@korea.ac.kr)  
Website: [www.cryo.or.kr](http://www.cryo.or.kr)

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## 13<sup>th</sup> Annual Course of Cryosurgery and Radiofrequency

Dates: April to November 2005  
Venue: Argentine Medical Association, Buenos Aires, Argentina  
Organised by: The Argentine Society of Cryosurgery  
Graduate School of the Argentine Medical Association  
Contact: Argentine Society of Cryosurgery  
Email: [bturjan@speedy.com.ar](mailto:bturjan@speedy.com.ar)

**The course will be transmitted via Internet**

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## 42<sup>nd</sup> Meeting of the Society for Cryobiology CRYO-2005

Dates: 24-27 July, 2005  
Venue: University of Minnesota, Radisson Hotel Metrodome  
615 Washington Avenue SE, Minneapolis, Minnesota, USA  
Contact: Allison Hubel  
Tel: +1-612-626-4451  
Email: [cryo2005@me.umn.edu](mailto:cryo2005@me.umn.edu)  
Website: [www.me.umn.edu/events/cryo2005](http://www.me.umn.edu/events/cryo2005)

Abstract submission: 1<sup>st</sup> May 2005

# Crete 2005

## CALL FOR ABSTRACTS

Instructions to Authors

**New Submission Deadline: 15<sup>th</sup> March 2005**

Abstracts must be submitted in English in Times New Roman Font, size 10-point, to fit one A4 page with 2 cm margins. Title in 12-point Bold with names of authors below in 11-point. On next line, Institution and address in 11-point Italics. Name of presenting author should be underlined.

The Book of Abstracts will be published before the meeting. Please ensure that your abstract is with us before the above deadline.

Abstracts, prepared as an MS Word document, should be submitted by email attachment to: [A.Dudhia@rbh.nthames.nhs.uk](mailto:A.Dudhia@rbh.nthames.nhs.uk)

## PRELIMINARY PROGRAMME

### Plenary lecture topics

BONE TUMOURS	LARGE TUMOURS
BREAST	LUNG TUMOURS
CRYOBIOLOGY	OPHTHALMOLOGY
DERMATOLOGY	PROSTATE
ENDOBRONCHIAL	RESEARCH
E.N.T	UROLOGY
HEPATIC	VETERINARY
IMMUNOLOGY	MISCELLANEOUS

### Hands-on Course

(with simultaneous video projection)

“Bronchial Obstruction” - demonstrated on pigs.

Course director: Dr A. Moniakis

Maximum number of participants is limited to 10



# Crete 2005

## Satellite Symposium

### *Image-guided surgery*

Chairman: Professor D.Tsiftsis

### Presentations

1. Navigator systems in neurosurgery. *T.Kombos: Germany, A.Vakis: Greece*
2. Sentinel lymph node biopsy. *E. Sanidas, Greece*
3. RF application for liver tumours. *A. Hatzidakis, Greece*
4. Cryoablation for liver and central nervous system tumours.  
*O.Zoras, Greece*
5. Radio-immuno guided surgery (RIGS). *E. Athanassakis, Greece*

## Round table discussions

- |    |                             |                                  |
|----|-----------------------------|----------------------------------|
| A. | Cryoablation in Cardiology: | Chairman - Asst. Prof. E. Manios |
| B. | Dermatology:                | Chairman - Prof. C. Zouboulis    |
| C. | Recto-Anal Cancer:          | Chairman - Dr A. Delbello        |

## Abstracts under review

A suggestion for cryosurgery utilizing ice formation from a glass, rather than from a liquid. *W.E.Brower, Jr*

Analysis of endobronchial cryosurgery and radiotherapy versus radiotherapy.  
*G. Asimakopoulus*

Ano-rectal cancer with skin invasion: What can be done? *A.Delbello*

Anorectal cancer: When the Miles procedure? *A.Amato*

Apoptosis. *D.Spandidos*

Argon-based closed cryoablation of bone tumours. *J.Bickels*

B.A.D. tidings and better news about cryosurgery for Lentigo Melanoma.  
*A.Jackson*

Biological effects of freezing. *M.O.Maiwand*

Bronchial cryotherapy: an overview. *J-M.Vergnon*

Characterization of single and multiple Oncura 17 gauge cryo-needle operation. *J.C.Bischof*

Comparison of the thermal history of skin surface temperature during the treatment of hypertrophic scars and keloids using contact and intralesional cryosurgery techniques - an experimental clinical study. *Y.Har-Shai*

# Teaching in Mexico

To achieve cancericidal temperatures inside bulky tumours, a thick spray must be applied for long periods. To avoid the running off of the drops of liquid nitrogen and the freezing of extensive skin areas, the drops must be stopped at the periphery with efficient perilesional protection:

- a) for cancers located on the head and extremities, many layers of bandages are used,
- b) for those on the trunk, fifteen-times-folded paraffinated gauze bandages originate a smooth and flexible plaque that is stitched on to the skin surrounding the target,
- c) a large, adherent silicone sheet (not commercially available as yet) with a central hole that limits the target.

The choice depends of the location and particular characteristics of the lesion. An important consequence of careful physical limitation is that the cryosurgeon can use liquid nitrogen spray continuously, and for as long as necessary, until complete freezing of the cancer is achieved. This can take between 15 and 60 minutes. The cryosurgeon does not need to worry about the risk of spreading the freezing beyond the intended limit, on healthy skin, and can concentrate on monitoring the progress of the ice front.

My lectures were delivered in Spanish and were followed with great interest, raising many questions from the audience.

I offered to give a more detailed practical course in any Latin American country the following year, which was accepted by Professor M.García Silva, from the University of Guadalajara, México. It was agreed that I would teach advanced cryosurgery to 10 medical doctors during August 2005.

Looking at the above experience, I believe that this type of activity by members should be acknowledged, encouraged and promoted by the I.S.C. for the future of Cryosurgery and the Society.



## Teaching in Mexico



Basal-cell carcinoma of the eyelid invading the orbit



12 years after cryosurgery. No recurrence

all cancers reduce in size or, at least, in thickness.

However, sometimes, after a treatment that did not include the safety margin, one month later, no visible lesion remains and it seems cured. In such cases, one must assume that the carcinoma is not biologically cured because the safety margin was not frozen, and it is mandatory to perform two freeze-thaw cycles on the original site, with adequate extent so as to treat the intended safety margin.

I have treated 99 patients so far (89 basal-cell carcinomas and 10 squamous-cell carcinomas). The results were excellent for tumours smaller than 20 mm, but the recurrence rate of the larger ones was higher than expected. Therefore, I modified the technique for larger tumours, which is currently being clinically studied.

In my lesson, I gave a summary of my work on advanced external cancers, namely, squamous-cell carcinomas, including those on the extremities, penis and vulva, advanced basal-cell carcinomas invading the orbit, and lastly, I finished the presentation with the description of cryomastectomy for inoperable cancers.

I should point out the criteria to consider a cancer as advanced is not primarily related with its size, but with the degree of difficulty or impossibility to eradicate it. The location, histological type and degree of local or distant metastatic spread is more important than the actual tumour size.

To treat advanced external cancers and to freeze bulky neoplastic masses, three rules are necessary: efficient protection of surrounding healthy tissues; the use of a thick spray from an apparatus with high pressure; adequate control of the advance of the ice front on the surface and in depth. I use thermocouples, but electric impedance and ultrasonography are also good.

## Crete 2005

Cryoablation on bone tumours. *A.Hatzipaulou*

Cryoablation of bone tumours using closed argon-based system. *J.Bickels*

Cryochemotherapy of a non-small-cell lung cancer xenografted into SCID mice. *V.Forest*

Cryologic preventive oncology. *V.I.Kochenov*

Cryosurgery of advanced pancreatic cancer. *D.Prokhorov*

Cryosurgery and cryo-radiotherapy of head and neck cancer. *I.Pustynskiy*

Cryosurgery in dermatological diseases. *P.Mintzias*

Cryosurgical interventions at pancreas diseases. *B.Alperovich*

Cryotherapy in the treatment of inoperable metastatic lung disease. *R.J.Chambers*

Cryotherapy of upper air passages for children who fall ill frequently and suffer from adenoiditis. *V.I.Kochenov*

CT imaging of the kidneys after percutaneous MR-guided cryoablation: Outcome of long-term follow-up. *J.Harada*

Direct cryosurgery to lung tumour. *M.O.Maiwand*

Enhancement of cryothermic injury to prostate tumours by targeted delivery of TNF bound gold nanoparticles. *J.C.Bischof*

15 years of bone tumour cryosurgery - A comprehensive summary, review of literature and consideration for the future. *J.Bickels*

Histopathologic studies of the tumour, peritumour and renal tissues after cryoablation of renal cell carcinoma. *Y.Yamaguchi*

History of cryosurgery in cryomedicine. *S.Sumida*

How long can we cryopreserve human block cells and stem cells as the genetic resources? *S.Sumida*

Improving the diagnostic yield of endobronchial biopsies in lung cancer by using a flexible cryoprobe. *C.Schumann*

Intralesional cryosurgery for enhancing the involution of hypertrophic scars and keloids - a new effective technology based on experimental and clinical data. *Y.Har-Shai*

Intralesional cryosurgery markedly enhances the involution of lobular and helical keloids. *C.C.Zouboulis*

In vivo late cryo-induced angiogenesis in a non-small-cell lung cancer model. *V.Forest*

# Crete 2005

## Abstracts

Liver cryosurgery for patients with metastatic colorectal cancer. *M.Watanabe*

Long-term adjuvant androgen deprivation after targeted-cryosurgical ablation of the prostate in localised and locally advanced carcinoma of the prostate (LTAD-TCSAP). *J.Cheon*

Long-term results and prognostic indicators after cryotherapy and hepatic arterial chemotherapy with or without resection for colorectal liver metastases in 224 patients. *D.L.Morris*

Lower rectum cancer: preoperative staging and sphincter saving surgical techniques. *A.Adami*

Lung metastases after liver resection or cryotherapy for hepatic metastases from colorectal cancer - There is a difference! *D.L.Morris*

Management of involved and close resection margins in 120 patients with colorectal liver metastases - Edge cryotherapy can achieve long-term survival. *D.L.Morris*

Scientific background of using low temperatures in the treatment of keloids. *C.C.Zouboulis*

Temperature mapping and comparison of the iceball of 3 different cryoprobes for prostate cancer: *in vitro* study. *S.Ahmed*

The speed of ice growth as an indicator in single and double freeze-thaw cycles in cryosurgery. *W-H.Yang*

The Improvement of cryogenic method for treatment of background and pre-cancerous diseases of the neck of the uterus. *V.I.Kochenov*

Tissue samples from cryorecanalization are of good histologic quality and suitable for immunocytochemistry. *J.Hetzel*

Usefulness of cryotherapy in a bronchoscopy unit of a general hospital. *J.Flandes*

## SOCIAL PROGRAMME

- Thursday, 12<sup>th</sup> May: Opening Ceremony and Welcome Dinner
- Friday, 13<sup>th</sup> May: Excursion to the Archaeological Museum and Knossos Palace (*additional activity*)  
Gala Dinner and entertainment - "Daedalos Pool"
- Saturday, 14<sup>th</sup> May: Full day excursion to Phaestos Palace and Antiquities (*additional activity*)

# Teaching in Mexico

Report by Dr JCA Gonçalves

## Cryosurgery of Advanced Cancer and Fractional Cryosurgery

The VII Venezuelan Congress of Dermatology was held in Puerto la Cruz, Venezuela, 10th-13th November 2004. Three thematic courses took place on the eve of the Congress, including one on Cryosurgery, under a general title "The Experts Speak"

I was invited by the Board of Directors of the Congress to give a talk on "Cryosurgery of Advanced External Cancer". I also proposed to present my method in "Fractional Cryosurgery for Skin Cancer", which was accepted. I was allocated 50 minutes for the first lecture and 15 for the second, which would cover more than half the duration of the course.

Fractional Cryosurgery was my first presentation. This is a new method that I have originally devised to treat roundish cancers located on the forehead and medial part of the face, when their sizes could originate retractile scars that might alter the physiognomic features. Indeed, cryosurgery of such tumours that are greater than 10mm, plus the adequate safety margin, will result in large ulcerations.

The first cryosurgical procedure is not intended to freeze the whole neoplasm. Freezing goes up to the tumour's apparent limits without a safety margin, or, if this is not feasible, only its centre is frozen. The extent of the frozen tissue is clinically appreciated. Temperature monitoring is not essential for the experienced cryosurgeon, but its use can be advantageous. This first procedure consists of one or two freeze-thaw cycles, in accordance with the following criteria:

- a) for tumours on the eyelids, one cycle always
- b) around the eyelids: for thin lesions, one cycle, for thick lesions, two cycles
- c) for tumours on other locations, two cycles.

The resulting ulceration slowly heals over the following 3/4 weeks. After healing, the remaining lesion has reduced in size or, at least, in thickness, and its measurements are compared with the initial ones and recorded. If its size indicates that there is no more danger of retraction, the second procedure is performed in the standard way (two freeze-thaw cycles with adequate safety margin). If it is still too large, the same procedure is repeated. The aim of this technique is to obtain successive reductions of the tumour with as many procedures as necessary, until it achieves a size that permits its complete freezing, with safety margin, without risk of retraction. After the first procedure,

## An I.S.C. Honorary member in Vietnam

field, has developed rapidly and medical CT scans, MRI and other new materials are now available in all big cities. Their first PET Scan is planned for 2005.

I cannot help remembering the day, some years ago, when I asked about the treatment modalities for an asphyxiating patient with an enormous cancer invading the trachea. The answer was: "Nothing.....". The day after, I was informed that this patient had committed suicide. I was immediately prompted to buy a rigid bronchoscope and the electrocautery material which is, with its immediate debulking "laser-like" effect, the best technique for developing countries. Three years later (2002), at the 3rd congress organised in Vietnam by the AFVP, our colleagues at the Pham Ngoc Thac Hospital in Ho Chi Minh City presented the results, using this technique. Their work was indeed impressive. Indications and results, images and videos - were no different than our own results.

During October 2004, the AFVP bought a second device for the Bach Mai Hospital (Hanoi), where I successfully treated 2 patients with severe tracheal obstruction: one with thyroid cancer invading the sub-glottic trachea, and one with tracheal stenosis (1mm) after intubation.

The AFVP is now present in different parts of Vietnam - Hanoi, Haiphong, Ho Chi Minh City and Dalat. We continue our training, not only for pulmonologists, but also for thoracic surgeons, radiologists, pathologists, intensive care physicians and general practitioners.

The 4<sup>th</sup> congress of the AFVP will be held in Ho Chi Minh City in November 2005. About 600-700 participants are expected to attend from as far as Cambodia and Laos.

As the new President of Commission C1 (Cryobiology - Cryomedicine) of the International Institute of Refrigeration (IIR) which is an inter-governmental association, I hope to gain Vietnam as the 62<sup>th</sup> country of the IIR. This goal is important to Vietnam, not only for medical applications, but also for the storage and transport of food, heat pumps development and air conditioning, thermodynamics, equipment and systems, cryology and gas processing.

For more information about the AFVP, please visit our website: [www.afvp.info](http://www.afvp.info)

## Crete 2005

### TRANSPORT

Special transport has been arranged for airport/hotel transfers. A shuttle service will be running between Hotel Capsis and University of Crete on 12<sup>th</sup> & 13<sup>th</sup> May 2005.

### REGISTRATION FEES

#### *I.S.C. Members*

Before 15<sup>th</sup> March 2005: US\$ 300. After 15<sup>th</sup> March 2005: US\$ 350

#### *Non Members*

Before 15<sup>th</sup> March 2005: US\$ 350. After 15<sup>th</sup> March 2005: US\$ 400

Accompanied persons: US\$ 100\*

Medical Companies: 1 Rep - US\$ 1,000, 2 Reps - US\$ 1,300

Registration fee includes:

A US\$ 50 membership fee for the International Society of Cryosurgery

Admittance to all scientific sessions (12<sup>th</sup> & 13<sup>th</sup>)

Meeting documentation

\*Welcome dinner and entertainment

\*Gala dinner and entertainment

Refreshments during the scientific sessions (12<sup>th</sup> & 13<sup>th</sup>)

### PAYMENT

By cheque, in US dollars, made payable to "**Society of Cryosurgery**", posted to:

International Society of Cryosurgery

FAO: Ann Dudhia

Harefield Hospital, Harefield

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# Crete 2005

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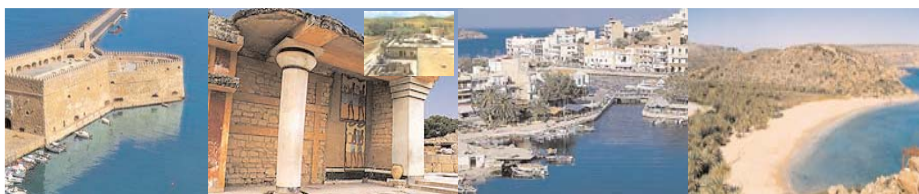
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# An I.S.C. Honorary member in Vietnam

A report by Dr Jean-Paul Homasson

First of all, I would like to thank Omar Maiwand who asked me, as an Honorary member and Past President of the I.S.C, and also the Past and Founding President of the former European Society of Cryosurgery, to write a short report on my activities in Vietnam.



1993: First initiation to the use of a fiberoptic bronchoscope

As a chest physician, interventional endoscopy was one of my poles of interest, including cryosurgery, which I have performed since 1984. I am proud to have given a renaissance to bronchial cryosurgery and have spread this technique throughout the world with Omar Maiwand. I was also the first to use brachytherapy in France and to develop electrocautery since 1994 for the treatment of tracheo-bronchial lesions. At the present time, I am interested in the use of radiofrequencies.



2004: Interventional Endoscopy (Hanoi)

My first trip to Vietnam was in 1990. I was extremely disturbed by the poor hospital and general medical conditions - no material, absence of adequate knowledge of pulmonology (except in the treatment of T.B.) and no available treatments. After my second visit to the same place two years later, I founded the French Vietnamese Association of Pulmonology (AFVP), with the aim to develop this speciality and form "up to date" chest physicians. After about 18 visits and countless missions undertaken by AFVP members, I can now say that our objectives have almost been achieved. In the main hospitals (Pham Ngoc Thach - Ho Chi Minh City and Bach Mai Hanoi) where the AFVP is present, the medical level is now comparable to ours.



Dr Homasson presenting a microscope for TB detection.

In the beginning, even material supplies had to be donated, but after the suppression of the American embargo in 1992, the country, including its medical

# Meeting Report

*Cryomedicine 2004*

There was a working luncheon with lectures on *International exposition of 2005 Aichi and a frozen mammoth* and *Cell structure and function revealed by cryo-techniques*.

Day three started with 3 concurrent workshops: *Cryopreservation of liver and pancreas, recent advantage of cryoimmunology and clinical strategy and evidence of the cryosurgery in aortic arch surgery*.

The invited paper for the Luncheon seminar was *Fifteen years of bone tumour cryosurgery* by Isaac Meller.

The afternoon and final session of the meeting presented another invited paper, *MRI guided cryosurgery* by Patrick Sewell, a symposium on *Mid-term results of MRI guided cryotherapy of kidney and uterine fibroids* and two workshops: *Organ injury and preservation in renal transplantation* and *Autologous transfusion of erythrocytes and platelets preserved by freezing*.

I was particularly impressed with the provision of the working luncheons, which proved very effective in saving time. All the social occasions were held at the hotel itself. There was a Conference reception on the first day and the Banquet, organised on the second day, took place straight after the meeting, outside the lecture halls, which was most convenient and worked very well. After the Banquet, invited guests enjoyed a "Friday Night Invitation" held at the hotel's New Tower.

Although the official language of the Conference was English, there were some presentations in Japanese (without interpreters), however, the slides were in English, therefore it was possible for everyone to follow the general aim of the talk.

Overall, it was a good meeting, well attended and very well organised.

My congratulations to the Meeting President Dr Junta Harada (Jikei University School of Medicine, Tokyo), his team, Prof Sajio Sumida and the board of directors of the Japan Society for Low Temperature Medicine, on the excellent organisation of Cryomedicine 2004.

# Abstracts

I.S.C. Symposium, Corfu, October 2004

## Biological Effects of Low Temperature

M.O.Maiwand

*Department of Thoracic Surgery, Harefield Hospital, Harefield, Middlesex UB9 6JH, U.K.*

The use of cryosurgery for the treatment of malignant and benign tumours has been popularised in the last two decades. This is mainly due to the painstaking work of the cryobiologists and cryosurgeons, combined with advances in cryosurgical technologies and the use of ultrasonic imaging techniques to monitor the freezing process. The aim of treatment is to destroy the entire abnormal lesion, whilst protecting the normal surrounding tissue to avoid complications. The biological effects of cryosurgery can be divided into early and delayed effects.

### Early / Direct Effects

The direct effects of freezing commence when the temperature falls into the hypothermic range. At temperatures of around  $-10^{\circ}\text{C}$  cell metabolism fails progressively. However, the cell membrane and contents protect the cell temporarily from ice crystal formation, but if this temperature is maintained for sufficient time, it can cause cell destruction.

When the temperature falls further, ice crystals initially form in the extracellular spaces. This causes the remaining liquid to become hypertonic compared to the intracellular fluid and leads to withdrawal of water from within the cell, causing increased electrolyte concentration with cell shrinkage and results in cell death. This mechanism is termed the *cell solution effect*. With further cooling ice crystals start to form within the cell which is virtually certain to be lethal. Intracellular ice crystals are also likely to form with rapid freezing as this does not allow time for water to be removed from the cell. Intra-cellular ice crystals may form inside the cell from around  $-30^{\circ}\text{C}$ . It is thought that ice crystals may enter the cell either through micropores in the membrane or through a damaged cell membrane. The thawing process causes further cell damage as small ice crystals fuse together to form larger, more destructive crystals, which can destroy the cell content and rupture cell membranes. When the ice crystals melt, water enters the cells and the cell volume increases. This can cause rupture of the remaining intact cells

### Delayed Effects / Vascular Stasis

The delayed or vascular effects of freezing follow with a brief period of vaso-

# Abstracts

I.S.C. Symposium, Corfu, October 2004

## *Biological Effects of Low Temperature*

constriction. When the tissue thaws vasodilatation and increased vascular permeability occur followed by oedema, and damage to the capillary endothelial cells. This causes platelet aggregation and micro-thrombus formation, resulting in stagnation and complete occlusion of small vessels, the lack of blood supply causes uniform cell death. This delayed or vascular effect may be as important as the direct physical effects.

A cryo-immunological effect has been suggested for some years. There is also evidence that some cells undergo apoptosis (gene regulated cell death) when exposed to temperatures around -6°C to -10°C, though much of the research in this area has been carried out *in vitro*.

In summary, to maximise the effectiveness of cryosurgery, it is important to use as low a temperature as possible, cool the tissue as rapidly as possible, thaw as slowly as possible and use more than one freeze thaw cycle, the choice of probes and cryosensitivity of the tissue have some role to play.

## **Liver and Central Nervous System Metastatic Lesions treated by Cryoablation**

Odysseas Zoras<sup>1</sup>, Saif Almarashdah<sup>1</sup>, Zenia Saridaki<sup>1</sup>, Antonis Vakis<sup>2</sup>

*Departments of General Surgery<sup>1</sup> & Neurosurgery<sup>2</sup>, University of Crete, Medical School, Greece*

Surgical resection is the treatment of choice for liver metastatic lesions from colorectal cancer, nevertheless, only a small percentage are suitable. Systemic and locoregional chemotherapies add little to tumour response and to regional control of the disease. Cryosurgery with the accurately performed detection of the lesion and the monitoring of the cryodestruction process by intraoperative ultrasonography (IOUS) has been established as an alternative treatment modality for unresectable liver tumours.

Fifteen patients with unresectable liver metastatic lesions from colorectal cancer underwent cryodestruction over a 40 month period in our department. The equipment used is the Candela CS5 Liquid Nitrogen Cryosurgery System (Spemby Medical Ltd) with five reusable probes. Freezing is achieved by liquid nitrogen producing a tip temperature of -196°C. Detection of metastases and monitoring of the cryoprocedure (freeze/thaw cycles) is achieved by IOUS. Two 30 min freeze/thaw cycles are applied in every lesion under IOUS detection and guidance. Simultaneous cryotreatment was applied in maximum to three metastatic lesions. There were no life-threatening postoperative complications

# Meeting Report



## CRYOMEDICINE 2004

18-20 November 2004

Tokyo, Japan

Omar Maiwand

The 31<sup>st</sup> Annual Meeting of the Japan Society for Low Temperature Medicine organised a joint World Conference of "Cryomedicine 2004" in collaboration with the International Society of Cryosurgery and the International Institute of Refrigeration.

The meeting was held at the Tokyo Conference Centre, Shinagawa on 18-20 November 2004. It was well attended with some overseas delegates present.

The Meeting started with an *International Evening Seminar*, with 9 lectures, mainly on the historical background of cryosurgery and cryomedicine. There were two very good papers on the new frontiers of cryosurgery in Japan - *MRI guided cryosurgery* by Tadashi Shimizu, Hokkaido University and *Intraoperative cryosurgery* by Go Wakabayashi, Keio University. *Direct pulmonary cryosurgery* - an indication of cryosurgery for direct pulmonary cancer treatment, was presented by Omar Maiwand. Other topics included *Cryosurgery of oral and maxillofacial regions*, *regulatory principles of tissue banking in Europe* and *Cryologic preventive oncology*.

The second day consisted of symposiums, free papers and workshops. The topic of Symposium 1 was *Mechanisms of freezing injury and protection with cryoprotectants - How are cells destroyed? How are cells protected?*, with very very good lectures on the mechanical action of ice crystals and on post-thaw viability. The symposium was followed by a session of free papers on *Cryopreservation*, followed by 2 workshops - *Recent topics of haematopoietic stem cell transplantation* and *Contributions of cryomedicine in regeneration medicine*.

Running consecutively with Symposium 1 was a Collaboration Symposium on *Hypothermic liver preservation*.

The topic of Symposium 2 was *Cryosurgery as a minimal invasive treatment of malignant tumours* with a very interesting lecture on *Ultrasound-guided cryosurgery for hepatic malignancies* by Minoru Tanabe from Keio University. This was followed by Workshop 3 - *Cryosurgery of hepatic cancer, comparison and radiofrequency ablation*.



# Meeting Report

*Cryosurgery in the Treatment of Cancer*



The benefit to associate cryotherapy with chemotherapy was demonstrated by V. Forest with an in vivo model in *Cryotherapy and chemotherapy performed alone or in combination in the treatment of a non-small-cell lung cancer xenografted into SCID mice*.

The symposium ended with an excellent round table discussion titled "*What have we achieved and what is the future?*", co-chaired by Mr M.O. Maiwand and Prof. O. Zoras.

The social program was also very rich, with entertainment arranged for every evening, including a guitar recital and a gala dinner with Sirtaki dancers.

To conclude, special thanks for the organisation of the meeting to: Mr M.O. Maiwand, President of the I.S.C., Prof. O. Zoras, ISC Meeting President and member of the Organising Committee of the IIAR conference and to Ann Dudhia.

For those who missed this meeting in Greece, the next opportunity is coming very soon with the 13<sup>th</sup> International Meeting of the I.S.C. organised in Heraklion (Crete), Greece, 12-14 May 2005, by Prof. O. Zoras.



ISC Board members  
From left to right, Franco Lugnani, Omar Maiwand,  
Alessandro Delbello and Odysseas Zoras

*Photographs by kind courtesy of Dr Arthur Jackson*

# Abstracts

I.S.C. Symposium, Corfu, October 2004

were observed. Four patients developed bile leak that was treated conservatively and eight developed pleural effusion, four of which were submitted to thoracic paracentesis. Eleven patients developed mild and reversible thrombocytopenia. Mild pyrexia and myoglobulinuria was observed in all patients. Crack of the hepatic parenchyma occurred in one patient causing intraoperative hemorrhage controlled by sewing. None of the patients developed cryoshock syndrome.

Cryoablation is a safe and effective modality which can be applied to unresectable colorectal metastatic liver tumours. It can be combined with other therapeutic modalities and in carefully selected patients can offer an important therapeutic benefit.

As far as the ablation treatment of central nervous system metastatic lesions is concerned a 43 year old male patient with 3 brain metastatic lesions from melanoma was submitted to cryoablation and surgical excision of the largest lesion located on the left frontal lobe. A left frontal craniotomy was performed and the tumour was detected with the assistance of a brain lab neuro-navigation system. A 3mm cryoprobe was inserted in the centre of the tumour under real time ultrasound guidance with the simultaneous monitoring of the ice-ball expansion. To avoid ischemic damage the time of exposure to low temperature was reduced. At the end of the cryoprocedure the tumour was surgically resected *en bloc* without hemorrhage. The histological examination showed 60% necrosis.

Although we cannot attempt any estimation in terms of local control of the disease or overall survival it is possible to excise some metastatic tumours of the brain using initial cryoablation in order to obtain *en bloc* and bloodless resection.

## Targeted Cryoablation of the Prostate: 11 years outcomes in Primary Treatment of Prostate Cancer. What happened to my first 57 patients?

Franco Lugnani<sup>1</sup>, Fabrizio Zanconati<sup>2</sup>

<sup>1</sup>Casa di Cura Salus, Trieste, Italy, <sup>2</sup>Histology Department, University of Trieste, Italy

### Introduction

Spreading of cryosurgery in prostate neoplastic pathology during the decades has brought to a progressive improvement of technology and surgical technique with improvement of results and reduction of morbidity.

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## *Targeted Cryoablation of the Prostate*

In the beginning of the 60's and 70's cryosurgery was applied to the prostate transurethrally with a special probe inserted under digital control and the length of the freezing was determined in a rather empiric way by palpation, an important attempt to get a better visual monitorisation was introduced by Reuter who attempted to verify the freezing with a soprapubic cystoscopy. In recent years, the reintroduction of cryosurgery was lead by ultrasound control, multiprobe devices and the use of thermocouples to monitor temperatures as refined by Chinn, Lee and Bahn. More recently Onik introduced the systematic use of instillation of liquid in the Denonvilliers fascia in order to easily obtain a lower temperature outside the gland during the procedure.

## Material and methods

We report our results on the first series of 57 consecutive patients treated with the CMS Accuprope System. This was the first high technology apparatus used in the recent past. Cryoablation of the prostate was achieved using up to 5 probes of 3mm of diameter that generated a tailored ice-ball. This liquid-nitrogen driven machine has been for years the golden-standard in cryotechnology and still is a reference.

It is very important to recall and mention that these series represent the first and steeper part of a difficult learning curve.

We always used free-hands technique without any grid or needle guide and no water injection in the Denonvilliers Fascia was used to prevent damage to the rectum and to permit a better freezing in the surrounding tissues outside the prostate gland.

The cryosurgical technique that we used in this period required exceptional skill to use properly multiple probes (4-5), urethral warming, thermocouples monitoring at bases, apex and external sphincter, during the double freeze-thaw cycle.

Indications for cryosurgery were cancer of the prostate stages T2/T4 that were not treatable by open surgery because of previous surgery or radiotherapy, age, patient conditions, local advanced stage, high PSA or Gleason, or patient's fully informed choice.

With this technique it was possible to obtain the cancer-killing temperatures lower than - 40°C in many cases but not in all. The difficulty to balance the effectiveness of freezing with the careful attention to avoid damage to the

# Meeting Report

Fundamental aspects, as well as clinical applications of cryobiology were presented.

The introductory lecture on the *Biological effects of low temperature* by Mr M.O.Maiwand, was followed by 10 lectures.

The clinical applications of cryosurgery were discussed.

Dr N. Korpan spoke about the place of *Cryosurgery in anticancer treatment*. Three clinical studies concerning the treatment of prostate cancer were reported.

*Prostate cryoablation for high risk prostate cancer: results after 161 cases in two different centers*, was presented by Dr F. Lugnani.

*Cryosurgery and radiofrequency delivery to the anal canal and lower rectum*, by Dr A. Delbello.

*Liver and central nervous system metastatic lesions treated by cryoablation* was the subject of Prof. Zoras's lecture.

The last clinical report was presented by Mr M.O.Maiwand: *Direct pulmonary cryosurgery in the treatment of in-operable carcinoma of the lung*.

Alternative tools were also discussed: Dr C. D'Hont talked about a new technology in the treatment of prostate cancer in *High intensity focused ultrasound: minimal invasive transrectal treatment for localized prostate cancer*.

Three lectures were dedicated to combined treatments: cryo-radiotherapy or cryo-chemotherapy.

Dr I.N.Pustynskiy demonstrated the benefit to combine cryotherapy and radiotherapy, firstly by presenting clinical data *Cryo-radiotherapy of locally-advanced forms of skin cancer of the head* and then by an experimental *in vitro* study *Survival of cultured human tumour cells exposed to cryo-radiation treatment*.



# Meeting Report



## CRYOSURGERY IN THE TREATMENT OF CANCER

26<sup>th</sup> October 2004

7<sup>th</sup> International Conference of Anticancer Research, Corfu, Greece

Dr Valérie Forest, Faculté de Médecine Jacques Lisfranc, France



The 7<sup>th</sup> International Conference of Anticancer Research (25-30 October 2004) took place in Corfu, the northerly island of Greece, in the Ionian Sea off the coast of Albania.

All sessions of the conference were held at the Hotel Chandris in Dassia Bay. Organised by Dr J. Delinassios, Director of the International Institute of Anticancer Research, this meeting attracted a large number of participants.

Recent advances in both broad and specialised areas of experimental and clinical cancer research were discussed. All abstracts have been published in a special issue of Anticancer Research: Volume 24, No 4D, 2004.

There were 60 sessions covering numerous fields such as New Anticancer Agents, Radiotherapy/radio-pharmaceuticals, Diagnosis and Prognosis, Complementary and Alternative Medicine in Cancer, Oncogenes, Tumour Suppressor Genes, Growth factors, Signal Transduction, Ageing and Cancer, Vitamin D and Cancer, Immunotherapy, Invasion and Metastasis, Apoptosis, Molecular Biology of Cancer, Experimental Chemotherapy, Clinical Chemotherapy, Interaction between Stroma and Tumour, Cancer Genomics, Predictive and Preventive Oncology, Angiogenesis, Carcinogenesis, Phytochemicals in Cancer (prevention and treatment), Multidrug and Drug Resistance.

The special symposium of the I.S.C. titled "*Cryosurgery in the treatment of cancer*" was held on Tuesday, 26<sup>th</sup> October, with Dr F.Lugnani and Prof. N.Korpan as co-chairmen.

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rectum and sphincter was the biggest issue that prevented in many cases obtaining good and homogeneous cold in the full gland. This is due to the fact that the  $-40^{\circ}$  isotherm lies somewhere around 8 mm inside the ice-ball external limit and this distance is seldom present in the normal anatomy between prostate and rectum.

Furthermore, the liquid nitrogen ice-ball produced by the CMS Accuprobe has a quite long inertia that makes difficult to stop the freezing process in the best and safest moment. Freezing maintained time was more than 7 minutes with an average of 10 minutes.

## Results

All the 57 patients treated are living into our regional area and this permitted us to get data from all of them and therefore no one was lost at follow-up.

The 57 patients (average age 69.85 range 58/82) were followed up to 135 months with an average period of observation of 92.4 months; 24 patients out of the 57 had biochemical progression. Of these 24 patients 12 had histological proven local recurrence of cancer.

If the cohort of patient is divided in 3 groups according to a risk criteria (low risk: T2a-b, psa up to 10, Gleason up to 6; intermediate group: one of the following T2c or higher, psa 10,1 or higher, Gleason 7 or higher; high risk group: 2 or all the 3 of the intermediate group conditions) we can observe:

- 1) 29 cases belonged to the high risk group and 16 of them progressed and 7 of these 16 had pos. biopsies.
- 2) 16 patients belonged to the intermediate group and 7 of them progressed and 4 of the latter were biopsy proven failure.
- 3) Only 1 of the 12 low risk group failed and also had a biopsy proven persistence of his cancer. It is likely that this patient failed for a surgical under treatment motivated by the excessive caution of the fear of causing complications and the subsequent "gentle" freeze used in this particular 82 years old patient.
- 4) 21 patients died during the observation period, cause specific mortality interested 5 of them and all these 5 belonged to the high risk group (2 of these 5 where also biopsy positive), of the remaining 16 patients who died for other cause 5 were also in a progressive phase. During the given period of observation no patients of low risk and intermediate risk groups died because of the disease.

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I.S.C. Symposium, Corfu, October 2004

## Targeted Cryoablation of the Prostate

With regards to PSA and Gleason score, clinical stage results were the following:

PSA				STAGE			
TOT	NO PR	PROGR	BIO +	TOT	NO PR	PROGR	BIO +
18,9	12,5	27,7	14,13	19 T2a	15 T2a	4 T2a	1 T2a
9,2	7	12	9,2	8 T2b	6 T2b	2 T2b	2 T2b
GLEASON				19 T3a	10 T3a	9 T3a	5 T3a
TOT	NO PR	PROGR	BIO +	6 T3b	2 T3b	4 T3b	3 T3b
3 = 1	3 = 1	3 = 0	3 = 0	5 T4		5 T4	1 T4
4 = 6	4 = 6	4 = 0	4 = 0				
5 = 8	5 = 5	5 = 3	5 = 3				
6 = 19	6 = 11	6 = 8	6 = 4				
7 = 12	7 = 8	7 = 4	7 = 3				
8 = 9	8 = 2	8 = 7	8 = 1				
9 = 2	9 = 0	9 = 2	9 = 1				

## Discussion and Conclusions

Achieving temperatures lower than -40° outside the prostate gland causes the destruction of all neoplastic cells. Recent technical and technological improvements have modified prostate cryoablation making it easier, safer and more effective also in high-risk patients and also for the less experienced cryosurgeons. But the results obtained in this first series raises the question on the efficacy that could have nowadays the same technology if used in conjunction with the matured experience and the Onik's tip of injecting saline solution in the Denonvilliers Fascia.

All the above considerations make also perfectly clear the reasons why using the old transurethral techniques the 60's and 70's cryosurgery pioneers had such a bad time in controlling the limit of the ice-ball at the level of the bladder neck, sphincter and rectum. In the same time it becomes comprehensible why also in more recent years it was difficult to control the highly effective ice-balls generated by the first high-technology apparatus. Also, it is clear that difficulties exist to teach and train new users on the appropriate probe placement strategy in order to achieve good results with few complications without the help of the saline injection and with only 5 cryoprobes at disposal. These were the reasons for the abandonment of this first technology and not its failure in terms of neoplastic control that, on the contrary, was almost always excellent as our results demonstrate!

# Meeting Report 10

was on their approach to treating viral warts and the practicalities of using cryosurgery spray guns. Very thought provoking were the differing approaches to cryosurgery for warts, sometimes covered by local anaesthetics and sometimes not. An important discussion point was, that as long as we counsel our patients well and fully, they do tolerate the side-effects of cryosurgery which temporarily can be very inflammatory and alarming to them.

Dr Buckley then gave a talk on more advanced cryosurgery with very practical tips on the way he manages patients in his clinics, emphasising the importance of certainty of diagnosis before cryosurgery, to ensure its successful and safe use. Advice sheets for doctors, nurses and patients were included in the course booklet to help anyone setting up cryosurgery in their practice. Finally, a panel discussion answered several of the outstanding questions from the audience and a short presentation by Mr Maiwand on the forthcoming conference of the International Society of Cryosurgery in Crete (Greece), 12-14 May 2005.

Special thanks goes towards the excellent organisation of this Study Day by Dr Jackson (Chairman) and the International Society of Cryosurgery based at Harefield Hospital.

A thoroughly practical and interesting day! Thank you!



# Meeting Report



## ASSOCIATION OF BRITISH AND IRISH CRYOSURGERY

Study Day on Skin Cryosurgery, 1<sup>st</sup> October 2004, Crewe, U.K.

Dr Lucy Black, Leighton Hospital, Crewe, U.K.



This was a fabulous day, set in the magnificent location of Crewe Hall. This is a splendid Victorian Manor, rebuilt after burning down in 1866 and owned by Ranulph Crewe, who was the son of a merchant from Nantwich. The galleried entrance hall leads into a beautiful tiny chapel with carvings and paintings that outshine many national landmarks. The lectures and workshops were held in equally grand and beautiful rooms such as the Long Gallery and the Kane & Abel Room whilst lunch and refreshments were served in the Great Library.

The talks and demonstrations managed to 'hit the spot' for a range of health care professionals. Mr Omar Maiwand (President of the International Society of Cryosurgery) from Harefield Hospital started off by showing us the range of applications for cryosurgery in skin cancers and also in other tumours, such as prostate, kidney, liver and bone. Particularly interesting was how he uses it to reduce the tumour mass in lung cancers to alleviate serious and debilitating symptoms. Dr Arthur Jackson, who had organised the day, then took us through cryosurgery for warts and suitable benign lesions to pre-malignant skin lesions. This was a very practical approach to dealing with a range of lesions backed up by detailed notes and pictures in the course booklet. Nurse-led cryosurgery clinics were the subject taken by Dr Johnny Loughnane - patient and lesion selection being important with suggested nurse protocols given in the handout.

The two workshops before and after lunch were very useful. Dr Jackson demonstrated cryosurgery for basal cell carcinomas on two patients and gave a running commentary on his approach to malignant cryosurgery with his clinic nurse in attendance. The other, given by Dr Buckley and Dr Loughnane

# Abstracts

I.S.C. Symposium, Corfu, October 2004

## High Intensity Focused Ultrasound : Minimal Invasive Transrectal Treatment for Localized Prostate Cancer. 3 years - 270 patients

C.D'Hont, M.Lantsoght, P.Van Erps

A Z Middelheim - Antwerp Belgium

HIFU delivers focused ultrasound energy via a transrectal U.S. probe - under transrectal ultrasound guidance - causing rapid thermal necrosis of tissue within the target area without damaging the surrounding tissue. HIFU is the least invasive curative treatment alternative to radical prostatectomy.

### Objectives

To present the preliminary clinical results on our first 270 biopsy proven T1-2 (3a) NOM0 prostate cancer patients, treated with transrectal High Intensity Focused Ultrasound (HIFU). PSA outcome and co-morbidity are analysed per stage and per risk group.

### Method

270 patients with biopsy proven localized prostate cancer T1-T3a have been treated with HIFU over a period of 36 months, using the Ablatherm HIFU unit (Edap -Technomed). The clinical outcome of the first 270 patients with a mean follow-up of 20 months (3 - 36) have been analysed.

### Results

95% of patients had PSA < 1 ng/ml within 3 months after treatment ; 82% of T1-2 patients had a nadir PSA < 0.5 ng/ml at 1 month upto > 24 months after single HIFU treatment. Per risk group we noticed that mean PSA stayed < 0.5 ng/ml during the entire follow-up period for the low risk group (100% PSA < 1 ng/ml), mPSA < 1 ng/ml for the Intermediate risk group (> 90% PSA < 1 ng/ml) and mPSA < 1.5 ng/ml for the High risk group (> 80% PSAT3a group more than 75% of patients kept a PSA < 1 ng/ml. No major < 1 ng/ml). In the complications were seen, urethral or bladder-neck stricture or sloughing was seen in 8% of patients. Temporary stress I-II / urge incontinence was seen in 14% of patients, recovering within 3 months in 98% of them. Potency preservation was possible in > 75% of patients who had a unilateral nerve-sparing treatment in all risk groups, > 30% in the completely treated patients and 8% in the T3 group (extension of the treatment well beyond the capsula)

# Abstracts

I.S.C. Symposium, Corfu, October 2004

*High Intensity Focused Ultrasound*

## Conclusion

HIFU proves to be a safe, minimal invasive and possibly curative treatment option for patients with localized prostate cancer. Re-treatment after EBRT-failure remains a safe option. Continued monitoring of follow-up studies is mandatory.

## Place of Cryosurgery in Anticancer Concept Treatment

Nikolai Korpan, Gerhard Hochwarter

*Vienna International Institute for Cryosurgery, Billrothstrasse 78, A-1190 Vienna, Austria*

## Background

A new way of thinking must determine the future of cancer research and treatment. We need new approaches to new discoveries and new therapies. Modern cryosurgery, which is a particularly sparing surgical technique, is today internationally respected and gaining ground. Long years of practical experience and numerous internationally published papers have provided evidence of the good results obtained with this method. For the first time the present study reports the effect of low temperature applications on the parenchymal tissue and its cryosurgical response in animal experiments such as the long term follow-up in cancer patients with the liver cancer, pancreas carcinoma, anal carcinoma, breast cancer, melanoma.

## Objective

The objective of this multi-purposeful and several years theoretical, experimental and clinical study was both to determine the applicability of modern cryogenic surgery in the anticancer treating concept and to elaborate a concept of technical requirements for the new high-efficiency universal cryosurgical technology.

## Material and Method

A total of 38 healthy mongrel dogs of both sexes, weighing between 12.1 and 14.5 kg were included in this experimental study. The experimental group consisted of 28 dogs, divided into four groups of seven each. In group A the pancreatic parenchyma was frozen to -40°C; in group B to -80°C; in group C to -120°C, and in group D to -196°C. At each temperature the cryoprobes were in contact with the animal pancreas for nine months. The remaining ten dogs

# Meeting Report

apoptosis by adding inductors. There are multiple ways to see death by cold: freezing kills if temperature is low enough; no single critical temperature equals a defined "dose"; time appears to be less critical. What seems to work best is chemotherapy applied first, followed by cryotherapy.

To conclude this meeting, the Mixed Session, chaired by Dr R.Jean-Francois and Mr M.O.Maiwand, Dr. K.Ripley's *Linear tissue ablation using articulating cryosurgical probe*, showed in a porcine shoulder muscle preparation, the advantages of a new cryosurgical probe with steerable curve that can both articulate and hold its shape - a useful characteristic when working with complex anatomical areas- with adequate depth of ablation.

Dr M.Dubuc presented *Combined simultaneous cryothermal and radio-frequency energy creates deeper ablation lesions*, which showed the benefits of combining cryo and radiofrequency since deeper lesions are created by this combination which is clinically useful for ablation of deeply located arrhythmogenic substrate.

In Dr. F.Deprez's *Catheter cryoablation of tachyarrhythmias in children and adolescents: The Montreal experience*, the use of catheter ablation using cryoeffect has been studied in adults for ablation of various arrhythmias specially AVNRT. This experience shows the safety and effectiveness in children and adolescents.



Dr M.Peralta from Chile ended the scientific programme with his presentation *Tracheobronchial stenosis due to external compression treated with cryotherapy and metallic stent*. This 50-patient experience shows the results of treatment with tracheobronchial cryotherapy primary lung cancer or endobronchial metastasis (for recanalization and palliation) combined with autoexpandable metallic stent to reduce the external tracheobronchial compression.

The main meeting of the International Society of Cryosurgery will be held during May in Crete, under the guidance of Prof. Odysseas Zoras, Faculty of Medicine, University of Crete and of course, the ISC President, Omar Maiwand.



# Meeting Report

*Cryosurgery in the Americas*



In Session 7, Orthopaedy and Basic Sciences, chaired by Dr C.Jean-Francois and Dr P.Le Pivert, *Cryosurgical management of 290 benign and malignant bone tumours: A 28-year experience* by Dr R.Henshaw showed a retrospective review of 290 patients that had undergone cryosurgery as a physical adjuvant to reduce the risk of locally recurrent disease following surgical excision of 170 benign tumours and 120 malignant bone tumours. The results show that cryosurgery as a powerful adjuvant therapy - by reducing the risk of local recurrence - permits intralesional treatment, maximises oncologic and functional outcomes. Risk of pathologic fracture has been reduced by the evolution of reconstructive techniques. In *Adjuvant cryosurgery using argon gas cryoprobes in the treatment of bone tumours: indications, techniques and clinical results*, traditional cryosurgery, with direct pour of liquid nitrogen, is substituted by a close cryoprobe using argon, reducing damage to adjacent structures. In aggressive tumours of bone, two freeze-thaw cycles thermo-coupled monitored, using saline as an effective thermoconductor, was followed by reconstruction of the defect with methylmethacrylate.

In *Bone necrosis by closed-circuit liquid nitrogen probes - a canine retrieval study*, Dr Hershaw had designed a study to determine the extent of tumour necrosis achieved using different sized cryoprobes applied to bone in a canine in-vivo model. Saline filled the bone cavity and close circuit LN probes, a single freeze-thaw cycle with  $-40^{\circ}\text{C}$  produced histologically confirmed cellular necrosis with no complications.

In *IMRI guided spine/bone cryosurgery*, Dr P.Sewell showed the application of cryotherapy in painful bone tumours for palliation. 18 patients with 28 tumours, with 8 vertebral, 5 in extremities, 4 in the scapula, 6 in sacrum. Among these, 17 patients had general anaesthesia, 3 were sedated. There was a considerable reduction in pain with an improvement in quality of life. None of the tumours grew back.



In *Molecular basis of improved cryosurgery*, Dr J. Baust talked about the different rates of cooling for different cells. Not all tissues experience the same changes when frozen. Cryo, like other methods, induces apoptosis of the cells. Adding 5FU or cisplatin prior to freezing exposure somehow "pushes" the cell to go into apoptosis. The system can then be driven towards

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were used as controls. A disc probe 15 mm in diameter was placed on the liver and pancreas. For cryoexposure a temperature range of  $-40^{\circ}\text{C}$ ,  $-80^{\circ}\text{C}$ ,  $-120^{\circ}\text{C}$ , and  $-196^{\circ}\text{C}$  in contact with the liver and pancreas parenchyma was selected by a temperature stabilization of 1%. A 3-minute freeze was used for each freeze-thaw cycle; this was followed by complete thawing of the liver and pancreas. Each cryolesion was observed for ten minutes after thawing. The freeze-thaw cycle was monitored by intraoperative ultrasound before, during and after cryosurgery. Liquid nitrogen was applied by Cryoelectronic, a cryosurgical device of our own, suitable for universal application. Liquid nitrogen was circulated through the probe at  $-196^{\circ}\text{C}$ . In the clinical study the following cancer patients were treated by means of modern cryosurgical approach: anal cancer (n=17), pancreas carcinoma (n=16), breast cancer (n=15), liver metastases (n=14), melanoma (n=12). Cryosurgery was performed in all cancer patients by means of probes of roughly disk design 10mm, 20mm, 35mm, and 55mm. The probes were refrigerated by liquid nitrogen. A temperature from  $-170^{\circ}\text{C}$  to  $-180^{\circ}\text{C}$  was used.

## Results

A unique phenomenon was observed and discovered in living substance, namely the phenomenon of a so-called 'lunar eclipse'. The tumour was cryoexcised significantly in all patients with anal carcinoma (<100%). The follow-up period in patients with anal carcinoma ranged from 7 months to 5 years and in control subjects from 5.3 months to 5 years. The 3-year and 5-year survival rate were higher after cryosurgical procedure (100%) than in control group (46%) and (32%) after conventional surgery accordingly. The tumour was reduced significantly (>90% <97%) in all patients with pancreas carcinoma and in all patients with nonresectable liver metastases treated by treated by cryosurgery. In 1 case with breast cancer the local recurrence was observed. All patients received systemic therapy. The 3- and 5-year survival rate was higher after cryosurgery in melanoma patients (100%) than in control group (46%) significantly.

## Conclusion

The phenomenon of the 'lunar eclipse' suggests that cryosurgery is the first surgical technique to use angiogenesis in the treatment of cancer. Modern cryosurgery can be used safely and efficiently by mostly patients with different kinds of cancer and it consists of necessary component in the anticancer treating concept.

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## Cryosurgery and Radio-Frequency delivery to the Anal Canal and Lower Rectum: A Safe Palliative Treatment for Advanced Cancer

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The aim of cryosurgery in advanced neoplasia of rectum and anus is to reduce symptoms associated with the disease and avoiding or delaying the need for a colostomy.

As it is a surgical approach with few complications, it has been employed for patients relapsing after a low anterior resection and/or unsuitable for surgery, due to both tumour pathological status and patients conditions, or presenting distal spread metastases.

In our surgical department, we followed 49 patients with an average age of 80.8 years, 20 males and 29 females. 33 patients were affected by adenocarcinoma, 13 by spinocellular carcinoma, 2 by a cloacogenic cancer and 1 by a melanoma. Because of their general conditions and elevated ASA score, no patient was treated under general anaesthesia thanks to cryosurgery which can be applied in outpatients and can be repeated frequently.

Symptoms presented by patients before treatment were tenesmus in 35 cases, bleeding or muchorrea in 45 cases, discharge in 38 and perineal pain in 30.

Cryosurgery can control haemorrhage because of tissue necrosis and deep thrombosis of tumoural vessels.

Each session of cryosurgery (1 to 5 per patient) was performed with a time interval of 30-90 days. We also delivered radiofrequency in association with cryosurgical approach to 4 patients. All patients were checked every 4 months. Symptoms improved within 3 months: 71.5% of patients for tenesmus, 87% for bleeding or muchorrea, 47.5% for discharge and 47% for perineal pain.

Morbidity rates were acceptable: we detected only 2 cases of urinary retention, 4 cases of pain in the first 24 hours and 1 case of gas incontinence. Moreover there were no major complications such as abscess, fistulas, bowel perforations and stenosis.

Therefore, cryosurgery, especially in association with radio-frequency, is a valid choice to treat advanced cancer of anus and lower rectum.

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*Dogs.* In the first presentation, adenomas and adenocarcinomas are treated with cryosurgery, this method being more function-preserving. It also allows treatment of multiple lesions that could not otherwise be treated, if conventional surgical techniques were to be used. In the second talk on perianal fistula, this well-known problem in dogs with multiple possible origins is dealt with a combination of radiofrequency, cryosurgery and medical treatment with excellent results.

The Gynaecology and Cardiology Session was chaired by Dr E.Turjansky and Dr A.Gage. Dr Juana Elida Mauro showed in *Cryosurgery plus radiofrequency: a new strategy in the treatment of vulvar cancer*, her work on 10 patients with vulvar cancer stage I-IV treated with a combination of radiofrequency - to debulk the tumoural mass - followed by cryosurgery, with a 5<sup>1</sup>/<sub>2</sub> year follow-up. Good results were accompanied by her own suggestion of further randomized research. In *Cryosurgery with liquid nitrogen: an option for vulvar intraepithelial neoplasia treatment*, Dr. Mauro showed the possibility of using cryosurgery in these pathology, conventionally treated with mutilating surgery.



Dr P.Sewell's *IMRI guided uterine fibroid cryosurgery* showed the uses of percutaneous, trans or perivaginal applied probes to destroy uterine fibromas. This technique has the advantage of preserving fertility, in comparison to miomectomy, where less than 50% preserves this function. Under general anaesthesia, 14 patients were treated with 3 freeze-thaw cycles. Best results were obtained in single, large or moderate tumours.



In *Cryoablation in cardiology*, Dr M.Dubuc used this technique for AV modification, accessory AV connections, ventricular tachycardia or atrial fibrillation. Several advantages were observed: there is lower incidence of thrombus formation; there is adherence of the catheter to the tissue, which reduces possible damage to adjacent structures; cold is enough to abolish electrical activity, but not enough to damage the target tissue, it is reversible; it can be visualized with ultra-sound. Another use is in AV re-entry, Wolff-Parkinson-White Syndrome.

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In *DNA ploidy type does not affect prognosis or targeted cryosurgical ablation of prostate cancer*, based on the observation of numerous studies that show that non-diploid tumour DNA configuration is an indicator of worse treatment response and prognosis in patients with conventional treatment when compared with diploid configuration tumours, a retrospective 474 patient analysis shows that the efficacy of cryoablation is not dependent on ploidy type. Patients with non-diploid tumours now have a treatment option that is both efficacious and safe.



Dr J. Lyne presented *Urological application for cryoablation*. He talked about the feasibility of percutaneous renal cryosurgery and its indication in peripheral tumours through hand-assisted cryoablation.

Dr P. Le Pivert presented preliminary experimental studies in *Micro-encapsulated echo-guided interstitial chemotherapy combined with cryosurgery for the treatment of prostate cancer*. The study tried to determine whether a combination of intra-tumour microencapsulated 5-Fluoracil and partial cryoablation increases tumour destruction compared with cryoablation alone in a xenogenic tumour model. The ice ball kill ratio was different in 5-FU treated tumours. Growth inhibition was greater in combined therapy. Encapsulation of different drugs leaves infinite possibilities of combination treatments.



The Surgery Session was chaired by Dr P. Sewell who began with his lecture on *IMRI guided renal cell carcinoma cryosurgery*. He presented a 5½ year study of 114 patients with 137 kidney tumours. The candidates had solitary kidney / bilateral renal masses / refused resection / tumour of less than 7 cms / located exophytically, parenchymally, hilar or mixed. 112 received general anaesthesia and with IMRI guidance and argon/helium gas system, cryosurgery was done. Among the results: 10/104 had residual disease, the most difficult cases were those where the tumoural mass was central (as it occurs with any surgical alternative). It is an excellent nephron sparing treatment. Overall survival was 86%, but when adjusted to exclude unrelated death cause was 97.4%.

Dr R. Lagarde showed his work in *Radiofrequency and cryosurgery in the treatment of perianal adenoma and adenocarcinoma in dogs* and *Cryosurgery and radiofrequency: contribution in the treatment of perianal fistulae in*

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Radio-frequency energy delivery can be safely applied and increases the possibility of debulking the exophytic tumour without bleeding.

Quality of life is improved for all patients who cannot undergo surgical treatment and colostomy can be avoided or delayed and the combined treatment gives more local control of the disease.

## Cryo-radiotherapy of Locally-advanced forms of Skin Cancer of the Head

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### Purpose

To create the method of cryo-radiotherapy which allows to improve the results of treatment of locally-advanced forms of skin cancer of the head and to evaluate the safety and efficiency of this method.

### Materials and Methods

Since 1988, 52 patients with locally-advanced forms (T3-T4 and recurrent tumours) of basal cell carcinoma (37) and squamous cell carcinoma (15) of the skin of the head were treated with cryo-radiotherapy. In most cases (47) tumours were located on the face. The method of treatment includes local freezing of the tumour. A steam of liquid nitrogen is used to achieve temperatures around -5°C near the margins of the tumour. Local or regional anaesthesia was not usually required because the method was not associated with intense pain. This procedure was performed every day (5 days a week) a few minutes before radiotherapy. The total dose of irradiation was 60-65 Gy.

### Results

Follow-up took place between 1 - 10 years. 47 (90.4%) patients had their tumours cured after cryo-radiotherapy without being surgically operated on. In cases where complete regression of the tumour didn't occur as a result of cryo-radiotherapy, surgical operations were performed. Recurrence disease was detected in 3 cases. No serious complications were noted during and after cryo-radiotherapy. All patients with complete regression of the tumour after cryo-radiotherapy have good aesthetic and functional results.



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*Cryo-radiotherapy of locally-advanced forms of skin cancer of the head*

## Conclusion

The method of cryo-radiotherapy allows to achieve a complete regression of the tumour in cases of advanced forms of basal cell carcinoma and squamous cell carcinoma of the head and to save local tissue with good aesthetic and functional results.

## Survival of the Cultured Human Tumour Cells exposed to Cryo-radiation Treatment

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Cryo-radiotherapy is an effective method of treatment of skin cancers of the head. Despite extensive studies of the mechanisms of cell death and survival after irradiation and freezing procedures, taken separately, the independent research of mechanisms of cryo-radiation combination treatment is required.

This study was conducted in order to evaluate the influence of cryo-radiation treatment on viability of tumour cells cultured *in vitro*. For that, human tumour cells of HeLa line were subjected to sublethal freezing temperature (-15°C), thawed at 37°C for 30 minutes and irradiated with the dose of 5 Gy. Using clonogenic assay, we compared the surviving fraction of HeLa cells after cryo-radiation treatment, cryo- treatment and irradiation exposure with that of intact cells. It was revealed that cryo-radiation treatment decreased the fraction of clonogenic cells to 3.9±0.5% compared to intact cells. This value was 14 times lower than survival after cryo-treatment and 2.5 lower than survival of irradiated cells.

Additionally, a kinetic analysis of cell viability was carried out using trypan blue dye exclusion. Both cryo-radiation combination treatment and cryo-treatment alone reduced HeLa cells viability to approximately 60-70%. In contrast, the irradiated cells were not significantly differed in their viability from the intact cells. It was observed, that after freezing, most of the lethally injured cells died in first 1-2h post-freeze-thaw, then the fraction of viable cells increased slightly. We examined the survival of cells in 3-4h after exposure of cells monolayer to different modes of tested treatments. In these experiments the surviving fraction of HeLa cells after cryo-radiation treatment was 6.0±0.8%,

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For the Dermatology session, chaired by Dr G.Graham, the marked absence was felt by all for Dr Castro-Ron from Venezuela, who had died a few days earlier. A short and heartfelt homage was given in his honour. *Palliative treatment of skin tumours* by Dr P.Pasquali (pictured right), showed the uses of cryotherapy in destroying large tumoural masses, either from primary carcinomas of the skin or secondary to metastasis. The treatment was applied in patients where no other options were available and its main objective was to improve quality of life.



Dr E.Turjansky showed in *Tumours of the orbit treated by surgery and cryosurgery*, the benefits of treating tumours of this location in association with surgery, as a way of eliminating and controlling the tumours while preserving peripheral anatomical structures. In his *Hand dermoabrasion and liquid nitrogen*, local abrasion with sand paper was followed by freezing of the entire face for 8-12 seconds. The author suggests that this combination produces improvement in collagen with simultaneous removal of keratosis, lentigos and wrinkles.



Dr G.Graham's *Combining cryosurgery with other treatments* discussed the different uses of cryotherapy in dermatology, from benign lesions to malignant skin tumours. Cure rates, relation to freezing times and cosmetic results were all discussed as well as the combination with diverse treatments, as shown in the literature.



In the Urology Session, Dr D.Bahn presented *Targeted cryoablation of the prostate (TCAP): 7-year outcomes in the primary treatment of prostate cancer*. In this retrospective study, a series of 590 patients who underwent TCAP as primary therapy with curative intent for localized or locally advanced prostate cancer, with 5.43 year follow up, showed that the rates of morbidity were modest and no serious complications were observed. TCAP was shown to equal and surpass the outcome data of other conventional treatment modalities. In *Salvage cryosurgery for recurrent prostate cancer after radiation therapy: a 7-year follow-up*, patients with recurrent disease, which account for up to 30% of patients who receive radiation therapy, while salvage radical prostatectomy for radio resistant disease is associated with high morbidity, cryosurgery stands as a promising form of treatment.



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Mr Maiwand's *The use of liquid nitrogen in the treatment of lung tumours* showed the experience of direct cryosurgery of lung carcinoma through a postero-lateral thoracotomy or via video assisted thoracoscopic surgery (VATS). When considering that over 80% of lung carcinomas are inoperable at time of diagnosis and radiotherapy is of limited benefit as it causes parenchymal destruction, then cryosurgery appears as a beneficial and potentially curative alternative for inoperable peripheral lung tumours and secondary lung tumours.

In *Management of tracheobronchial tumours with cryotherapy*, Dr Peralta showed, by means of symptom improvement, lung function test, blood gases and saturometry, the benefits of cryotherapy in the management of malignant or benign tracheobronchial disease. In his work, external compression of the tracheobronchial tree could be resolved with autoexpandable metallic stents in association with immediate cryotherapy to obtain a rapid airway patency.

The host, Dr R.Jean-Francois brought in the following question in *Cryotherapy and radiotherapy association in NSCLC* - is endobronchial cryotherapy before radiotherapy in NSCLC beneficial only for its deobstructing effects or is there more to it that can meet the eye? In a randomized 62-patient study, no significant results were obtained, although two conclusions could be made: Cryotherapy has no harmful side effects and it is probably beneficial before radiotherapy due to the apoptotic effect on cells.



*Biological effects of cryotherapy in a non-small-cell lung cancer xenografted into SCID mice*, Dr V.Forest showed - using a xenograft system - where ADC cells were injected subcutaneously into SCID mice - the effect of cryotherapy vs. chemotherapy compared to a controlled group with no treatment, with time related evaluations.

The results showed that cells treated with cryotherapy showed time related cell death by necrosis and apoptosis, while chemotherapy induced apoptosis in a fewer number of cells in a non-time-dependent manner. These differences in chronology and efficiency may suggest potential benefit in combining treatments.

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but still significantly lower than that of irradiated cells.

The data obtained demonstrate that the cryo-radiation combination treatment resulted in an enhanced loss of viability of cultured tumour cells compared to that for either treatment alone.

## **Cryotherapy and Chemotherapy performed alone or in combination in the treatment of a Non-Small-Cell Lung Cancer xenografted into SCID mice**

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Lung cancers are among the most frequent tumours. They are mainly treated by surgery or by chemotherapy, but for the most advanced stages a local cryotherapy, a method based on the cytotoxic effects of low temperatures, can be proposed as a palliative option for bronchial clearance. Cryotherapy can be performed alone or in combination with other therapeutics.

The aims of this study were : 1) to investigate in vivo the biological effects of cryotherapy and chemotherapy performed alone or in combination in a model of human non-small-cell lung cancer xenografted into immunodeficient mice, 2) to determine if this combination offered a therapeutic benefit and if so, 3) to determine by which mechanism.

Cells from the A549 cell line (adenocarcinoma) were injected subcutaneously into SCID mice. Mice were treated either by cryotherapy (3 cycles, nitrous oxide cryoprobe) or by chemotherapy (intravenous injection of Navelbine®, 4.8 mg/kg) or by the combination cryochemotherapy. Tumour nodes were excised at variable time points and studied morphologically. The induction of apoptosis was analysed by immunohistochemical staining of cleaved caspase-3 and by TUNEL. Intratumoural Navelbine concentration was assessed by HPLC.

Results showed very different effects of the two therapeutic modalities: cryotherapy was found to be an efficient technique to induce cell death either by necrosis or by apoptosis. Necrosis was found near the cryoprobe impact and was maximal after 2 hours and 4 days. Around this central necrotic area, apoptotic cells were found. Apoptosis was maximal after 8 hours (47%). Chemotherapy induced apoptosis in a lower number of cells (about 20%) and this effect was not time-dependent. The induction of apoptosis was enhanced in tumours treated by cryochemotherapy compared to tumours treated by

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*Cryotherapy and Chemotherapy performed alone or in combination in the treatment of a Non-Small-Cell Lung Cancer xenografted into SCID mice*

a single method. This effect was more noteworthy at early times of analysis (58% of apoptotic cells after 2 hours).

Navelbine concentration was found to be more important in tumours treated by chemotherapy alone than in tumours treated by cryochemotherapy, suggesting that the benefit of cryochemotherapy previously observed was not a concentration-dependent phenomenon, at least in our model.

## Keywords

Non-small-cell lung cancers, Xenograft, SCID mice, Cryotherapy, Chemotherapy, Apoptosis, Necrosis, Mitosis.

## Prostate Cryoablation for High Risk Prostate Cancer: Results after 161 cases in two different Centres

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## Introduction

Cryosurgery technique can be considered as a minimally invasive option in selected patients with localized (T2) or locally advanced (T3) prostate cancer.

We report the experience of 2 centres assessing cancer control and morbidity after medium term follow-up in selected patients who were excluded from standard therapy (surgery or radiation) due to specific contra-indications (old age, high-risk for open surgery, co-morbidities).

## Methods

161 patients were consecutively treated with cryosurgery and selected in two hospitals (AH= Ancona 70 pts, CH= Civitanova M. 91 pts) according to the guidelines of the European Study Group of Urologic Cryosurgeons. Clinical parameters were: mean age 71.6 yrs (SD±5), clinical tumour stage was: 2 T1b, 6 T1c, 35 T2a, 70 T2b-c, 38 T3a, and 8 T3b. Biopsy grading of prostate cancer identified 93 (59%) cases with high-grade disease (Gleason score ≥7) and 68 cases without (Gleason score 6 or less). Baseline serum PSA was 13.0 ng/ml ±10 (mean, ±SD, min 2.2 - max 60). 3 out of 161 had salvage cryosurgery for local recurrence after definitive radiotherapy. 3 out of 161

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prevent destruction in adjacent areas, an advantageous effect for fibrocollagenous matrix involved in the healing process.

Dr W.Berger showed through videos *Aggressive ice crystals during the invasion of small organs via paracellular pathways*. During freezing, the gland becomes encapsulated by crystals which later bump forcefully against the cell membrane and finally grow in, via paracellular pathways. Finally, intracellular ice formation develops in the cytoplasm and later in the nucleus.



In the line of maximizing cryoinjury in a selected target region while minimizing damage of healthy surrounding tissues, was born the idea of *Computerised planning of cryosurgery using cryoprobes and cryoheaters*, presented by Dr Y. Rabin. Since positioning of the cryoprobe is currently based purely on experience and soft rules of the thumb, computerised planning of placement in association with cryoheaters to limit collateral cryoinjury around the target lesion may minimise the frequency of cryotherapy provided to a patient and collateral tissue damage.

In the search for optimising cryoprobes for hepatic cryosurgery, Dr Berger presented *Technical aspects of a computer-aided placement of cryoprobes for hepatic cryosurgery*. A computer program was developed that allowed to display a digitalized ultrasound image of the tumour for later positioning of the cryoprobes.



The Pulmonary Session was chaired by Dr. P. Mathur and Dr M.Peralta. *Cryotherapy for endobronchial disorders* by Dr Mathur took us through the cryogens available for a pulmonologist, the cryomachine and its probes, and the different uses. Prime candidates for this technique are polypoid lesion with a large endobronchial component. With a flexible cryoprobe, the tip is directly applied to the tumour area, one to three one-minute freeze cycles applied with devitalized or necrotic tissue removed during or at completion of bronchoscopy. The results, judged in several different ways, included improvement based on subjective patient manifestations as well as clinical, radiological, respiratory function and histological appearance. Mr Maiwand's experience, the French experience and his own were discussed. Of extreme interest was the use in benign conditions such as the removal of foreign bodies or mucous plugs.



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## CRYOSURGERY IN THE AMERICAS 25-26 September 2004, Montreal, Canada



Dr Paola Pasquali, Instituto de Oncologia Luis Razetti, Venezuela



With Dr Rita Jean-Francois as the Chairlady, beautiful Montreal was the inviting city for the I.S.C.'s regional meeting, "Cryosurgery in the Americas". The Welcome Dinner was held on Friday, 24th September at The Notre Dame Hospital, the congress site. All the speakers, mainly from North & South America and Canada were warmly welcomed.

The first session was dedicated to Basic sciences, with Mr M.O.Maiwand and Dr A.Gage as Chairmen. *Basic science of cryobiology*, by Mr Maiwand presented the required introductions to the biological effects of low temperatures, from its early/direct effects of freezing on the cell metabolism at around  $-10^{\circ}\text{C}$ , the extracellular ice crystal formation, the eventual hypertonicity of the intracellular fluid-cell solution effect at around  $-20^{\circ}\text{C}$ , to the lethal intra-cellular ice crystal formation. The delayed effects related to the vascular stasis are responsible for the rest of the local damage. His introduction to a concept that stayed in the air for days to come was on cryo-immunology of freezing and the evidence of apoptosis (gene regulated cell death). The motto: "use the lowest temperatures as rapidly as possible, thaw as slowly as you can with more than one freeze-thaw cycle" was a good introduction for all lectures that followed.



In *Selective cryotherapy*, Dr A.Gage, based on concepts that different cells have different sensitivities to low temperatures, showed, how by adjusting the freeze-thaw cycle to an appropriate program, the tissue response may be manipulated to achieve a selected goal. In this order, cancer cells are more resistant to freezing injury but can be turned more liable by adjunct therapy with drugs or irradiation, which will influence the fate of cells in an apoptotic state in the frozen volume. Warming techniques can, instead,

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underwent a second cryoablation for persistent disease. Out of 161 pts, 47% were  $>73$  yrs old, 39% had significant co-morbidity factors with surgery being a high-risk option (A.S.A. class 3), and 20% patients refused surgery or RT, 1.8% had TCT failure. All underwent preoperative neoadjuvant therapy for at least 3 months. Patients in AH underwent a short-term adjuvant medical treatment with LHRHa (1-3 months), while patients in CH a medium term adjuvant treatment (6 months).

Two cycles of freezing/heating were carried out according to the technique described by Bahn and Lee using urethral warmer device and Argon/Helium gas device (Endocare). 6 to 8 cryoprobes were used according gland volume. In all cases temperature monitoring using 3 up to 5 thermocouples was performed. Since 2000, Denonvillier Fascia infiltration with 60cc of saline solution has been performed.

Pre-operatively all patients were without distant metastases (N0 M0) (staged using abdominal CT or MRI, Chest X-ray, Bone scan, transrectal ultrasound). Only few patients with high PSA or advanced disease underwent preoperative laparoscopic pelvic lymph node dissection. All patients were evaluated during follow-up by serum PSA and testosterone every 3 months, DRE, transrectal ultrasound with power-Doppler. Echo-guided biopsies were scheduled at 6-12, 24, 36 months or anytime if serum PSA raised or became  $>1.0$  ng/ml. In each biopsy set, 6 up to 10 core specimen were collected. Clinical staging with CT and bone scan was performed yearly. Treatment failures were considered: only PSA failure if  $>1.0$  or PSA increasing over the time (ASTRO criteria) or cancer found in follow-up biopsies or discovering of distant metastases. In cases with raising PSA, negative staging and prostate biopsy, Positron Emission Tomography (PET-TC) was performed.

## Results

After a mean follow-up of 36 months (min. 6, max. 72), 1 patient was lost to follow-up, 3 patient required a second treatment. 160 patients were assessed - 6 of 160 patients died (3.7%): 5 due to causes not related to disease (1/5 with dosable PSA), 1 (1.6%) due to disease progression 2 yrs after the treatment. 154 of 160 patients are alive.

At the time of the last follow-up, 114/160 (71.3%) were disease-free with stable PSA level over the time ( $<1.0$ ) without any hormonal therapy. In particular, serum PSA was  $<0.5$ ng/ml in 67/160 (41.8%), PSA between 0.5 and  $<1.0$  ng/ml in 47/160 (29.3%).

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## *Prostate Cryoablation for High Risk Prostate Cancer*

The overall treatment failure rate was observed in 46/160 (28.7%): only PSA failure was recorded in 29/160 (18.1%), positive follow-up biopsies in 15 (9.3%), distant metastasis in 2 (1.25%). Positive biopsy rate is significantly different between 2 centres after the first treatment (20.0% AH vs. 4.4% CH), but the rate of PSA failure is not (18.6% AH vs. 17.7% CH). That difference could be related to different strategy in follow-up biopsy.

Disease recurrence caused death in 1 pt (1/46), development of distant metastases or androgen-independent disease in 6 of 46. Treatment management of failure was: in 28/46 cases hormonal therapy, 13/46 watchful-waiting, 5/46 radiation therapy, 1 is scheduled to repeat cryoablation. Erectile dysfunction was assessed in 69% of sexually active patients before surgery. Definitive severe urinary incontinence was observed in 2 patients (1.2%). The rate of early (<30 days) and late morbidity was acceptable and included only minor complications that were managed conservatively with medications, urethral catheter. 6.2% (10/160) needed of transurethral resection. Any rectum damage was observed, 2/160 cases developed a perineal fistula that was managed conservatively with drainage.

### Conclusions

Cryoablation has satisfactory cancer control rate observed in 71.3% after medium term follow-up. Cryoablation is a mini-invasive treatment, efficient and repeatable method resulting in slight post-operative morbidity with no intra-operative mortality even in patients subject to high risk with open surgery. Modern cryoablation with temperature monitoring it is effective in cancer control in selected patients also in the category considered at high risk for cancer progression and not suitable for other mini-invasive treatment.

## **Direct Pulmonary Cryosurgery in the treatment of Inoperable Carcinoma of the Lung (original work)**

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### Introduction

Carcinoma of the lung is an aggressive disease with a poor 5 year survival of about 8%. Over 80% of patients at the time of presentation are at an advanced stage of the disease and treatment options are severely limited. We present a preliminary, retrospective analysis of 15 patients treated with nitrous oxide

# Abstracts

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cryo-equipment and 5 patients with liquid nitrogen cryo-system who were found to be inoperable at planned surgical resection for non-small cell carcinoma, patients instead, received direct, intrathoracic cryosurgery at thoracotomy. The aim of this study was to evaluate the effects of direct cryosurgery on symptoms, performance score, pulmonary function and survival.

### Method

Between January 1992 and December 2002, 15 patients underwent direct intrathoracic cryosurgery with a nitrous oxide cooled probe (BP -89°C) and since July 2003, 5 patients were treated with liquid nitrogen (BP -196°C) for pulmonary NSCLC. All patients were scheduled to undergo thoracotomy and surgical resection but during the operative procedure were deemed to be unresectable. Symptom quantification and performance status were recorded before and after cryosurgery.

### Results

The mean age of the patients treated with nitrous oxide cryo-equipment was 64.0 years (range 49-71). Histological classification squamous cell carcinoma 12, adenocarcinoma 1 and large cell 2. Preoperative TNM staging was IIa 7%, IIb 73% and IIIa 20%, surgical staging were upstaged with IIb 7%, IIIa 15%, IIIb 71% and stage IV 7%. Major symptoms including cough, dyspnoea, haemoptysis and chest pain were assessed and showed improvement in 63%, 75%, 93% and 25% respectively. Mean FEV1 increased from 1.72 to 2.05 litres (p<0.001) and FVC from 2.32 to 2.95 litres (p<0.001). Karnovsky performance status increased from a mean of 67.5 to 70.0. The five patients treated with liquid nitrogen technology show Radiological tumour regression and all are alive and well.

### Conclusion

This preliminary analysis shows that the procedure is safe with encouraging symptomatic improvement and quality of life. Survival compares favourably with studies of similar groups. Based on current knowledge of the biological effect of extreme cold, a temperature of about -50°C is required to the periphery of the tumour mass to guarantee total cell destruction. Therefore, we have recently acquired a liquid nitrogen cryo-system with greater destructive effects to continue this work.