

ENLIGHT and the present and future of clinical perspective

fondazione **CNAO**



Pavia CNAO 2012, 15th September

To date

*Thousand and thousand and thousand of
patients treated with protontherapy*

*Thousand and thousand of patients treated
with neutron therapy*

*Thousand of patients treated with carbon ion
therapy*

P+ / C12 **10:1**

Published Data in the years

STUDIES YEARS	CLINIC	PHYSICS	BIOLOGY	TOTAL
2004-2007	100	41	21	162
2000-2003	46	29	18	93
1995-1999	27	33	8	68

2008-2012:

“Particle Beam Therapy”

501 papers (more than 150 related to clinic)

Hadrontherapy:

EBM?

VOLUME 26 • NUMBER 2 • JANUARY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Should Randomized Clinical Trials in Proton Radiotherapy?

Michael Goitein, Department of Radiation Oncology, Harvard Medical School
James D. Cox, Division of Radiation Oncology, The University of Texas M

Special communication

Radiotherapy and Oncology 86 (2008) 142–147
www.thegreenjournal.com

Randomized controlled trials in health technology assessment: Overkill or overdue?

Søren M. Bentzen*

Departments of Human Oncology, Medical Physics, Biostatistics and Medical Informatics,
University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

VOLUME 25 • NUMBER 8 • MARCH 10 2007

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

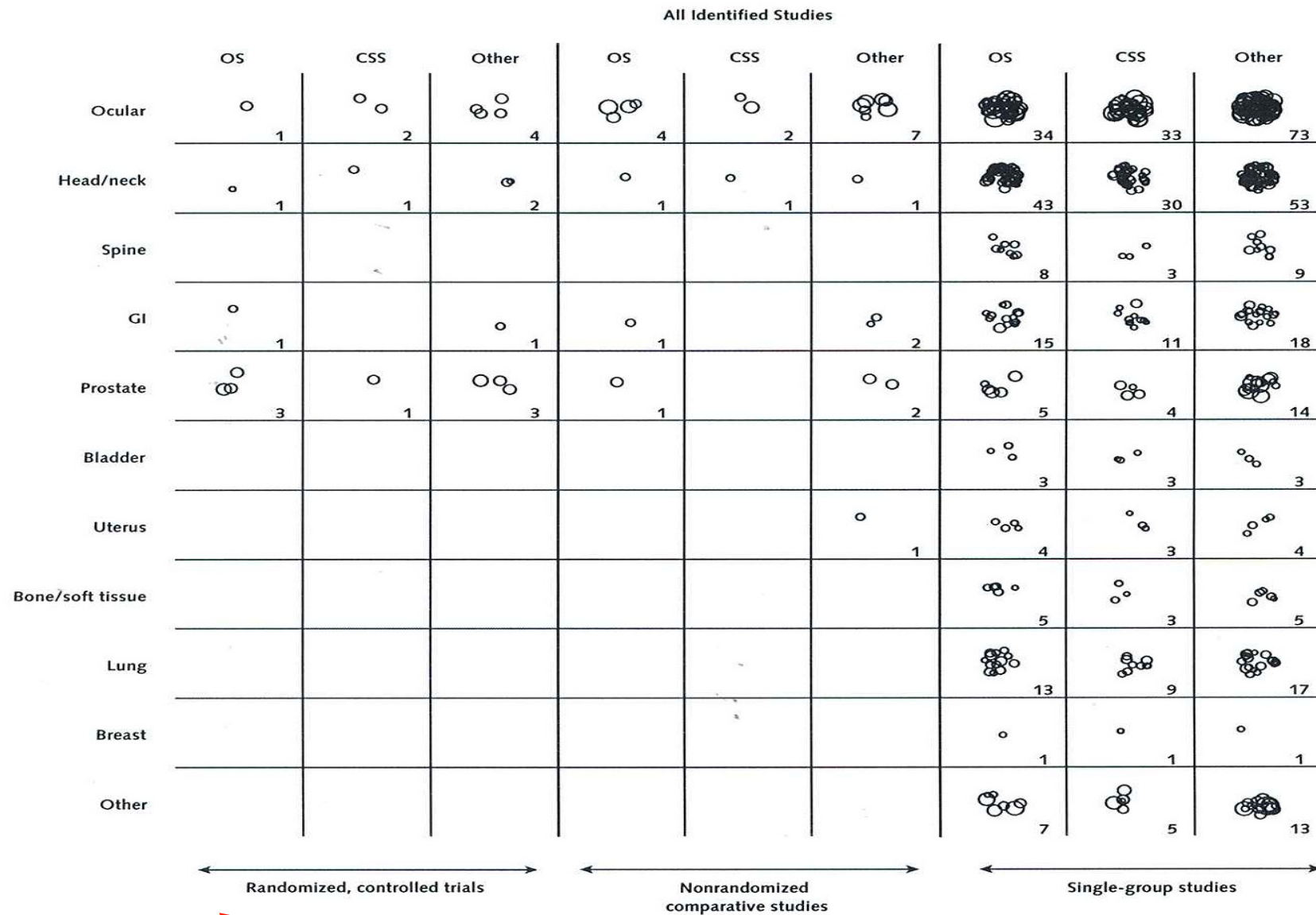
Proton Therapy in Clinical Practice: Current Clinical Evidence

Michael Brada, Madelon Pijls-Johannesma, and Dirk De Ruyscher

Proton beam therapy — Do we need the randomised trials and can we do them?

Bengt Glimelius^{a,b,*}, Anders Montelius^a

^aDepartment of Oncology, Radiology and Clinical Immunology, Uppsala University Hospital, Uppsala, Sweden, ^bDepartment of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden



Terasawa T et al. Systematic review:
Charged-Particle Radiation Therapy for Cancer
Ann Intern Med 2009; 151: 556-65

EBM & Hadrontherapy in EU

- In all disease sites including pediatric, ocular, GI, lung, and base of skull, low evidence for proton therapy (prostate for dose escalation?)

[Olsen DR et al, R&O, 2007]

- No evidence for the use of protons and ions in GI, pelvis, H&N, lung, and sarcoma. Evidence for chordomas and large ocular tumors

[Lodge M et al, R&O, 2007]

- Insufficient evidence in any of the disease sites

[Brada M et al, JCO, 2008]

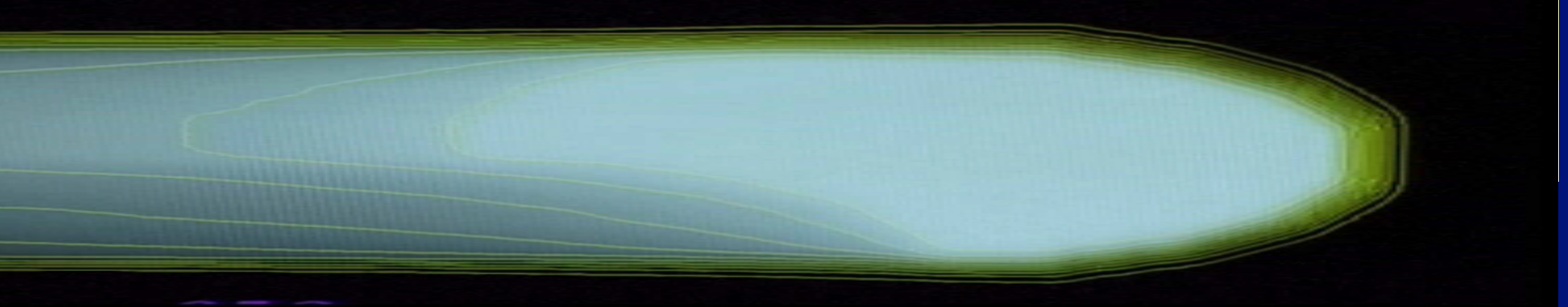
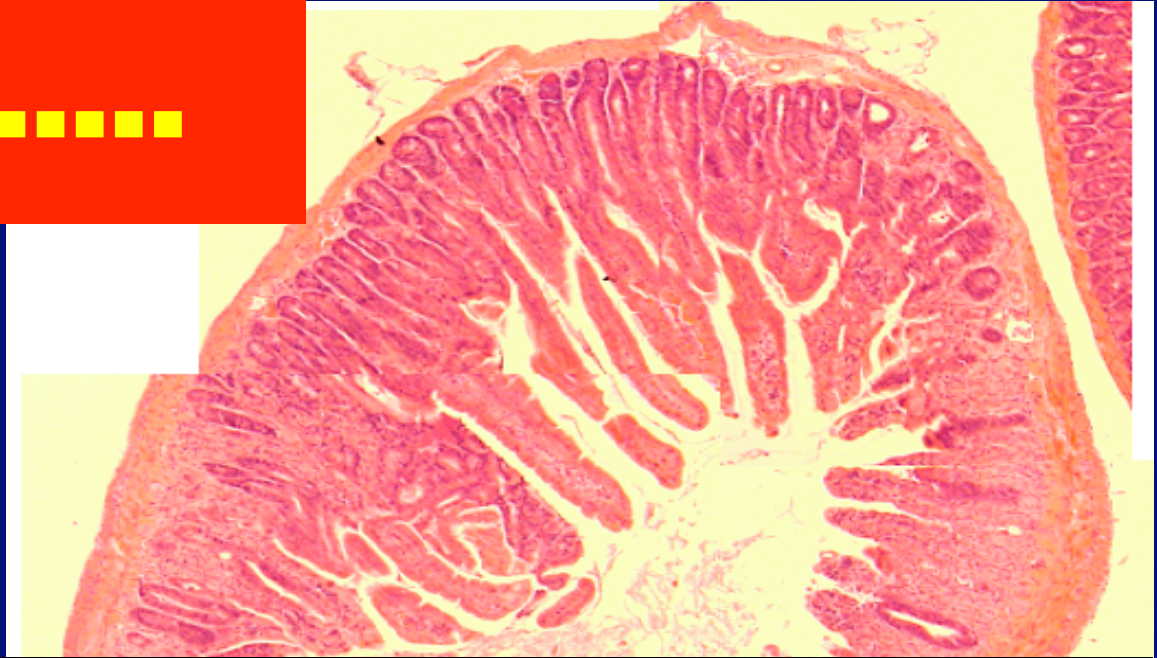
EBM & Hadrontherapy in US

ASTRO's emerging technology committee,

Allen AM et al, R&O, 2012

- ... there is reason to be optimistic about the potential developments in proton therapy
- ... current data do not provide sufficient evidence to recommend PBT outside of clinical trials
- ... in HCC and prostate there is evidence for the efficacy of PBT but no suggestion that it is superior
- ... in pediatric CNS insufficient data to support a firm recommendation

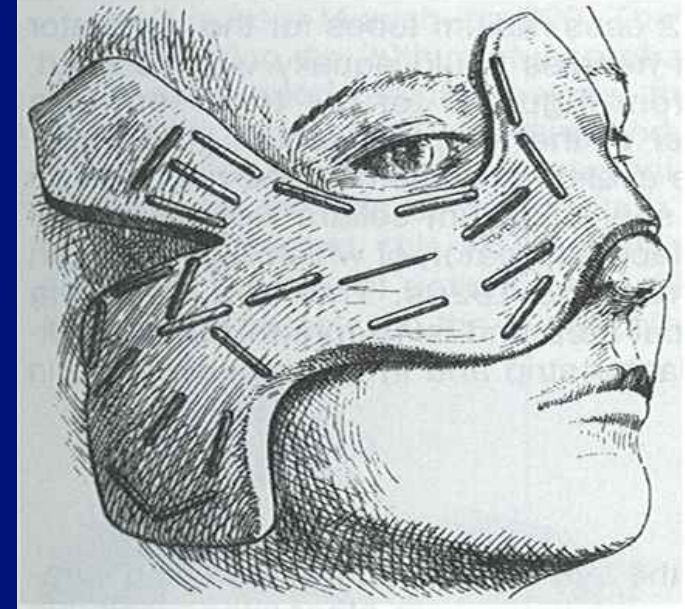
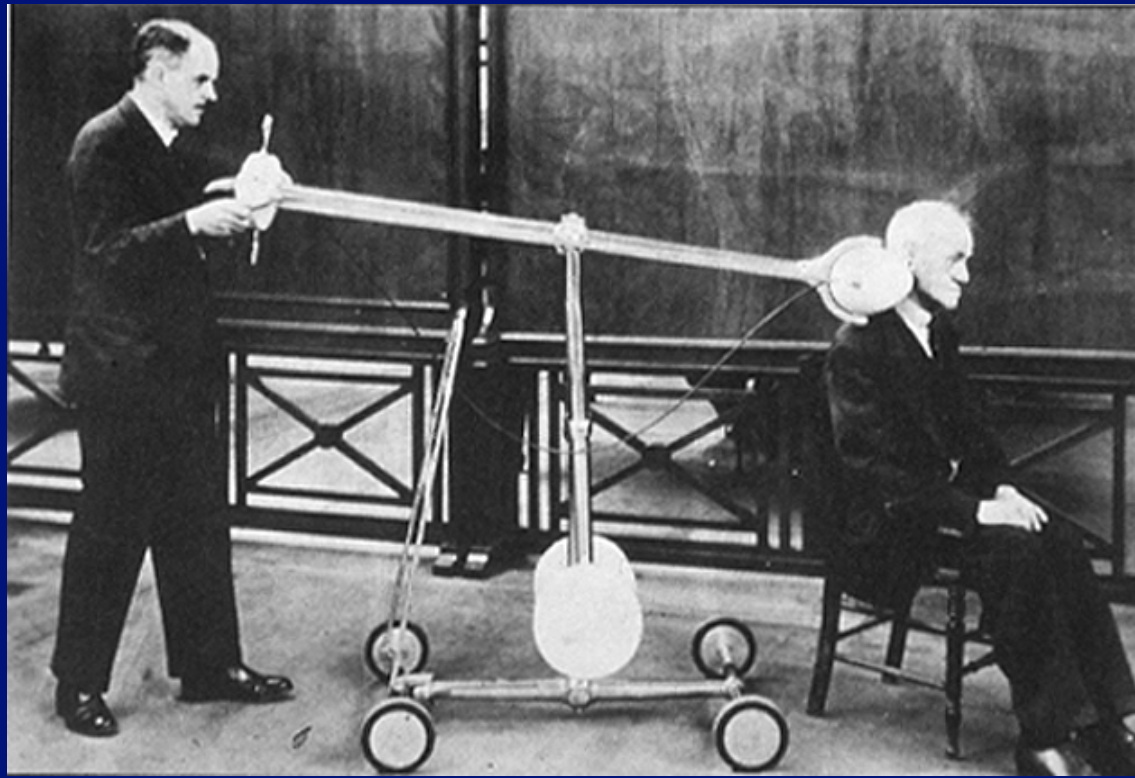
**a new
dimension**



Hadrontherapy



**Dose
distribution ?**

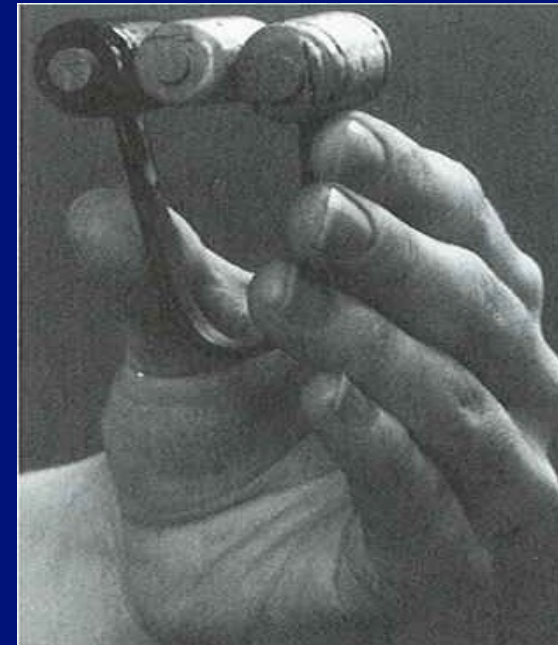


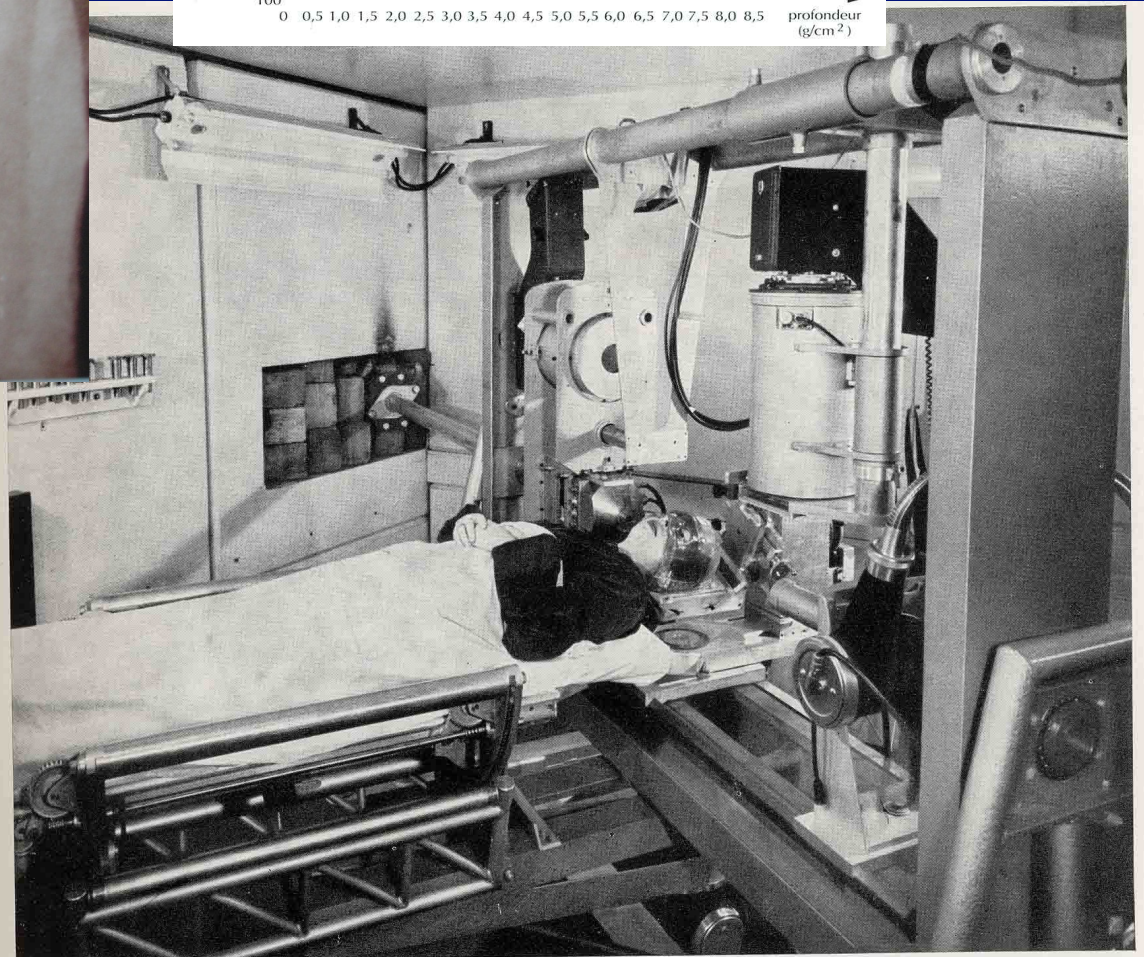
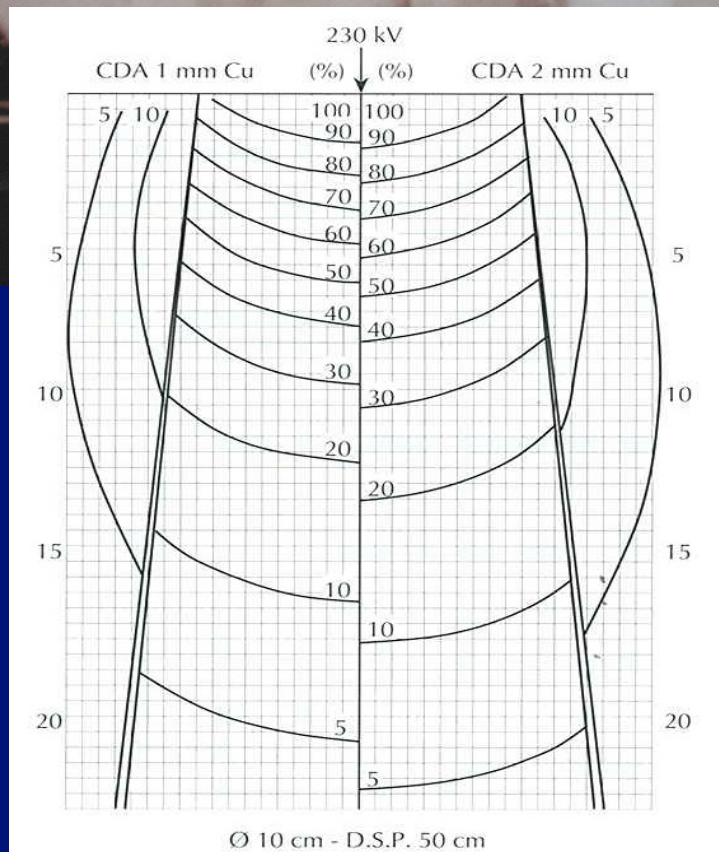
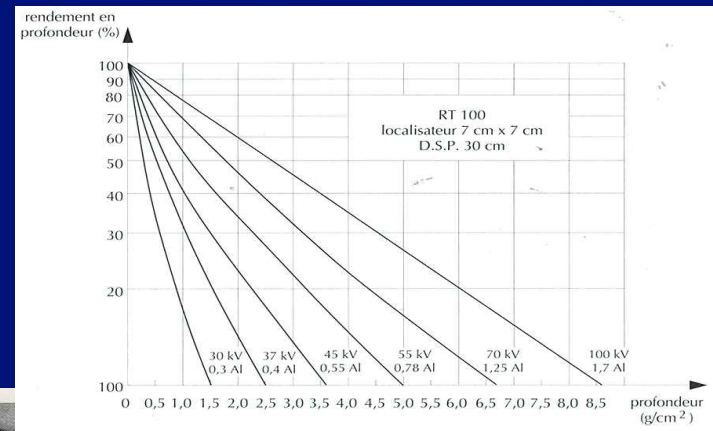
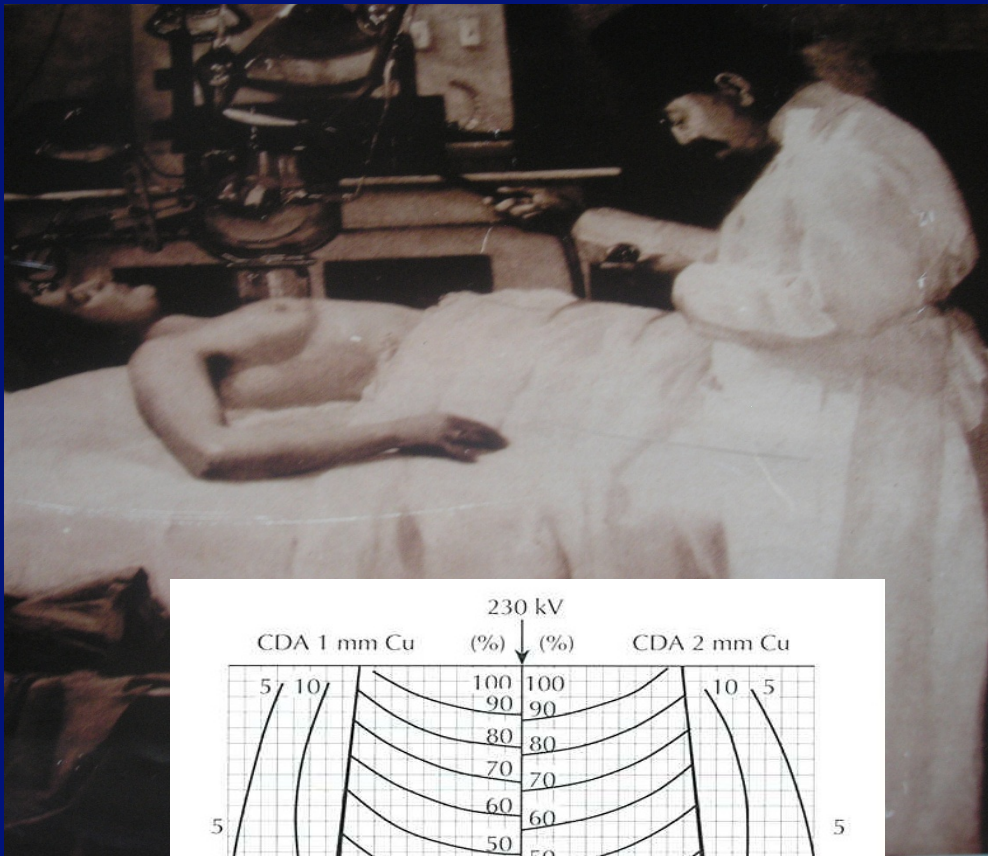
Paris schedule cervix uteri

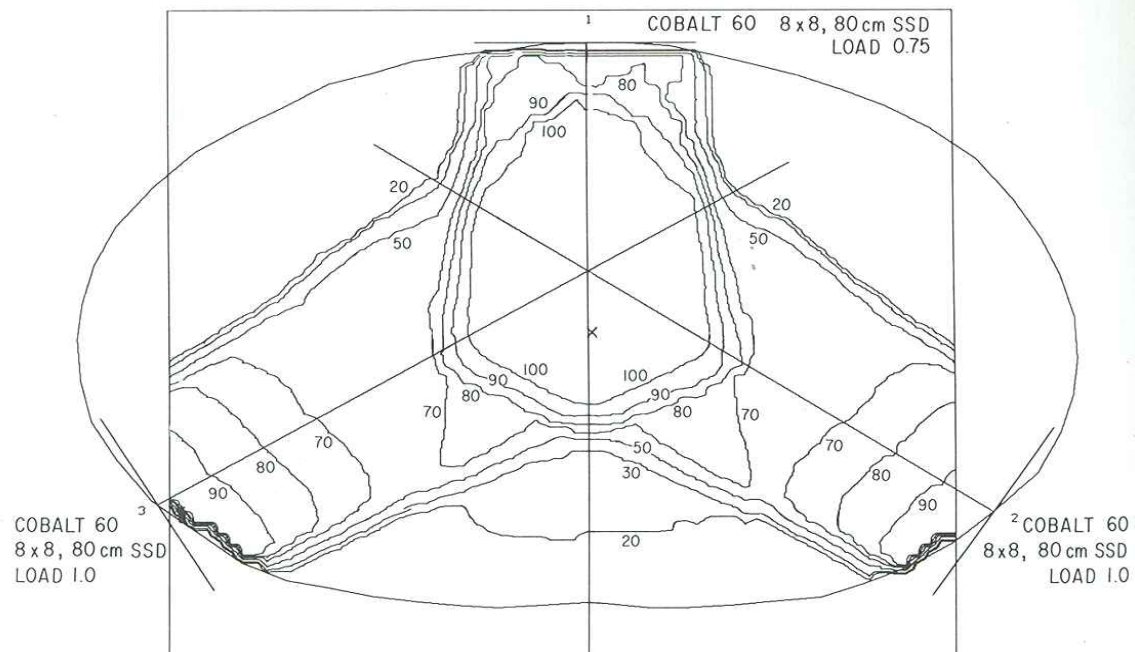
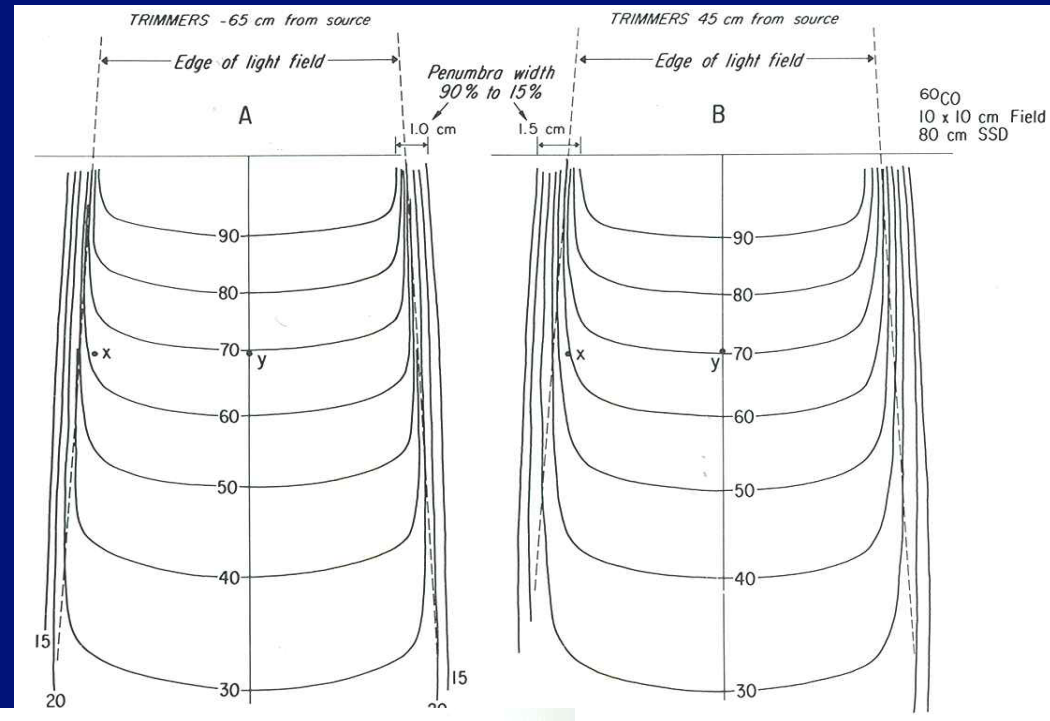
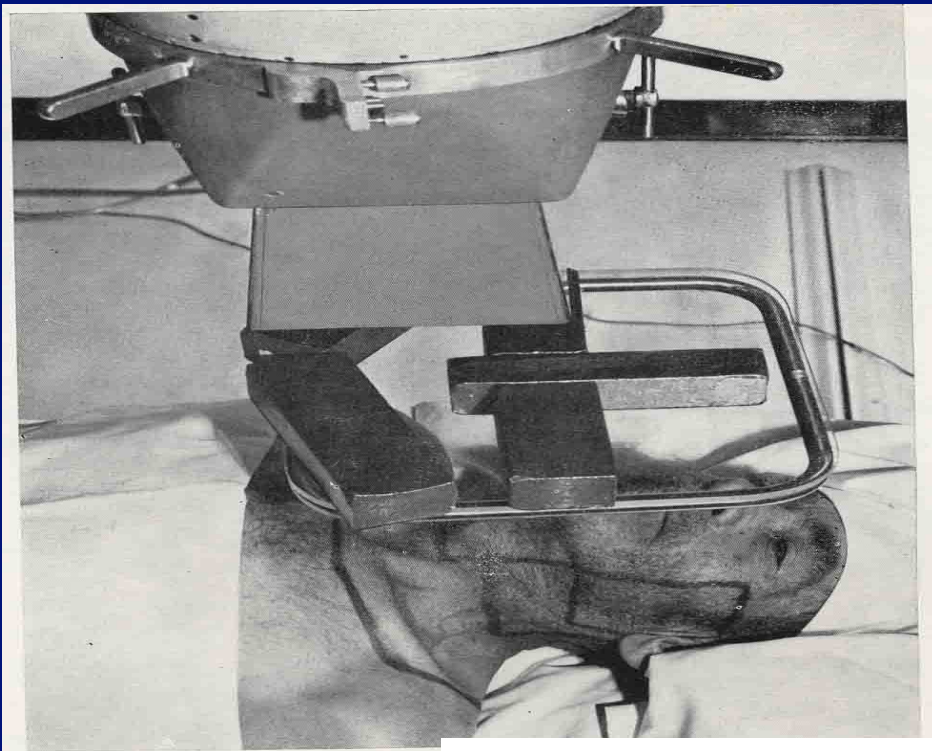
Continuous treatment for 120 hours

Uterine tube of 33.3 mg radium

Two vaginal cylindrical corks: 13.3 mg radium each



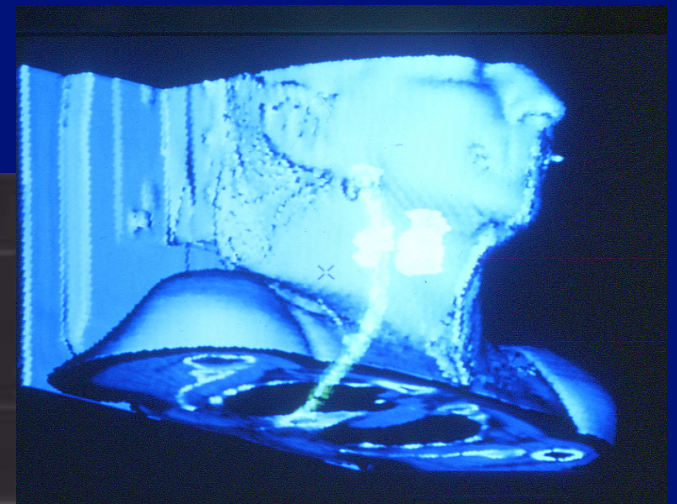
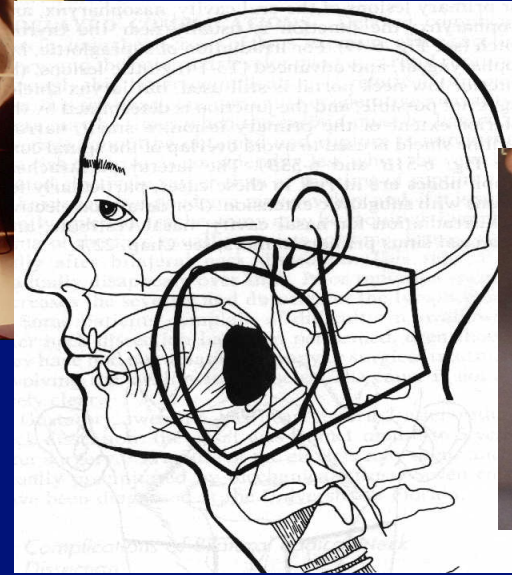
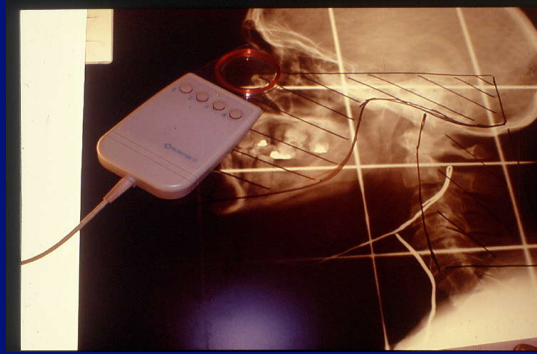


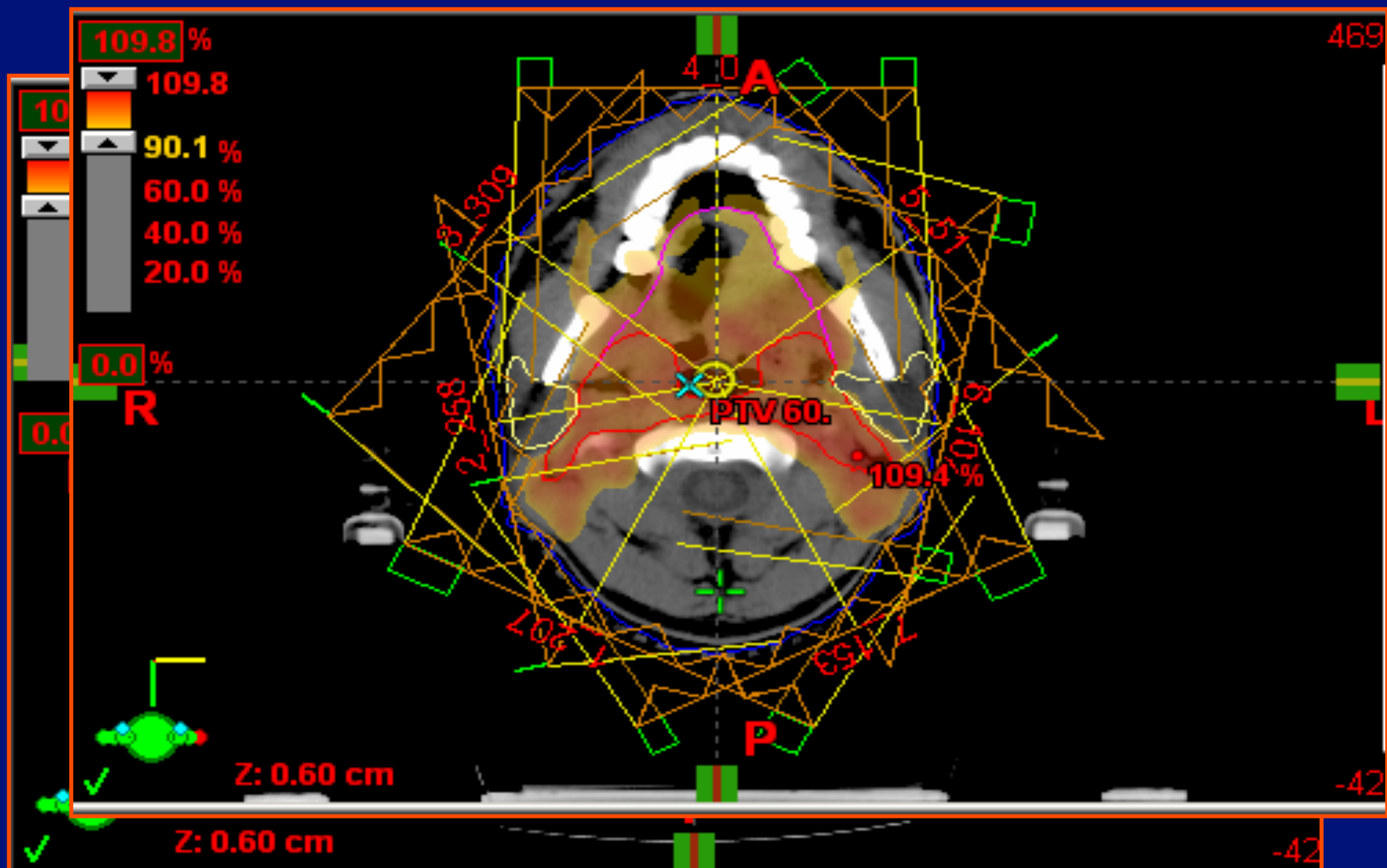


From 2-D



To 3-D





Il nostro obiettivo

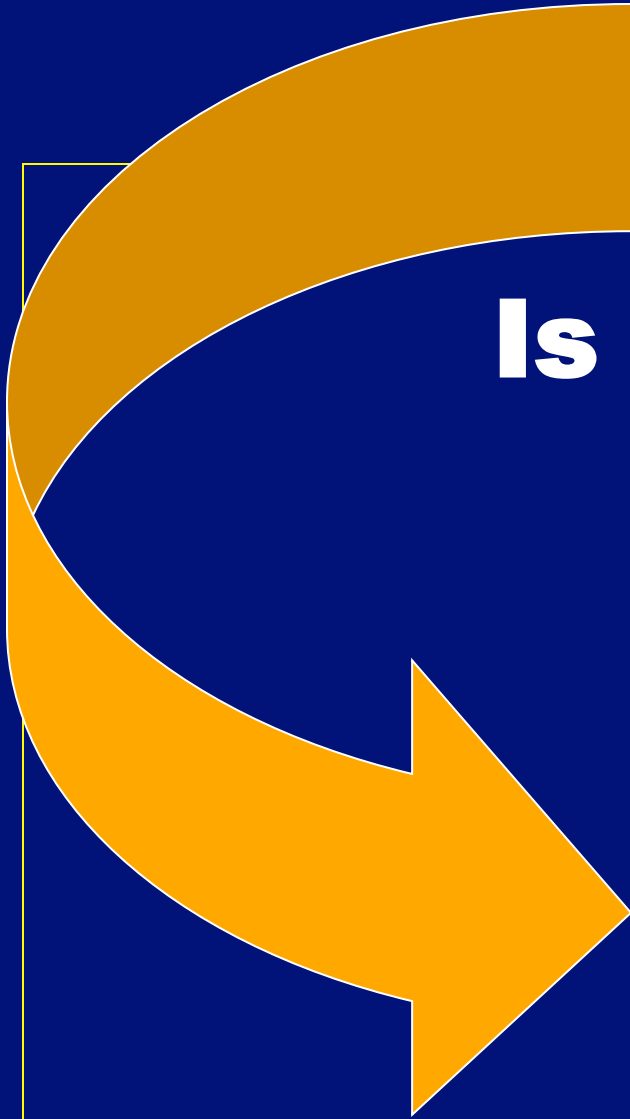


Dose Distribution ?

Is not a clinical issue

but

**It's the condition
necessary to improve
clinical outcomes**



Marketing

The screenshot displays the Cyberknife website interface. At the top, there is a navigation bar with links: [Español](#), [Locations](#), [Home](#), [About Us](#), [Blog](#), [Contact Us](#), and [Email Signup](#). Below this is a secondary menu with links: [Cyberknife System](#), [Clinical Team](#), [The Procedure](#), [FAQ's](#), [Media Articles](#), [Case Studies](#), and [Conditions Treated](#).

The main content area features the Cyberknife logo on the left, which includes the text "CYBER KNIFE" and "CENTER OF PALM BEACH" above a stylized patient silhouette. To the right of the logo is a box with the text: "For information on the STARS Study for Lung Cancer 561-799-2828". On the far right, there is a link to "Other Morse Cyberknife® Centers" and a smaller version of the Cyberknife logo with the text "MIAMI" below it.

Below the navigation and logos, the text "HEROES IN MEDICINE" is prominently displayed in a large, serif font, accompanied by a green leaf-like graphic on the left. Directly beneath this, the words "THANK YOU!" are written in a bold, sans-serif font.

At the bottom of the page, there is a group photograph of approximately 20 people, mostly men in suits, standing in front of an American flag and another flag.

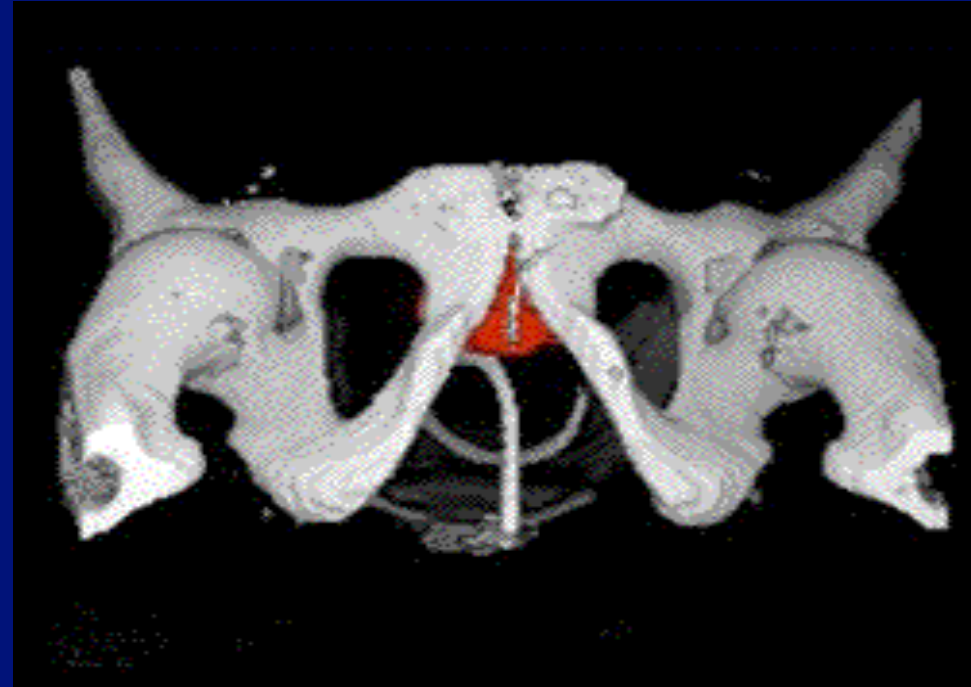
- No incision
- No blood
- No anesthesia
- No pain
- No recovery or rehabilitation time

30 YEARS AGO or more

Radical prostatectomy

or

External beam irradiation



15 YEARS AGO and more

Radical prostatectomy

or

Conventional
external beam

or

Conformal external
beam

or

Brachytherapy

or

Brachytherapy/external beam

TODAY

Radical prostatectomy

Nerve sparing prostatectomy

Laparoscopic
prostatectomy
Robotic surgery

or

Conventional
external beam

Conformal external
beam

3-D

IMRT

Proton/Ion

IGRT

High dose rate

High-dose conformal

Dose escalation

Low dose rate

Brachytherapy

Hypofractionation

HIFU

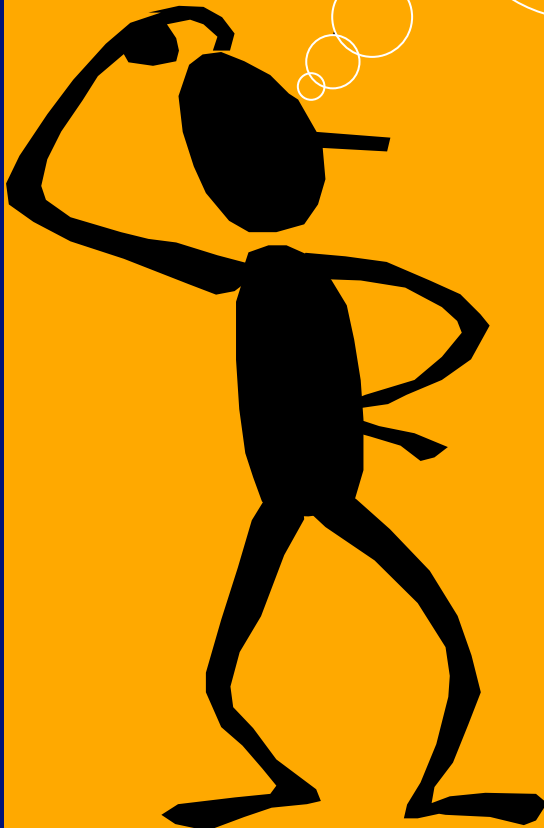
Brachytherapy/external beam

RITA

Any of the above with
androgen deprivation

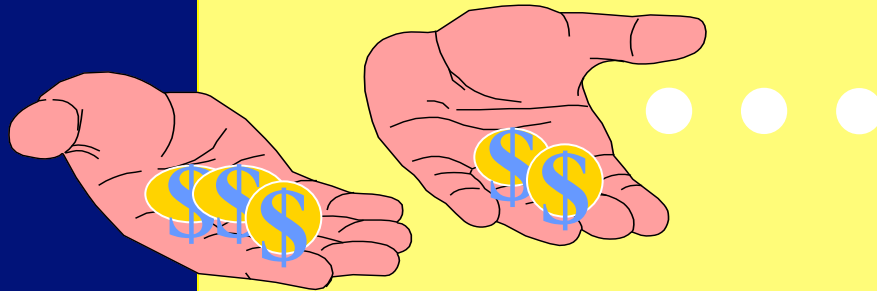
Cryotherapy

**How much
does't
cost?**



**Life, Liberty, and the Pursuit of Protons:
An Evidence-Based review of the role of Particle
Therapy in the treatment of prostate cancer**

Hadrons



(Efsthion JA et al, The Cancer Journal, 2009)

See physics article EEE website for
revised abstracts only

ed. Book abstracts available at

in September 2005
in October 2005 only
in October 2005 only
in October 2005 only
in October 2005 only

TERA

Accelerator and Particle Physics
Department, STFC, Rutherford
Laboratory, Chilton, Oxon OX10 9FA
United Kingdom
www.tera.ac.uk

TERA Website

Accelerator and Particle Physics
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Laboratory, Chilton, Oxon OX10 9FA
United Kingdom
www.tera.ac.uk

HCPBM

10th Workshop on
**HEAVY CHARGED PARTICLES
IN BIOLOGY AND MEDICINE**
and
ENLIGHT
4th Meeting of the
**EUROPEAN NETWORK
FOR LIGHT ION HADRON THERAPY**

OROPA (Biella) 15 - 19 June 2005

Chair:

Chairman for all sessions: **Michael
Mancusi**

OROPA, University of Biella, Biella
Italy. Participants of the first group

Chairman, **Michael Mancusi**, **University of Biella, Italy**
Chairman, **Michael Mancusi**, **University of Biella, Italy**
Chairman, **Michael Mancusi**, **University of Biella, Italy**
Chairman, **Michael Mancusi**, **University of Biella, Italy**

Created by the Italian Ministry of Health at the beginning of 2001

21st November 2001, the Board has been established

to build a Centre with two main goals:



To treat patients using hadrontherapy

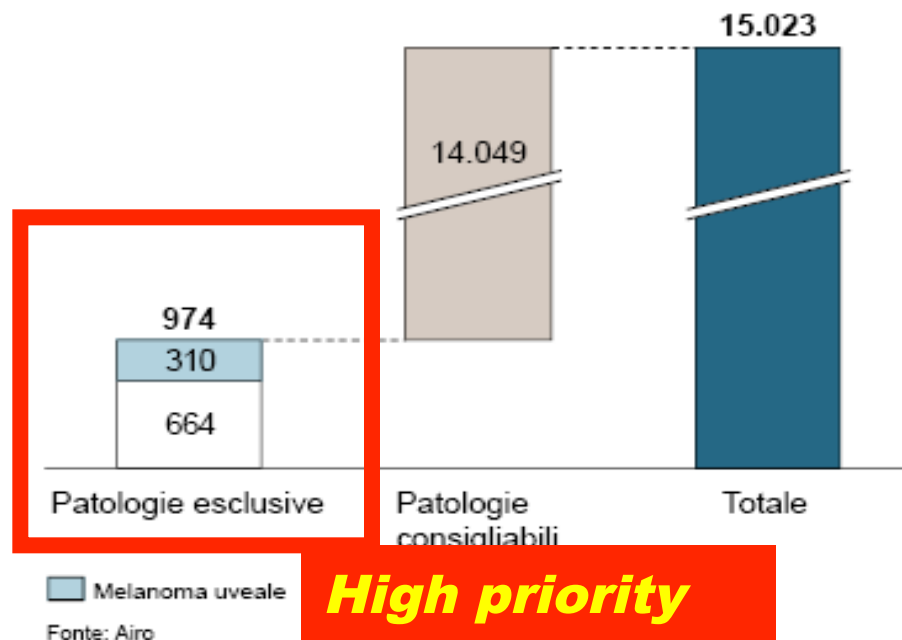


To perform clinical and radiobiological research



Working Group 2003, 2008, 2009

***Estimated 15.000 new eligible patients
in Italy for protons***



High priority

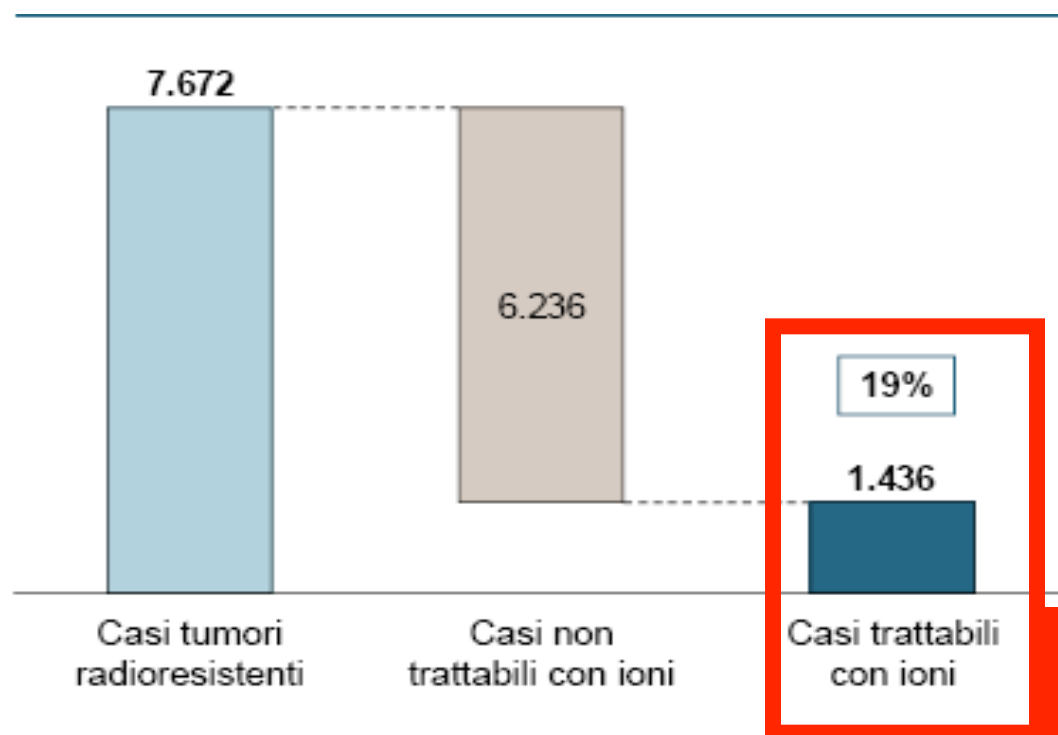
- Le principali patologie esclusive sono il melanoma uveale (corrispondenti al 47% delle patologie elettive), i cordomi della base cranica e della colonna vertebrale, i condrosarcomi dell'estremità cefalica e del tronco, i meningiomi della base cranica, i tumori paraspinali, gli schwannomi dei nervi cranici, gli adenomi ipofisari e i tumori solidi pediatrici
- Le principali patologie consigliabili, su cui risulta particolarmente vantaggioso, sono i tumori alla prostata, al pancreas, ai polmoni e al fegato
- In futuro si prevede una crescente estensione del campo di applicazione della terapia a protoni ad altre patologie anche non oncologiche



Working Group 2003, 2008, 2009

Estimated 7.000 patients with “radioresistant tumors” in Italy

About 20% of these tumors should be treated by ions



- Le terapie con ioni di carbonio potrebbero essere adottate in quasi 20% dei casi di alcune categorie di tumori radioresistenti
- Le principali patologie neoplastiche trattabili con ioni sono: i tumori delle ghiandole salivari, i melanomi mucosi delle VADS, i adenocarcinomi dei seni paranasali, i sarcomi ossei e dei tessuti molli e i epatocarcinomi/tumori pancreatici e delle vie biliari
- Ad oggi l'applicazione della terapia a ioni Carbonio è piuttosto limitata, tuttavia in futuro si prevede una crescente estensione

High priority

The Phases of CNAO

Phase 1: construction

 Years: 2005 - 2009

Phase 2: experimentation

 Years: 2010 - 2012

Phase 3: start-up

 Years: 2013 - 2014

The CNAO has been completed
end 2009



PROGETTO DI SPERIMENTAZIONE CLINICA

A CURA DI:

Erminio Borloni – Presidente
Roberto Orecchia – Direttore Scientifico
Sandro Rossi – Segretario Generale e Direttore Tecnico



IL CENTRO NAZIONALE DI ADROTERAPIA ONCOLOGICA

Strada Privata Campeggi – 27100 Pavia



Sedi: Via Caminadella, 16 - 20123 Milano
Iscrizione al Registro delle Persone Giuridiche della Prefettura di Milano n. 192
P.IVA n. 03491780965
Codice Fiscale n. 97301200156

Presented to:

- Ministry of Health
- Region Lombardy

Main Tasks:

- Dosimetry characterisation
- Radiobiology characterisation
- Patient treatments

Approved Protocols

01/2011 Studio clinico di fase II: trattamento con protoni (adroterapia) di cordomi e condrosarcomi della base del cranio

02/2011 Studio clinico di fase II: su radioterapia mediante protoni (adroterapia) dei cordomi e condrosarcomi del rachide

03/2011 Studio clinico di fase II: su radioterapia mediante protoni (adroterapia) dei meningiomi intracranici

05/2011 Studio clinico di fase II: su radioterapia mediante protoni (adroterapia) delle recidive di neoplasie del distretto cervico-cefalico

06/2011 Studio clinico di fase II: su boost di radioterapia mediante protoni (adroterapia) di neoplasie localmente avanzate del distretto cervico-cefalico

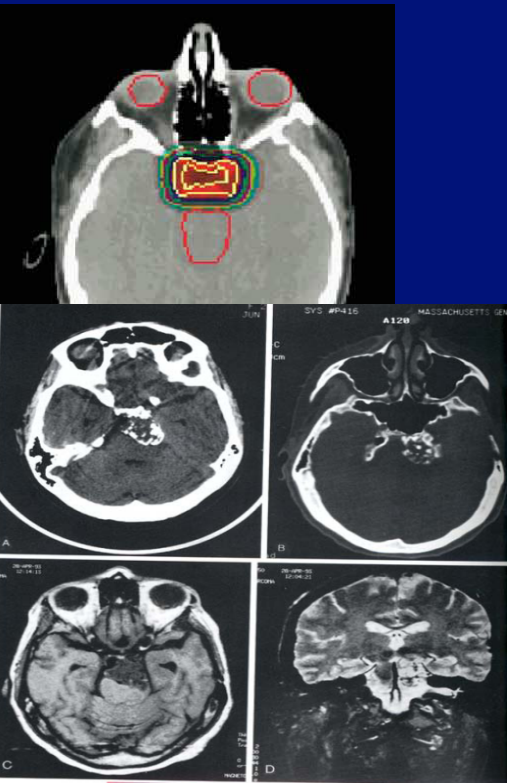
22 September 2011



Chordoma/ low grade chondrosarcoma

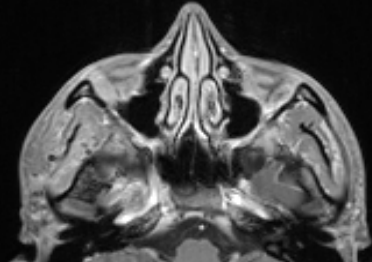
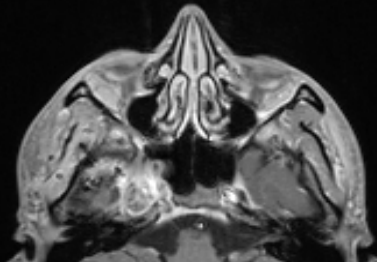
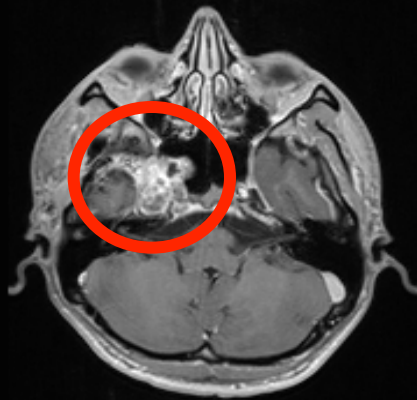
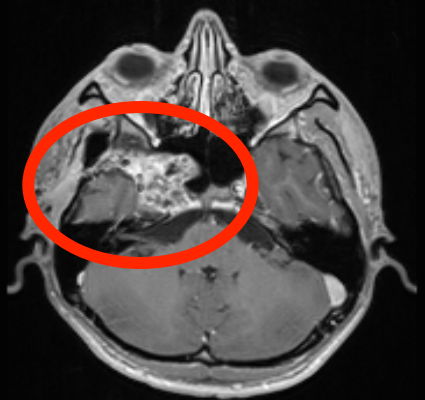
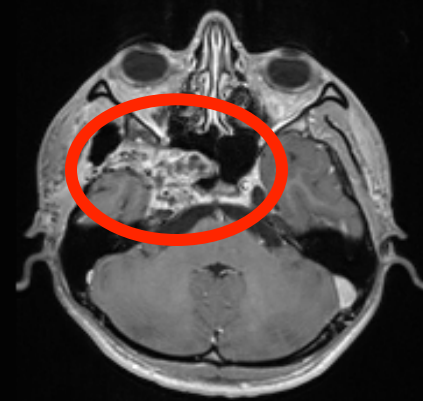
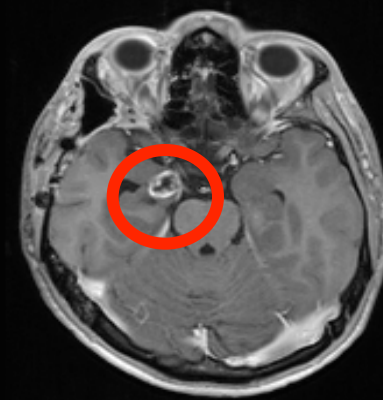
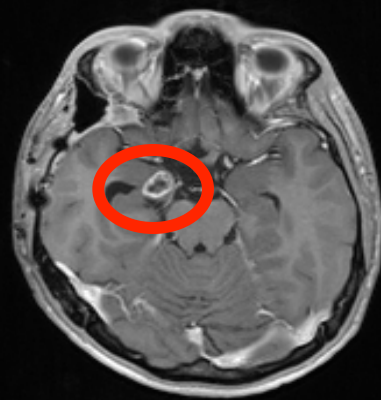
Skull base and spine

- Post op, Recurrent, Inoperable
- M0N0
- Contouring based on CT and MR fusion



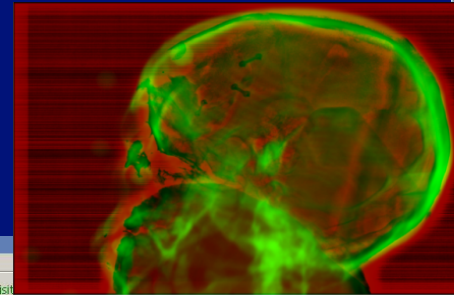
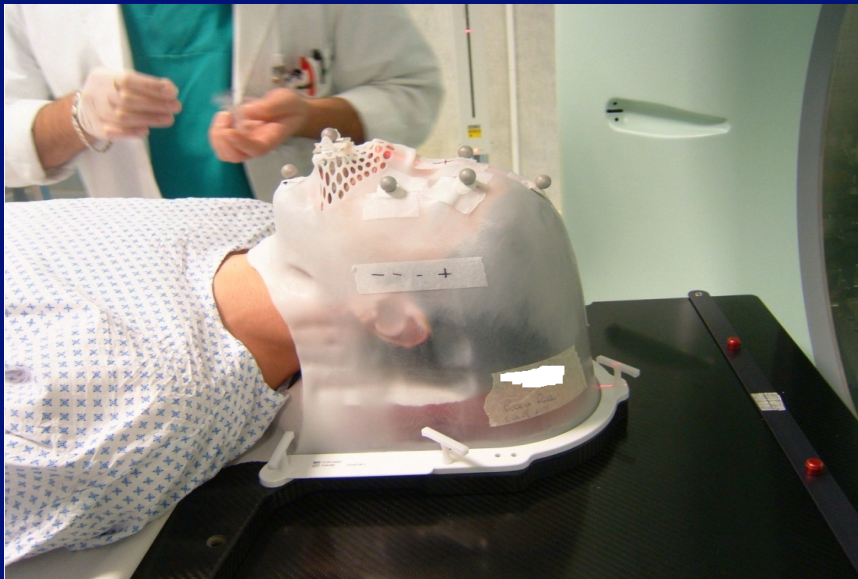
Dose chordoma: 74 GyE in 37 fractions,
2 GyE per fraction, 5 fractions per week

Dose chondrosarcoma: 70 GyE in 35
fractions, 2 GyE per fraction, 5 fractions per week



Chondrosarcoma G2

Optical & X-ray tracking systems for set-up verification



File Acquisition Graphics view Help

09.11.2011 12:30:34 Guido Baroni logged in Administrator

Acquisition Network NOT connected CNAO Timing NOT connected

Treatment Data

Patient Name: [REDACTED]

Patient Sex: M

Date of Birth: 1 - 1 - 1985

Patient ID: [REDACTED]

Study Description:

SOPInstanceUID: 1.2.840.113854.58952404827512000607707661004982304949

Treatment support: TABLE

Number of Beams: 3

Treatment Sequence: [1-240:TX]

Volume Center: X=-9999.0 Y=-9999.0 Z=-9999.0

Isocenter: X=0.0 Y=-273.0 Z=0.0

Indexing position: F10 Bar DISTAL

Table Lateral[mm]: 3.8

Table Longitudinal[mm]: -1123.6

Table Vertical[mm]: -194.1

Table Pitch[deg]: 0.4

Table Roll[deg]: -0.8

Table Rotate (Yaw)[deg]: 71.7

Acquisition Data

Acquired Frames: 762

Displayed Frames: 586

Saved Frames: 94

Sample Rate [Hz]: 1.4

Lock PPS/Treat/Enable

Correction Parameters

X(RCS): -1.0 [mm]

Y(RCS): -0.3 [mm]

Z(RCS): 0.4 [mm]

Pitch(RCS): -0.5 [deg]

Roll(RCS): 0.8 [deg]

Rotate(RCS): -1.4 [deg]

Send Correction to PPS

3D [mm]

Start

2.JPG - Paint

C:\OTS\Data\gCurrentD...

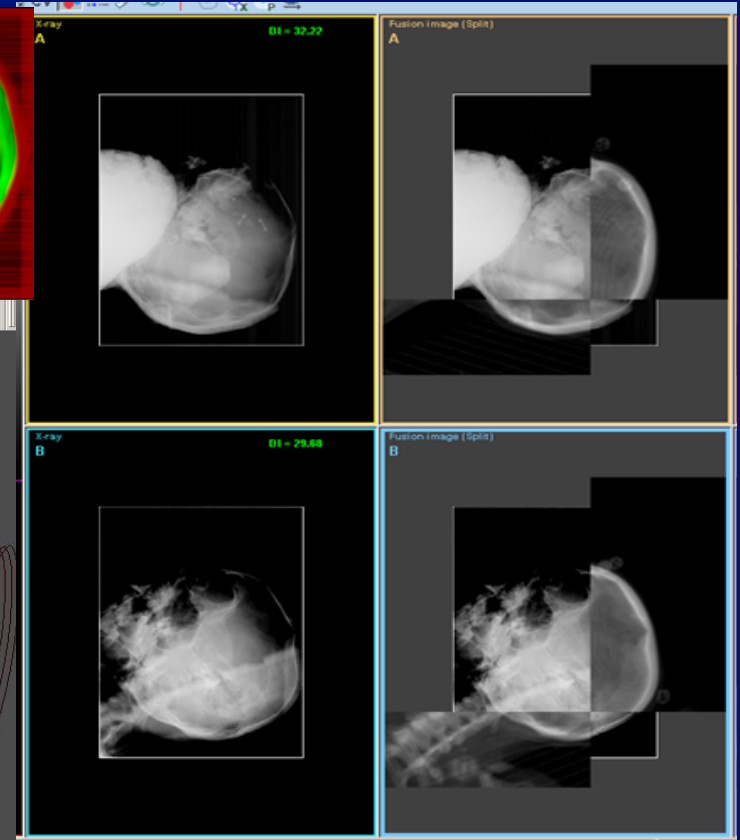
C:\OTS\Data\gCurrentD...

C:\Documents and Setti...

SMARTcapture

CNAO-OTS v1.0.3

12:30



OK M 6 49

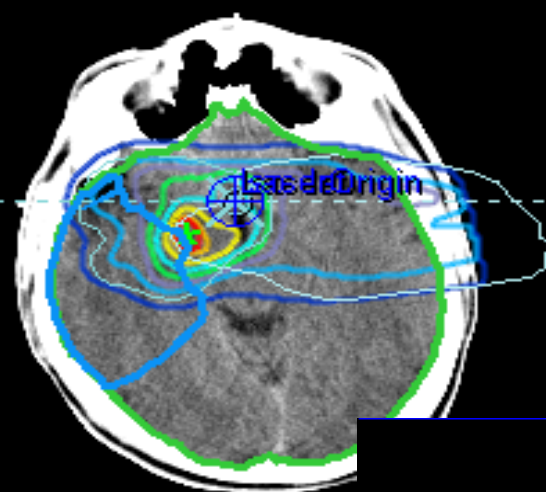
OK M 7 40

Z (RCS)[...] Y (RCS)[...] X (RCS)[...] 3D [mm]

p-2011

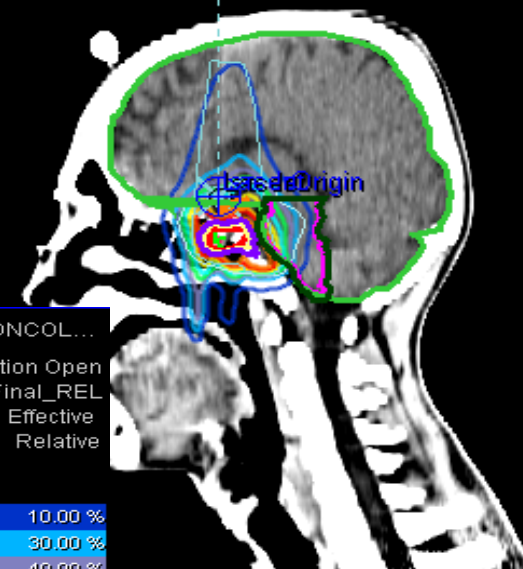
Effective
Relative

CENTRO NAZ. ADROTERAPIA ONCOL...
Sensation Open
2B340_260_Final_REL
Effective
Relative



10.00 % # SDM24EI
30.00 % STUDY 08-Sep-2011
40.00 % 08-Sep-2011
50.00 % 12:31:53 PM
60.00 % 2 FRM 1
70.00 %
80.00 %
90.00 %
100.00 %
110.00 %

100% = 70.00 GyE



10.00 %
30.00 %
40.00 %
50.00 %
60.00 %
70.00 %
80.00 %
90.00 %
100.00 %
110.00 %

100% = 70.00 GyE

SDM24EI
STUDY 08-Sep-2011
08-Sep-2011
12:31:53 PM
2 FRM 1

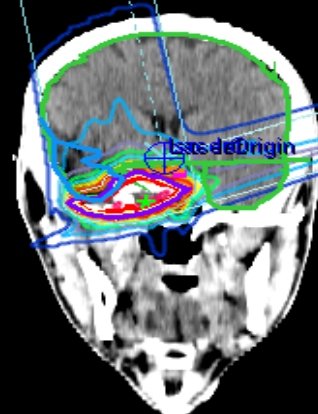
H CENTRO NAZ. ADROTERAPIA ONCOL...
Sensation Open
2B340_260_Final_REL
Effective
Relative

10.00 %
30.00 %
40.00 %
50.00 %
60.00 %
70.00 %
80.00 %
90.00 %
100.00 %
110.00 %

100% = 70.00 GyE

R

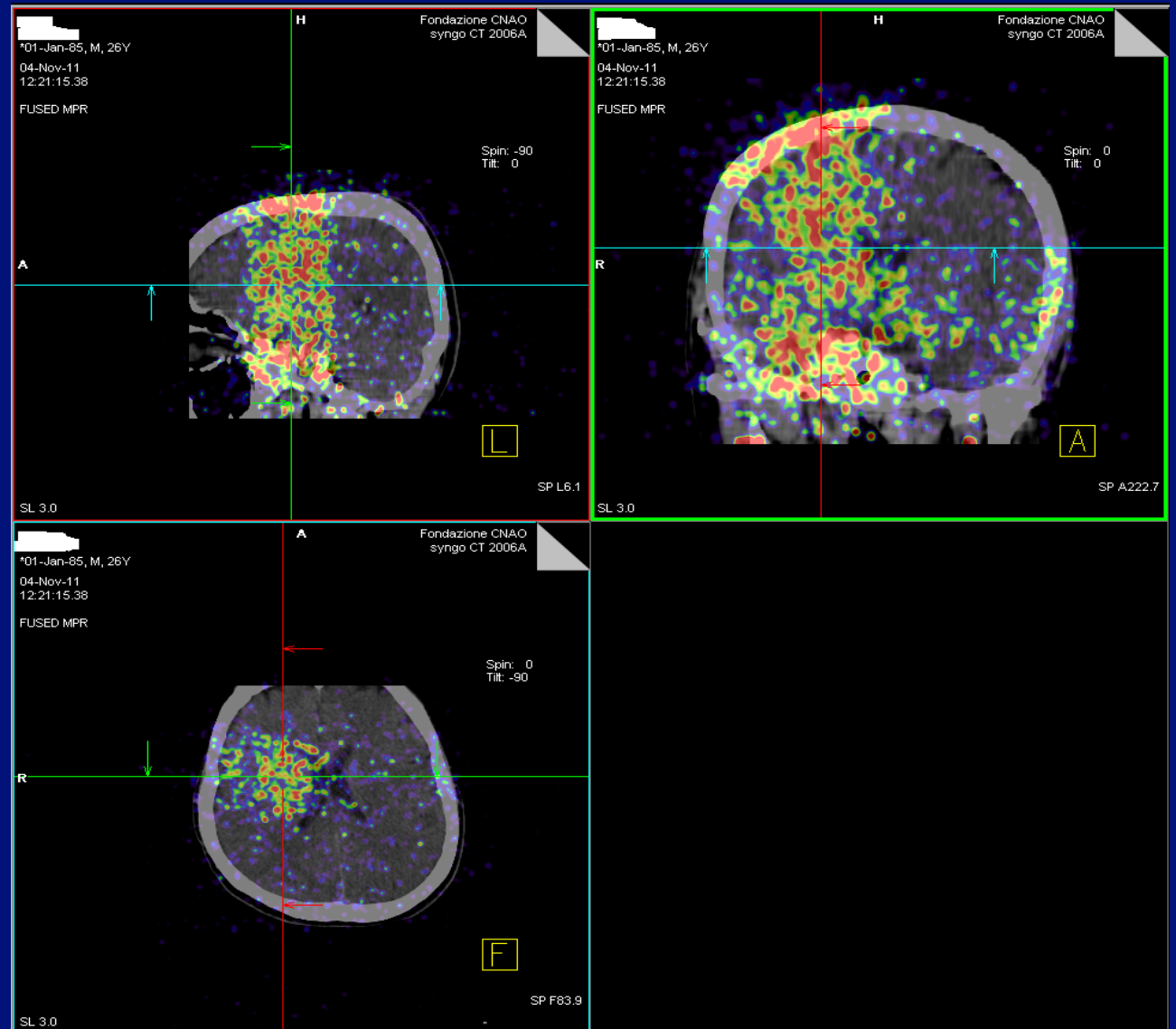
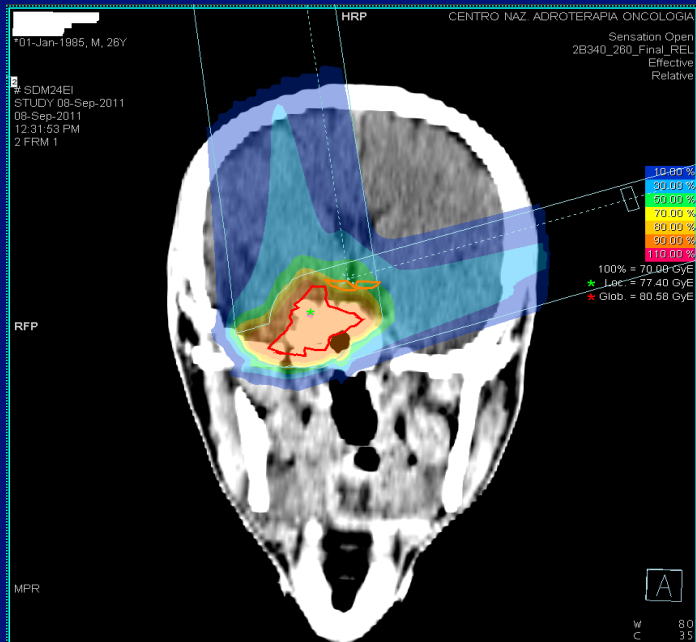
MPR



W 80
C 35

RBE value 1.1

Off-line PET for treatment qualitative verification



Clinical Activity at CNAO:

22 September 2011- 6th September 2012

30 patients treated

20 base of skull

8 spine

1 oropharynx

1 nasopharynx

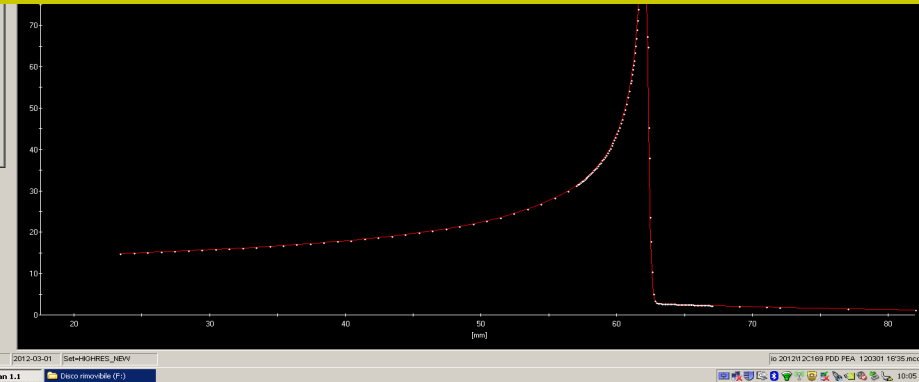
Tumor type

Chordoma	23
Condrosarcoma	5
Head & Neck carcinoma	2

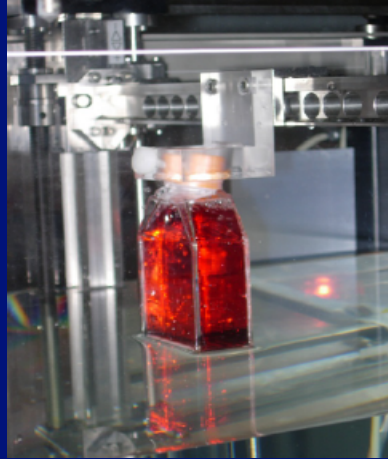
10 under treatment

Carbon Ions

Physics



Group Leader: Mario Ciocca



Carbon Ions

Cells

- *in vitro*:

Clonogenic survival of cell lines

- V79 (Chinese hamster lung fibroblast)
- HSG (Human salivary gland tumor)
- T98G (human glioblastoma)

Group Leader: Roberto Cherubini

Carbon ions

Animals



Group Leader: Yoshiya Furusawa

Approved Protocols

- **CNAO 04/2011 v4 “Studio clinico di fase II su radioterapia mediante protoni (adroterapia) dei tumori dell’encefalo”**
- **CNAO 07/2012 v1 “Studio clinico di fase II su radioterapia mediante protoni (adroterapia) dei glioblastomi”**
- **CNAO 08/2012 v1 “Studio clinico di fase II su ritrattamento mediante radioterapia con protoni (adroterapia) dei Cordomi e dei Condrosarcomi del rachide recidivi”**

CNAO C-01 /2012 “Studio clinico di fase II: radioterapia mediante ioni carbonio del carcinoma adenoideo cistico delle ghiandole salivari”

CNAO C-02/2012 v1 “Studio clinico di fase II su ritrattamento mediante radioterapia con ioni carbonio (adroterapia) degli adenomi pleomorfi recidivi”

CNAO C-03/2012 “Clinical phase II study: Reirradiation of recurrent rectal cancer using Carbon ions”

Hadrontherapy



Proper design of
clinical trial

1982-1995, T3-T4, 67.2 Gy vs 75.6 Gy

Shipley, IJROBP, 1995

MGH

Boston

PBT-History

■ MGH Phase III results:

- Decreased local failure in all patients treated with PBT. Reached statistical significance in Gleason 8-10 tumors only.
- Increased rectal bleeding (primarily grade 1) in high-dose group.
- No difference in survival.



C. Rossi-LLUMC. ESTRO 2008

First Phase III randomized trial

MGH & LLUMC

392 patients with early stage

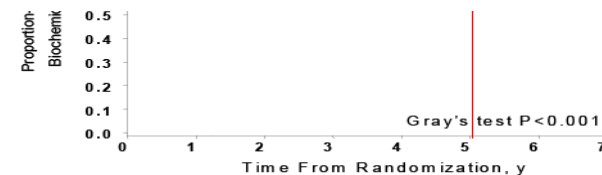
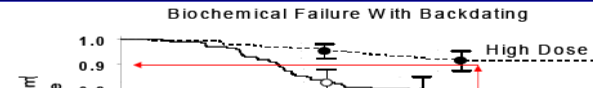
Same results of MD Anderson phase III trial (70 vs 78 Gy) with photon EBRT

Pollack A et al, IJROBP, 2002

Zietman AL et al, JAMA, 2005
Update at 10 years
b-NED

High Dose 83.7%
Conventional Dose 64.7%
(P=0.0001)

**PROG 9509-Overall bNED
Survival-ASTRO Definition**



No. at Risk	116	116	114	111	105	69	29	14
High Dose	111	110	99	92	90	58	23	8
Conventional Dose								

C. Rossi-LLUMC. ESTRO 2008

Efstathiou J, Bekelman J (MGH, Uni Penn).

Phase III Randomized Trial of Protons vs IMRT (79.2 Gy)
for low or low-intermediate risk Prostate Cancer

***Primary endpoint *EPIC bowel
scores at 6 months***

350 patients randomized

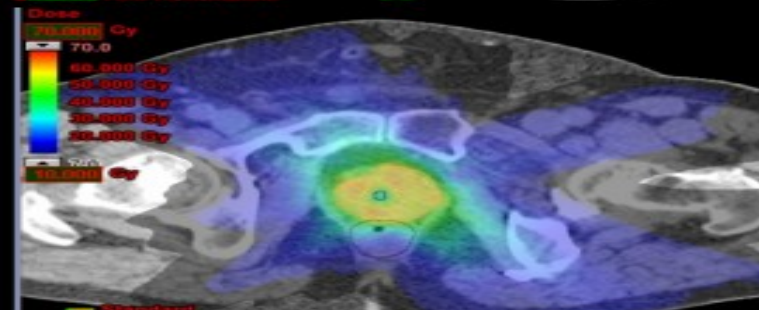
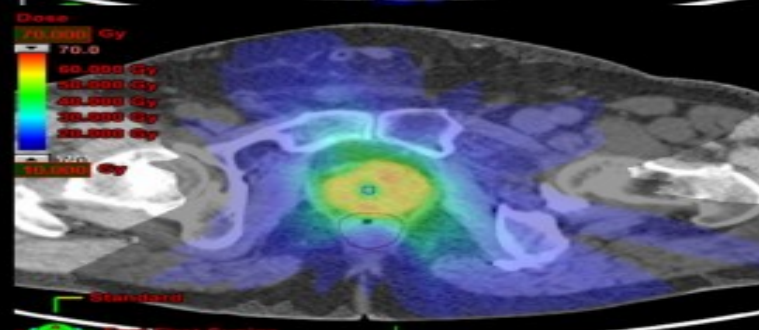
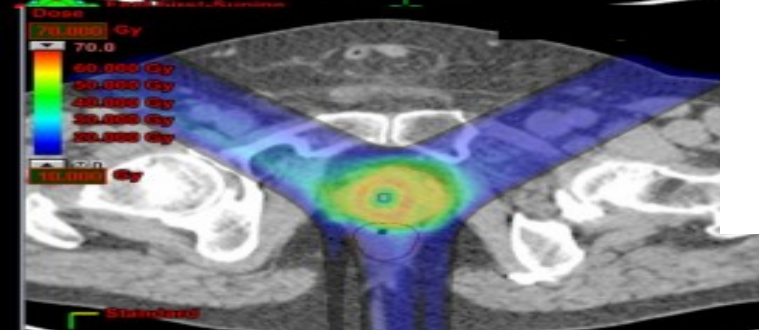
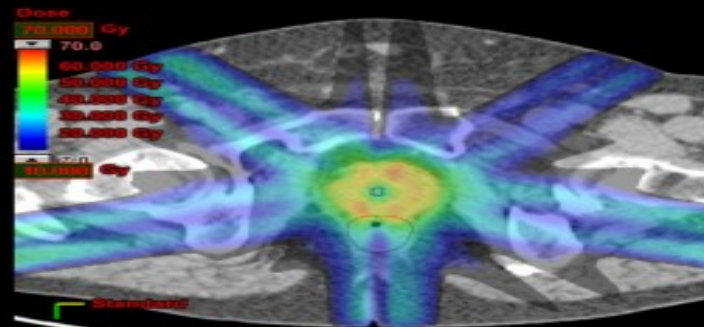
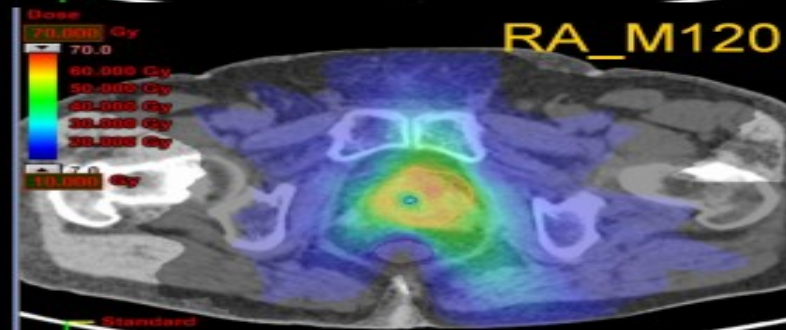
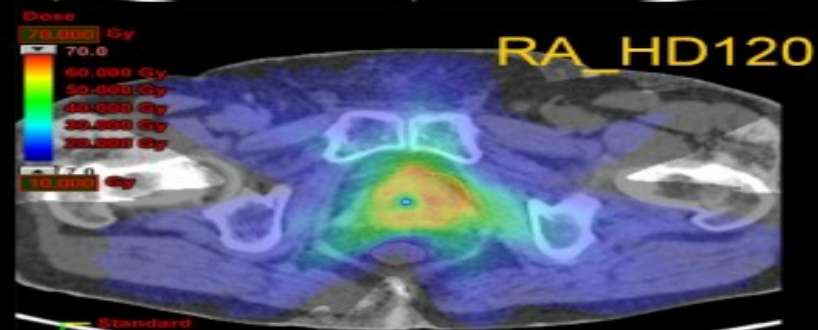
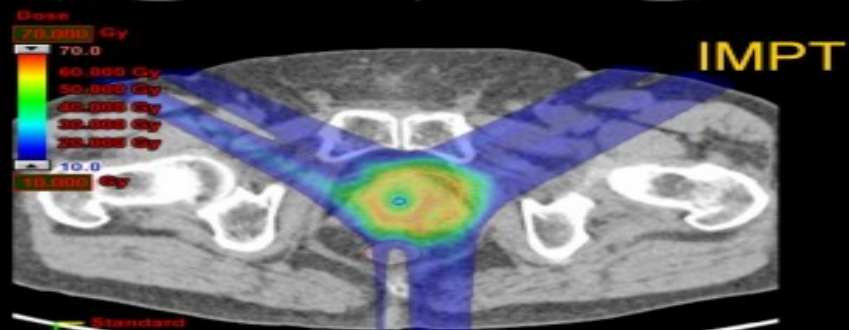
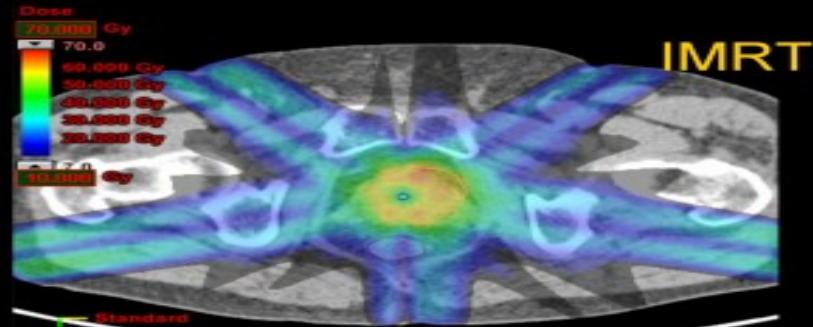
****EPIC: Expanded Prostate Cancer Index Composite***

Hadrontherapy



Which endpoint?

**Integral Dose
3 times higher
for all
photon's
techniques**



Chung CS et al (Harvard & MGH, Boston).

Comparative analysis of second malignancy in patients treated with proton therapy versus conventional photon therapy.

50 th ASTRO Meeting, Boston, 2008

“treatment with photon therapy was significantly associated with an increased risk of a second malignancy (1.87 to 3.98, $p < 0.0001$)”

How many patients would one need to demonstrate a significant reduction in 2 nd tumors?

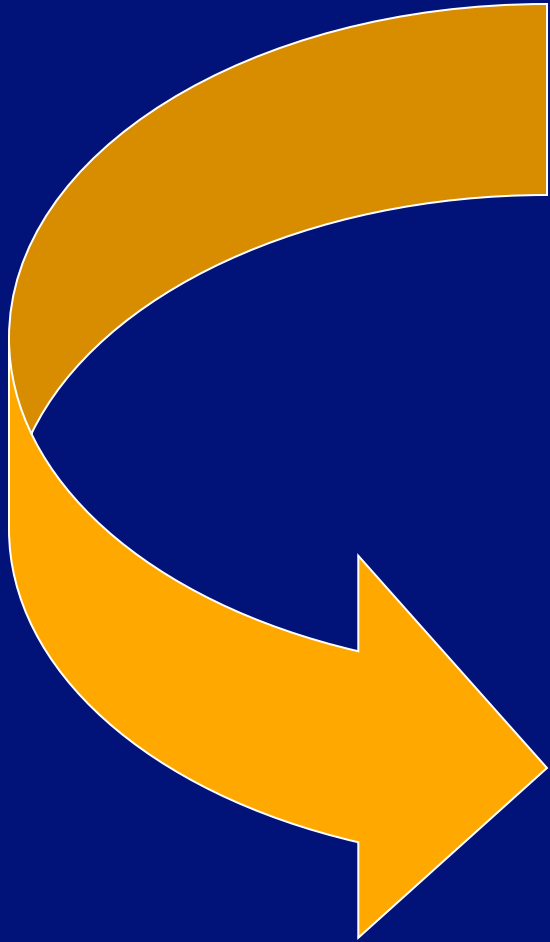
-Assume 60% decrease in 0.5% incidence at 15 y (NCI)

-For 80% power at $p=0.05$

	1-sided	2-sided	
5 y average FU	13509	17280	(pts per arm)
10 y FU	6759	8646	
15 y FU	4510	5768	

T De Laney, PTCOG, Seoul, 2012

In conclusion. What we know today on hadrons?



- **Ideal dose distribution**
- **Excellent results in specific tumour sites**
- **At least equivalent results in almost all cancer, including radioresistant tumours**
- **Less morbidity, in principle**

*What we have to do for
improving our evidence?*

*Produce well designed
clinical trials*

Very interesting studies

Hadrons versus surgery

Heavy ions versus Protons

Concurrent chemo/molecular drug

Multidisciplinary approach for poor prognosis sinonasal tumors

Induction chemotherapy, concomitant radiochemotherapy, and surgery, if operable

Endpoints: *increase PFS (P), OS, decrease late toxicity, preserve visual functionality*

Techniques: *IMRT, V-Mat or Helical up to 50.4 - 54Gy, plus boost (18-21 Gy) with PBT or CIRT (anticipated)*

Functional & molecular imaging

Biological markers on biopsy: P53, P16, EMT (Epithelial-mesenchymal Transition), Radioresistance (SPK-II)

Other protocols in developing

- Glioblastoma: operable and inoperable, IMRT plus PBT vs CIRT boost (and TMZ)
- High grade sarcoma, operable: EBRT, brachytherapy boost (anticipated) vs PBT vs CIRT boost (postoperative)
- Pancreas/Biliary tract: induction CT, EBRT only vs EBRT plus PBT vs EBRT plus CIRT

Some Issues for Innovative Studies

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graph TD; A[Some Issues for Innovative Studies] --> B[Multicentric/ Multidisciplinary ESTRO, EORTC]; A --> C[High Tech RT vs Proton Vs Carbon]; A --> D[Altered Fractionation]; A --> E["Difficult" tumors, not only for dose distribution, but for radioresistance]; A --> F[Different endpoints, not only in LC & S, but in QoL]; A --> G[Molecular Imaging & Biology driven];
```

**Multicentric/
Multidisciplinary
ESTRO, EORTC**

**High Tech RT
vs Proton
Vs Carbon**

**Altered
Fractionation**

**“Difficult” tumors,
not only for dose
distribution, but for
radioresistance**

**Different endpoints,
not only in LC & S,
but in QoL**

**Molecular Imaging
& Biology driven**

ULICE

Union of Light Ion Centers in Europe



An aerial photograph of a modern architectural complex at dusk. The buildings have large glass windows and some are illuminated from within. The ground is covered in a layer of snow. In the foreground, there is a parking lot with several cars. A small, circular structure, possibly a guardhouse or entrance kiosk, is visible near the parking lot. The sky is a mix of blue and orange, indicating the time is either dawn or dusk. A blue rectangular box with white text is overlaid on the bottom portion of the image.

**Thank you very much
for your attention !!!!!**