ENLIGHT and the present and future of clinical perspective

fondazioneCNAO

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 T
Proton Radiotherapy?

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

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

Special communication

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

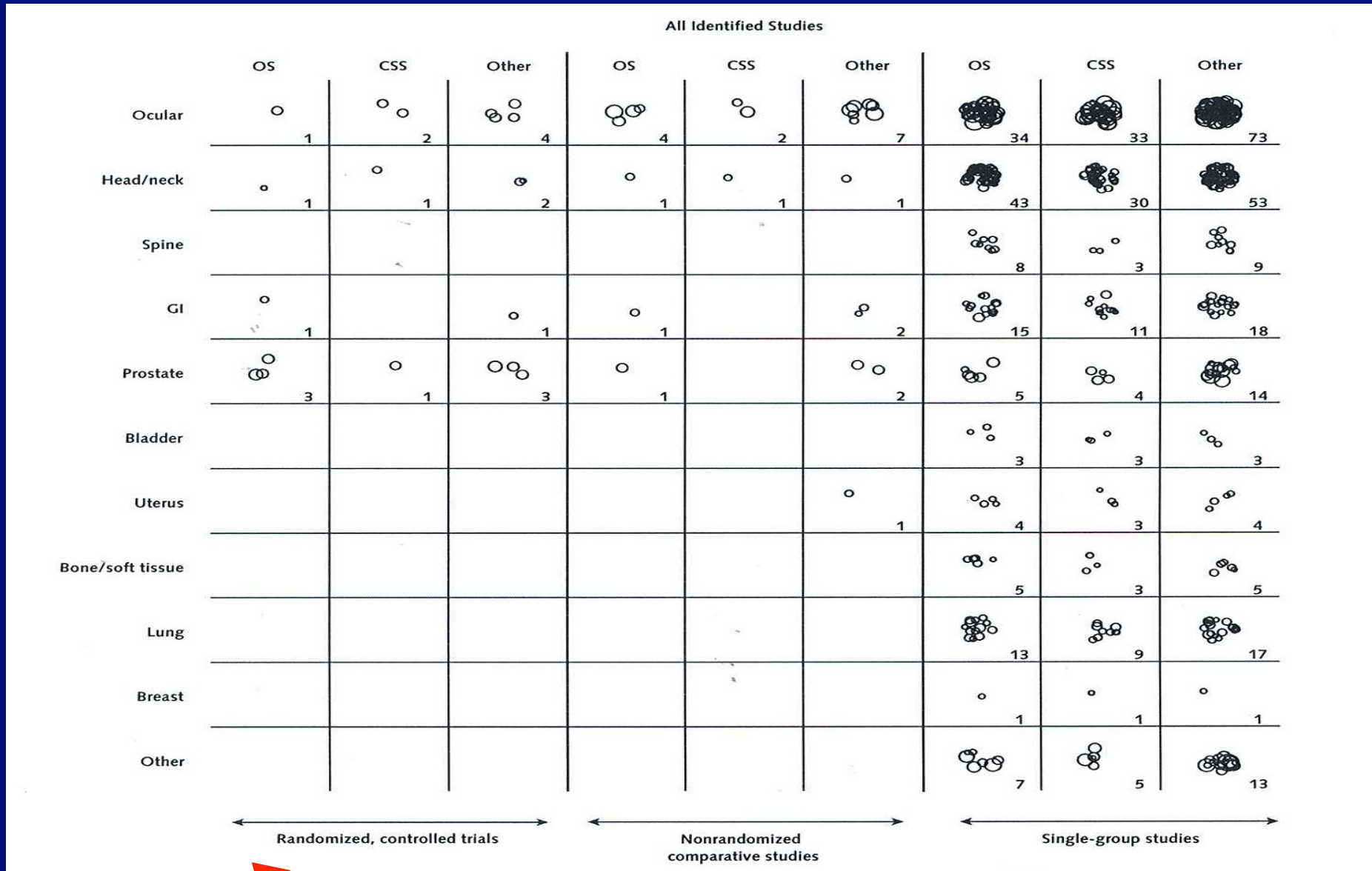
Proton Therapy in Clinical Practice: Current Clinical Evidence

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

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

Bengt Glimelius[a,b,*], Anders Montelius[a]

[a]*Department of Oncology, Radiology and Clinical Immunology, Uppsala University Hospital, Uppsala, Sweden,* [b]*Department 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]

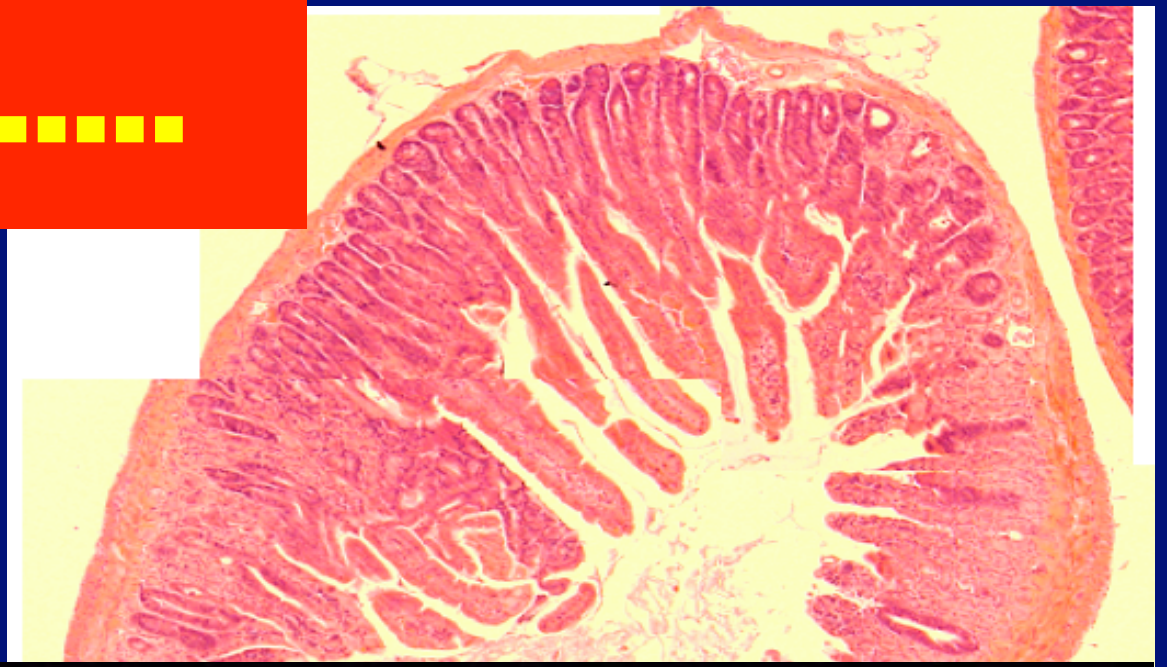
- Insufficient evidence in any of the disease sites

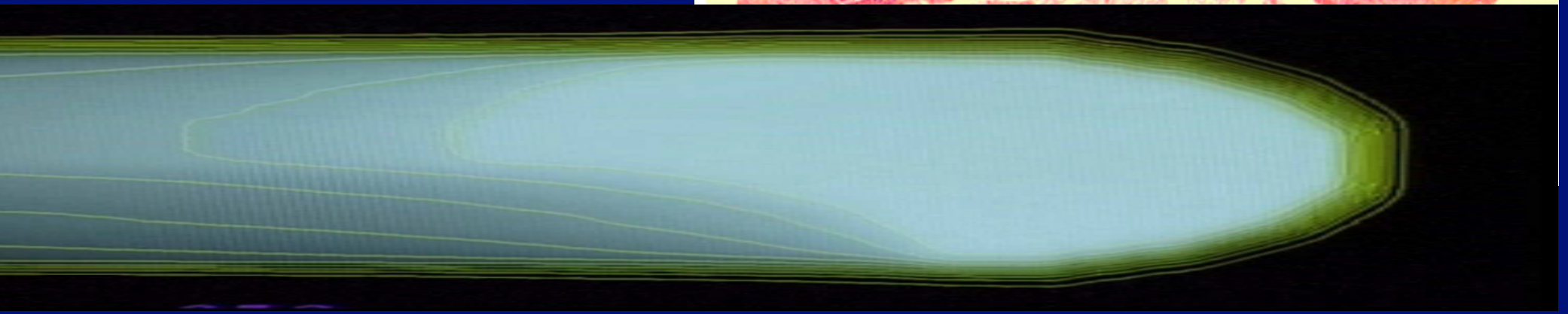
  [Brada M et al, JCO, 2008]

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 ouside 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

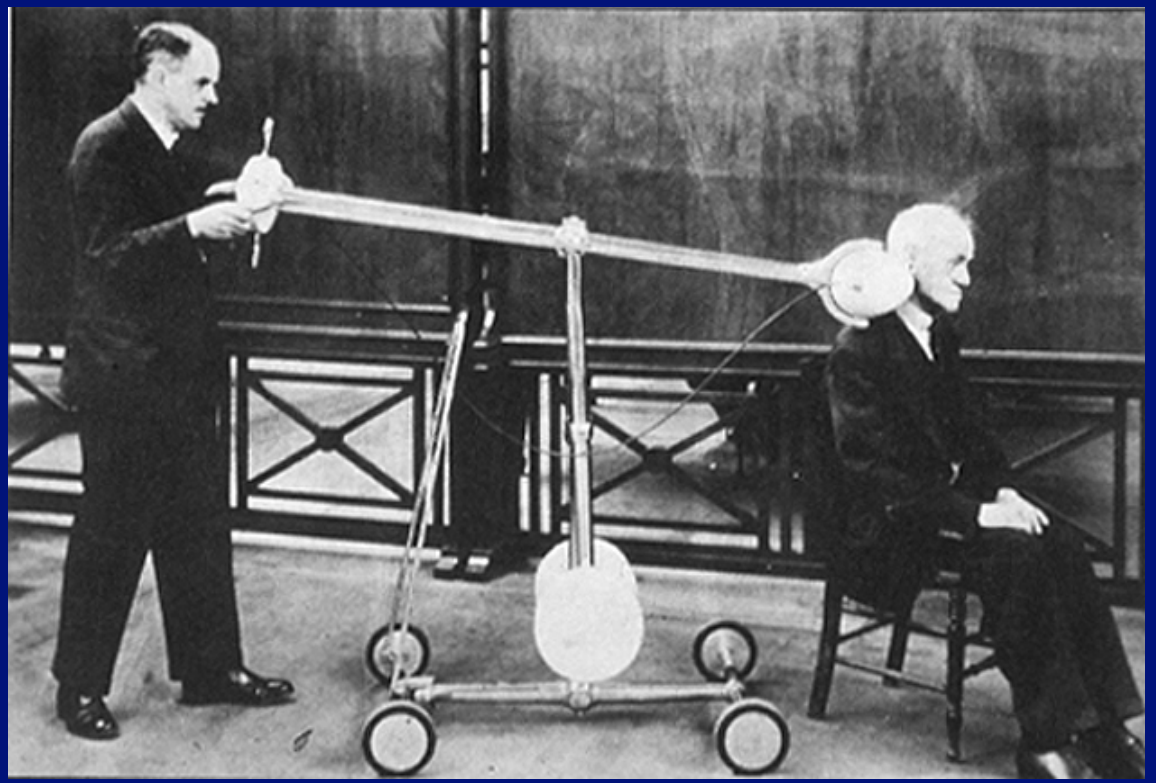
a new dimension .....

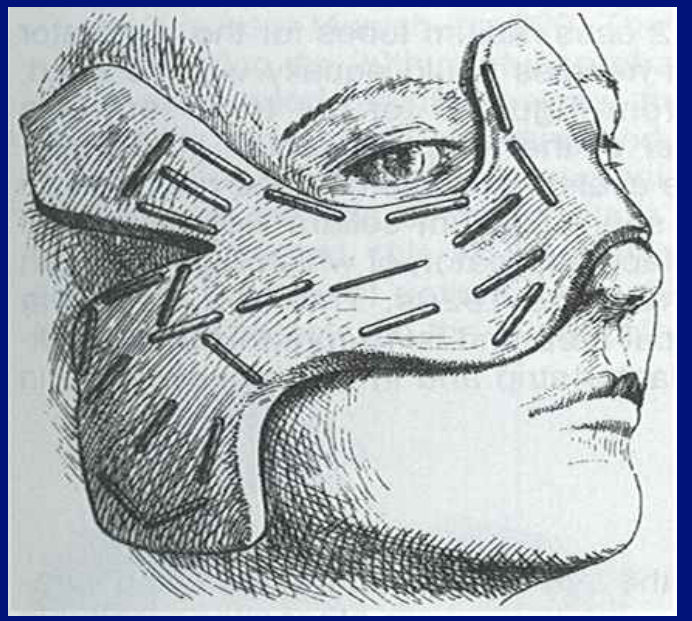


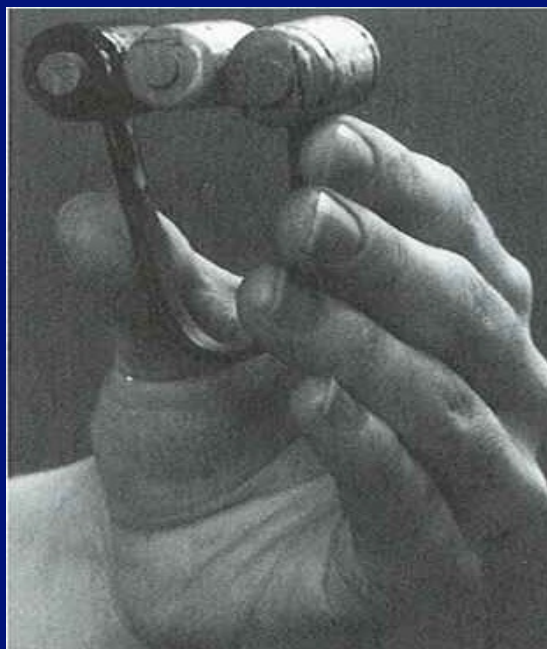


Hadrontherapy

Dose distribution ?

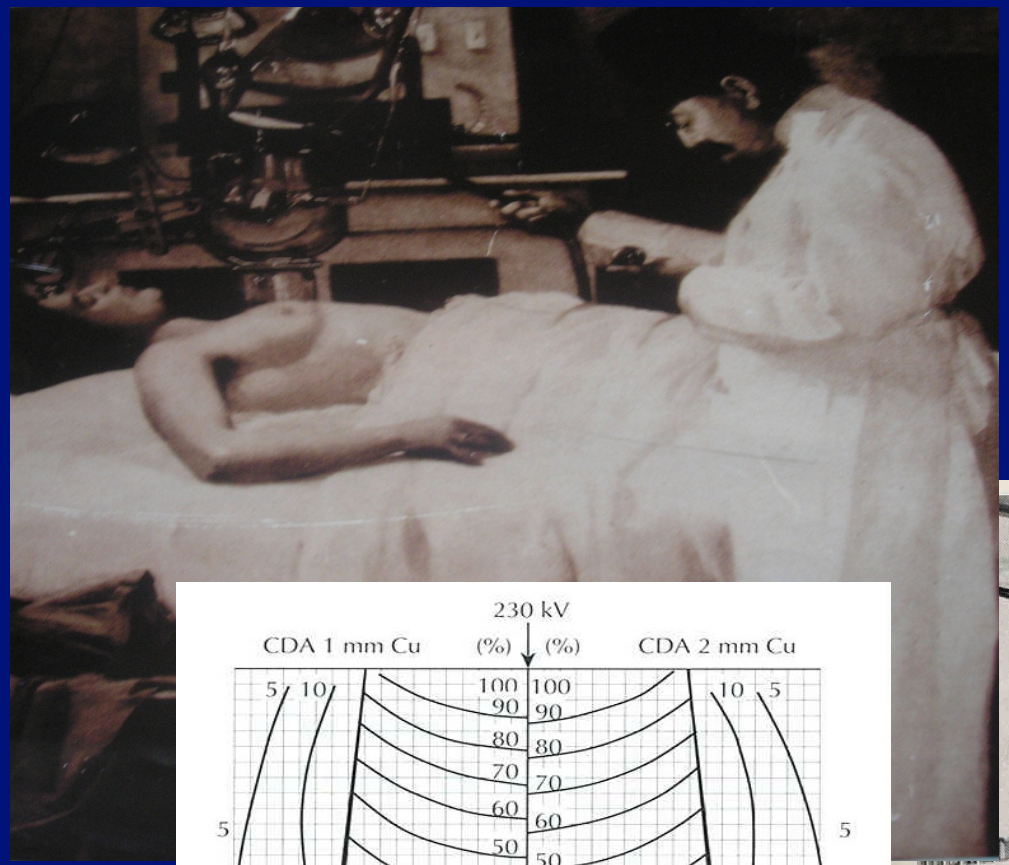


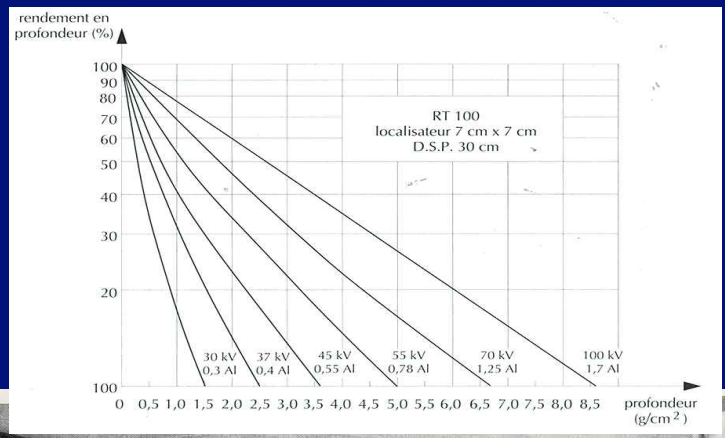


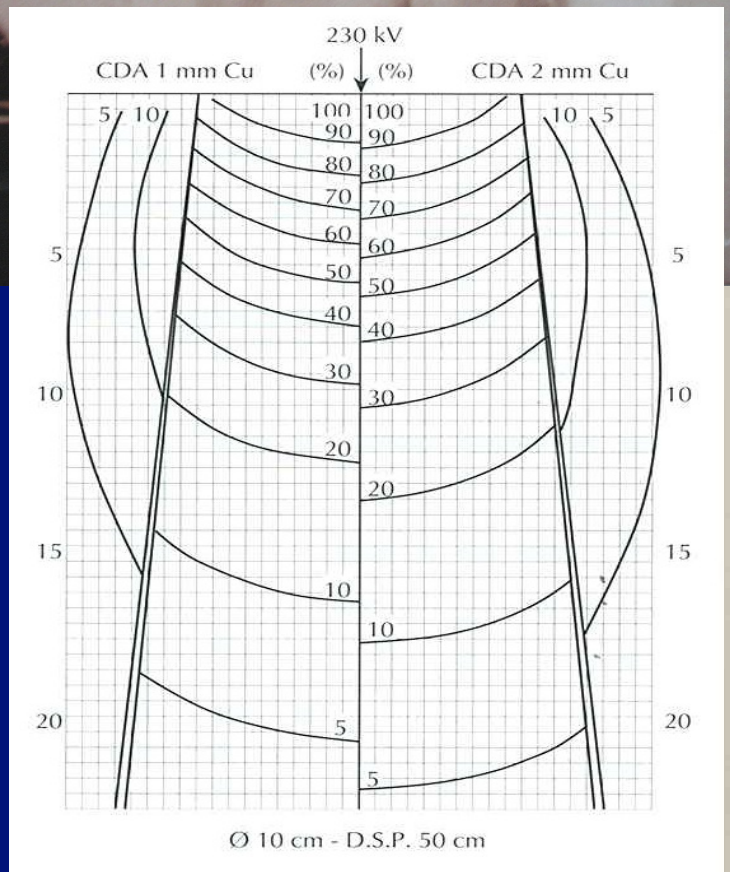


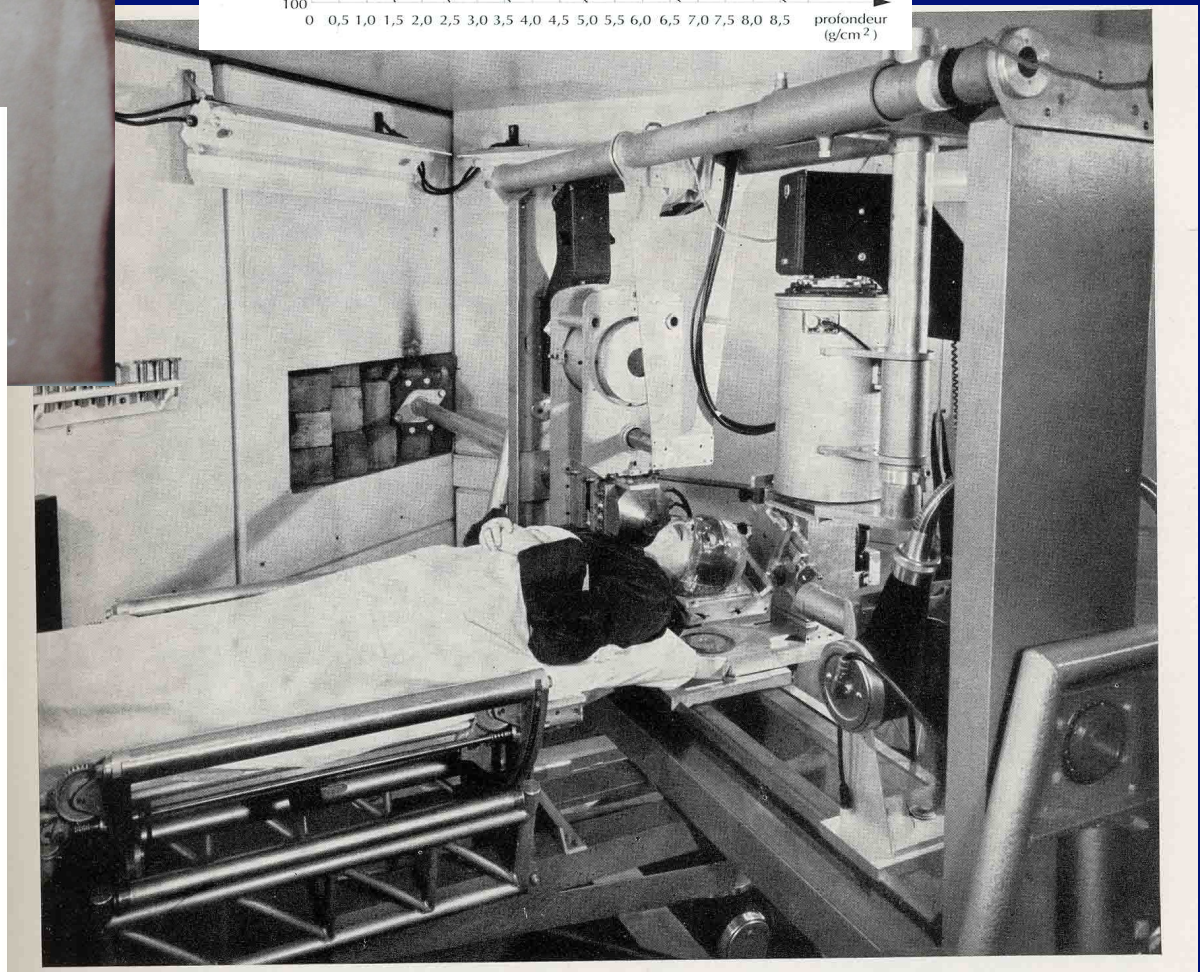
Paris schedule cervix uteri

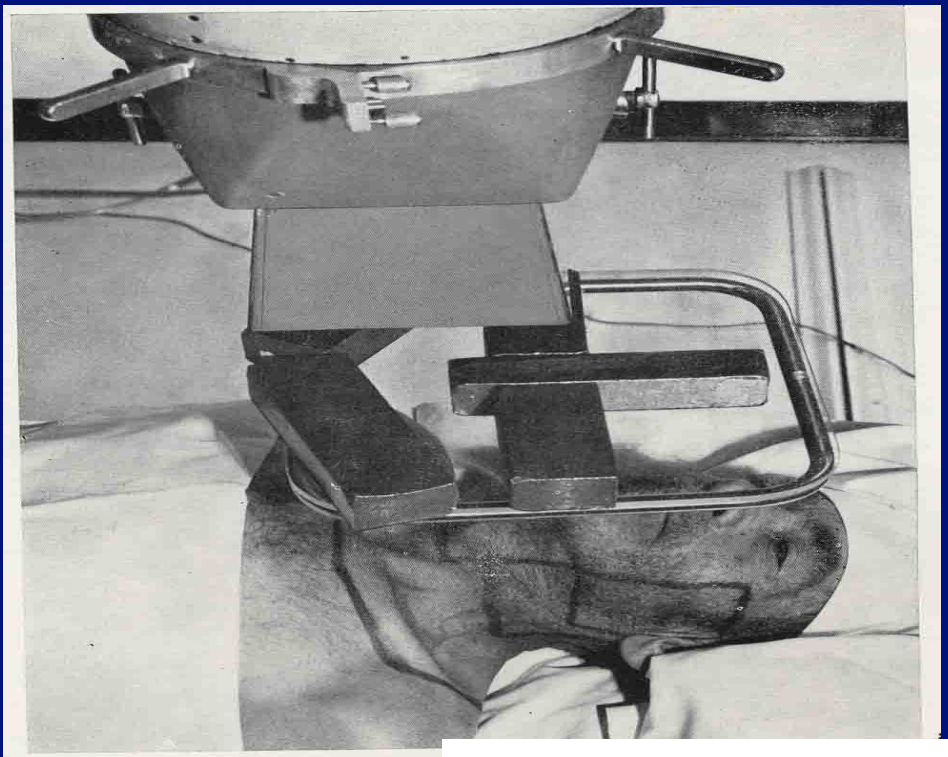
Continous treatment for 120 hours
Uterine tube of 33.3 mg radium
Two vaginal cylindrical corks: 13.3 mg radium each

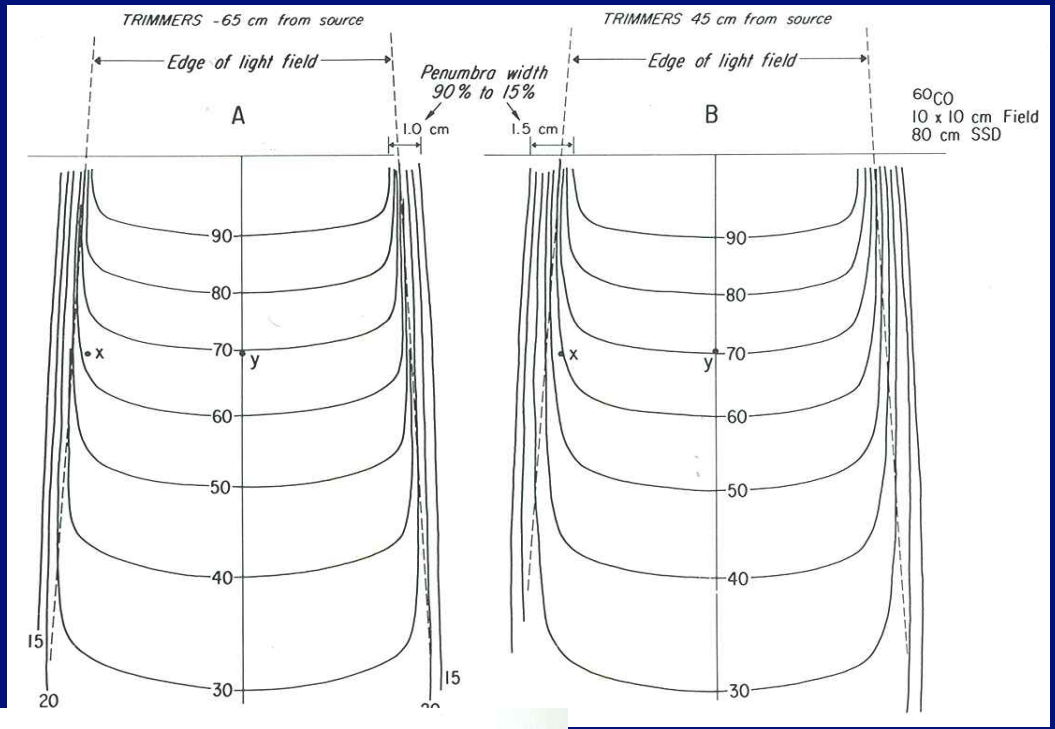


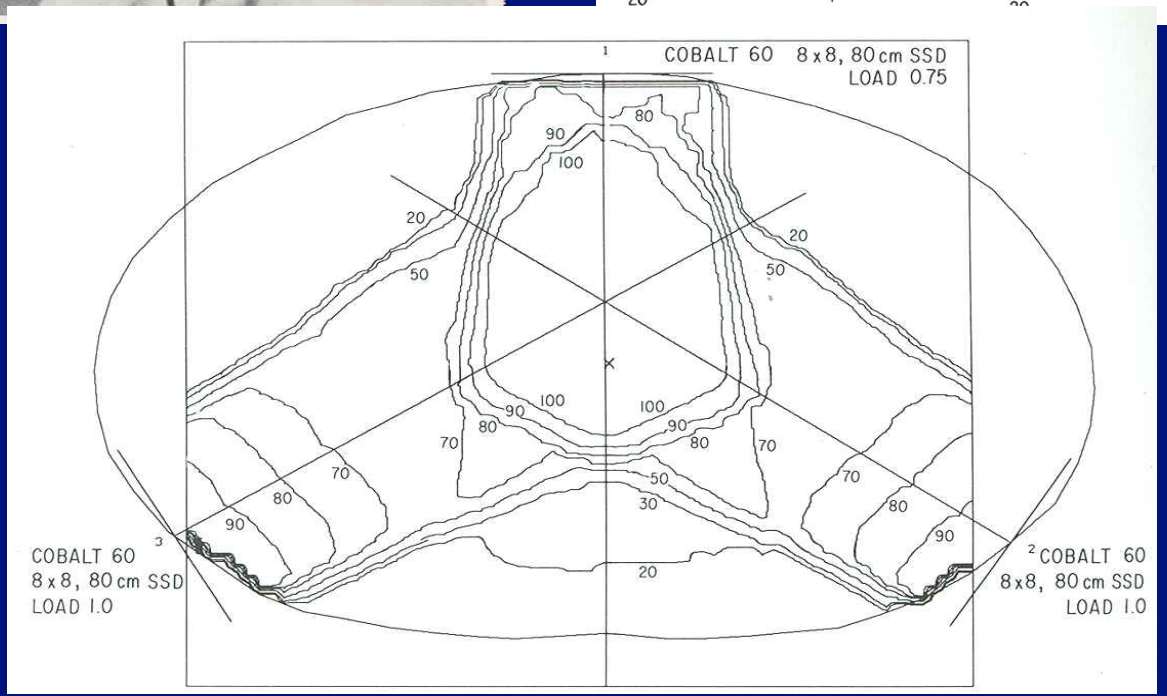

rendement en
profondeur (%)
100
90
80
70
60
50
40
30
20
100
RT 100
localisateur 7 cm x 7 cm
D.S.P. 30 cm
30 kV
0,3 Al
37 kV
0,4 Al
45 kV
0,55 Al
55 kV
0,78 Al
70 kV
1,25 Al
100 kV
1,7 Al
0 0,5 1,0 1,5 2,0 2,5 3,0 3,5 4,0 4,5 5,0 5,5 6,0 6,5 7,0 7,5 8,0 8,5
profondeur
(g/cm²)


230 kV
CDA 1 mm Cu
(%)
(%)
CDA 2 mm Cu
5
10
100
90
80
70
60
50
40
30
20
10
5
Ø 10 cm - D.S.P. 50 cm

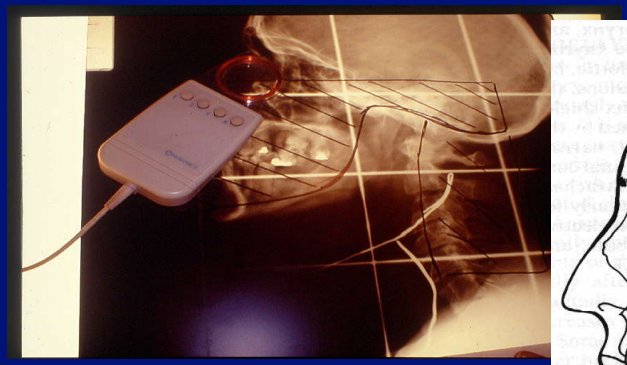


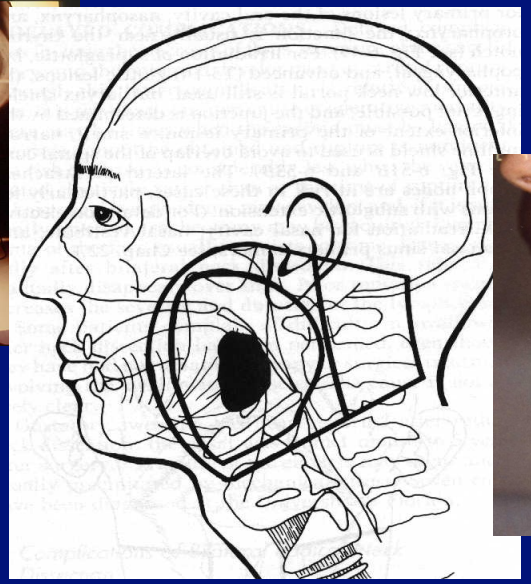



TRIMMERS -65 cm from source
Edge of light field
A
1.0 cm
Penumbra width
90% to 15%
TRIMMERS 45 cm from source
Edge of light field
B
1.5 cm
60CO
10 x 10 cm Field
80 cm SSD
90
80
70
60
50
40
30
x
y
15
20

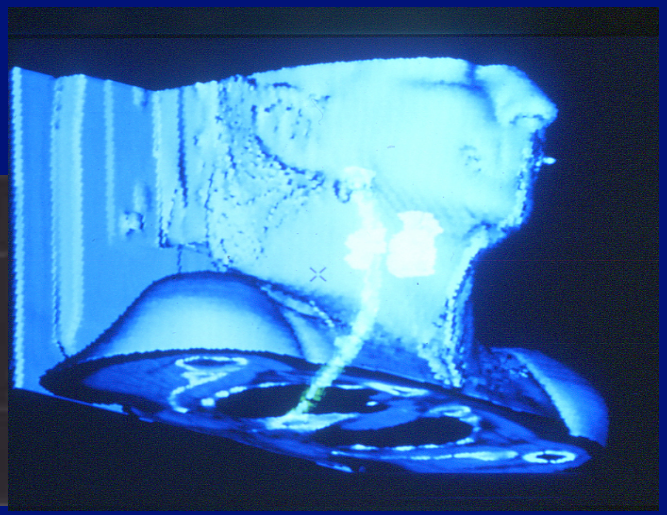

COBALT 60 8x8, 80cm SSD
LOAD 0.75
1
2
3
COBALT 60
8x8, 80 cm SSD
LOAD 1.0
COBALT 60
8x8, 80 cm SSD
LOAD 1.0
90
80
100
20
50
70
30
x

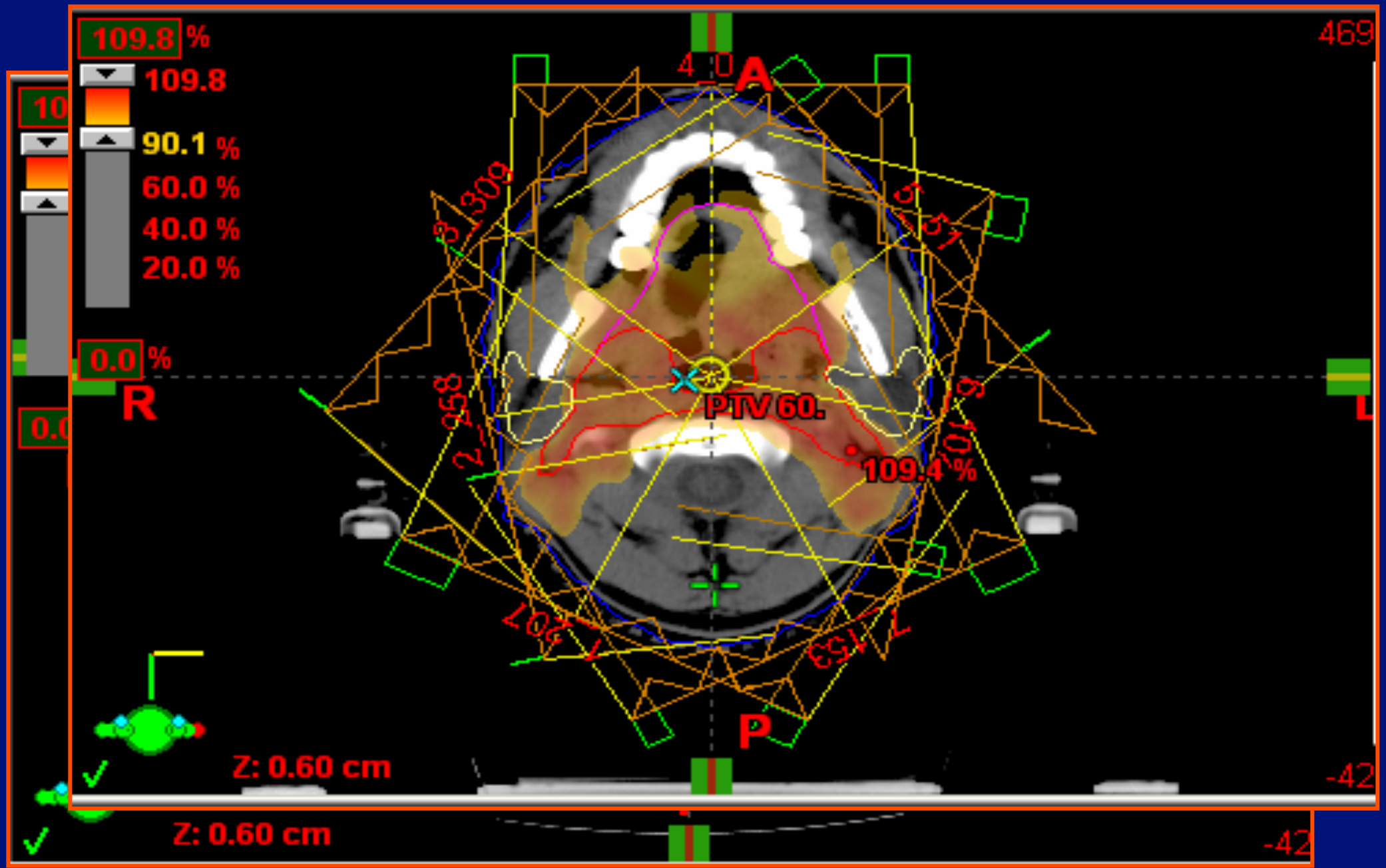
From 2-D

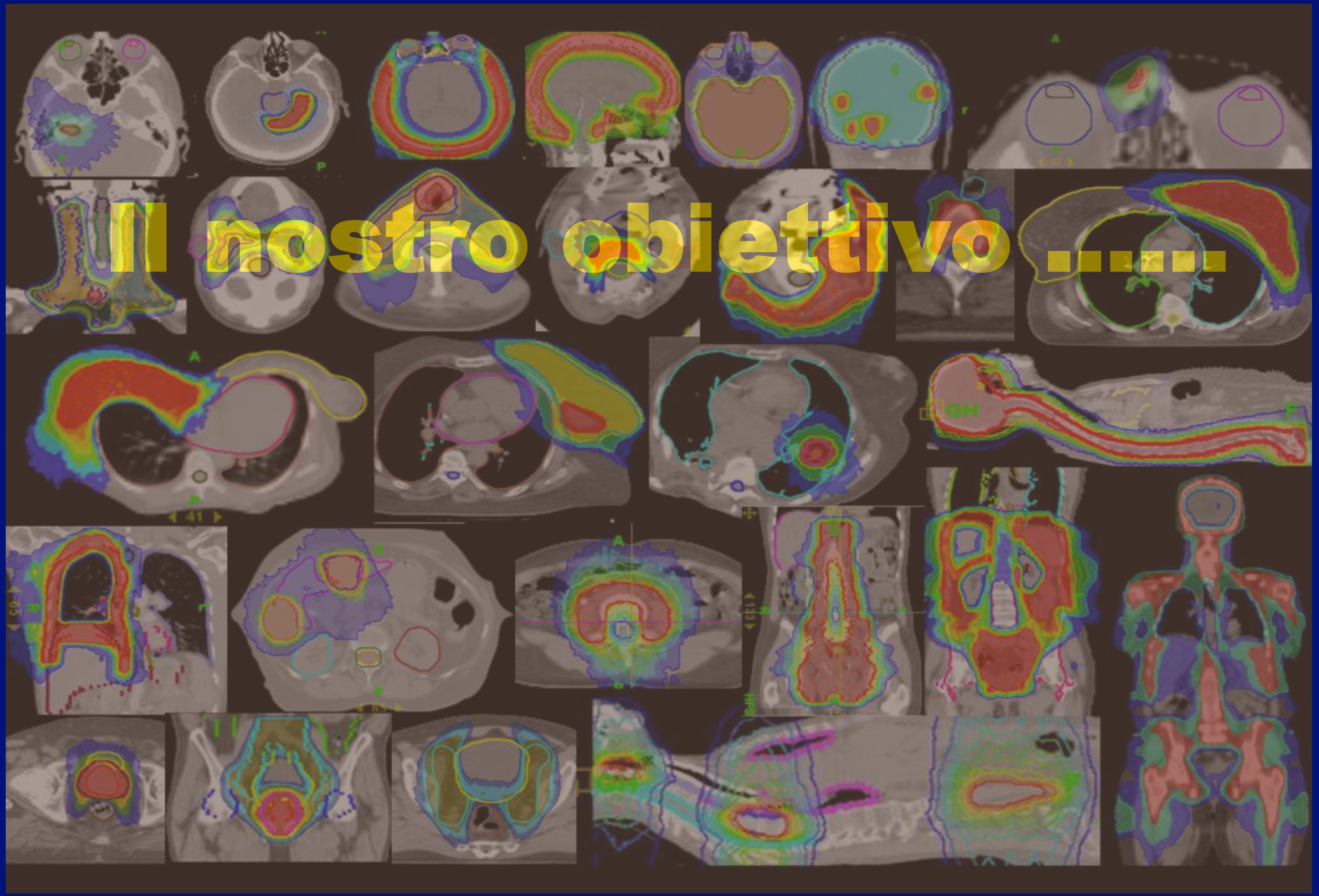




To 3-D




109.8 %
109.8
90.1 %
60.0 %
40.0 %
20.0 %
0.0 %
469
A
R
L
P
PTV 60.
109.4 %
Z: 0.60 cm
-42
Z: 0.60 cm
-42


Il nostro obiettivo .....

Dose Distibution ?

Is not a clinical issue

but

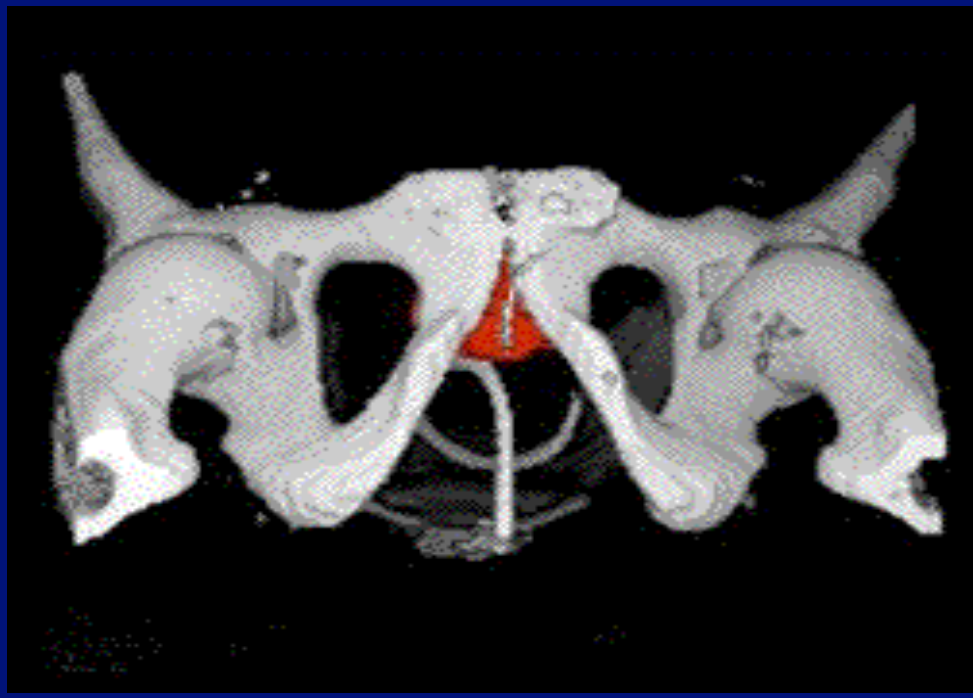
It's the condition necessary to improve clinical outcomes

Marketing

- 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

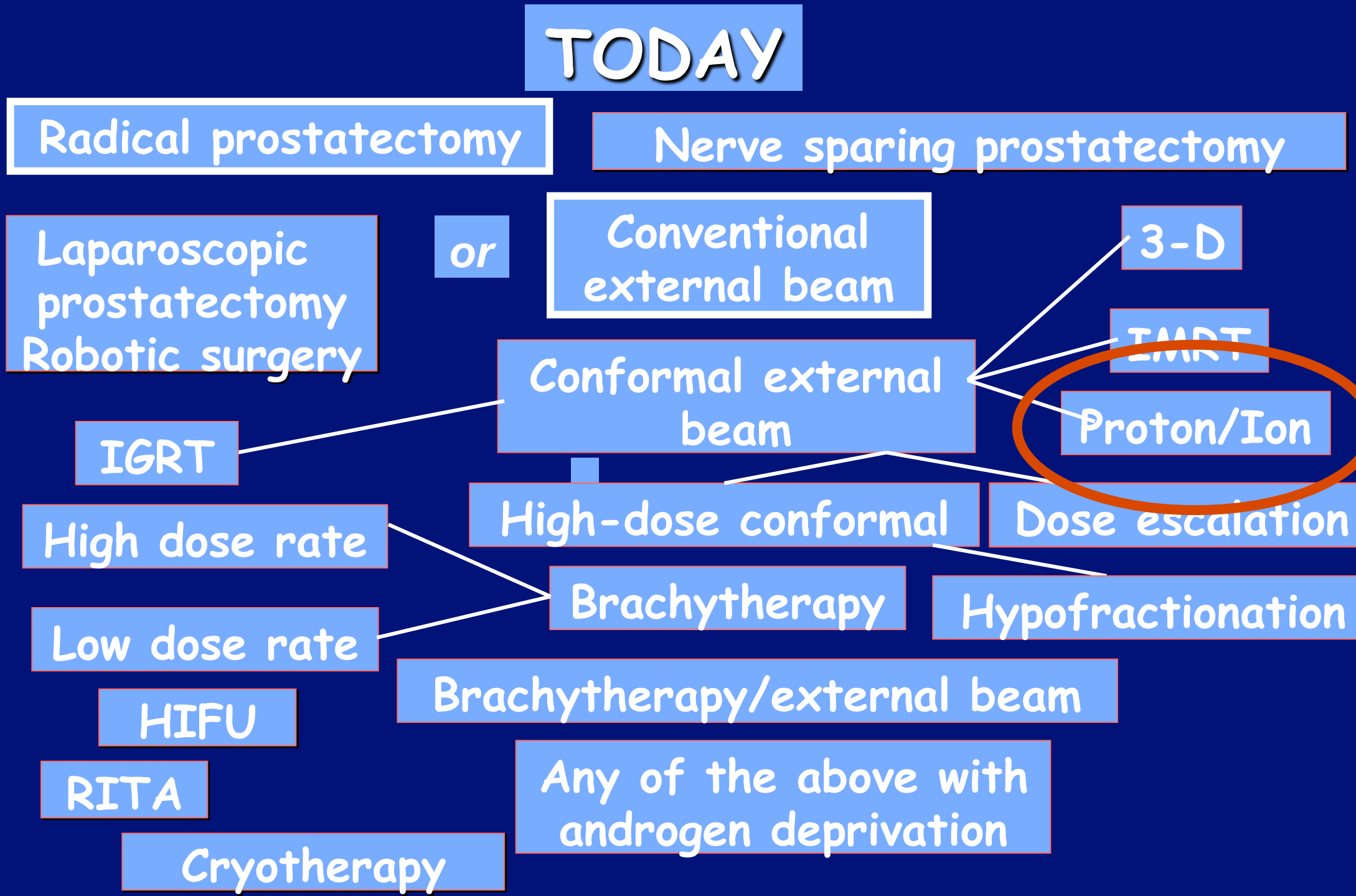
Conformal external beam

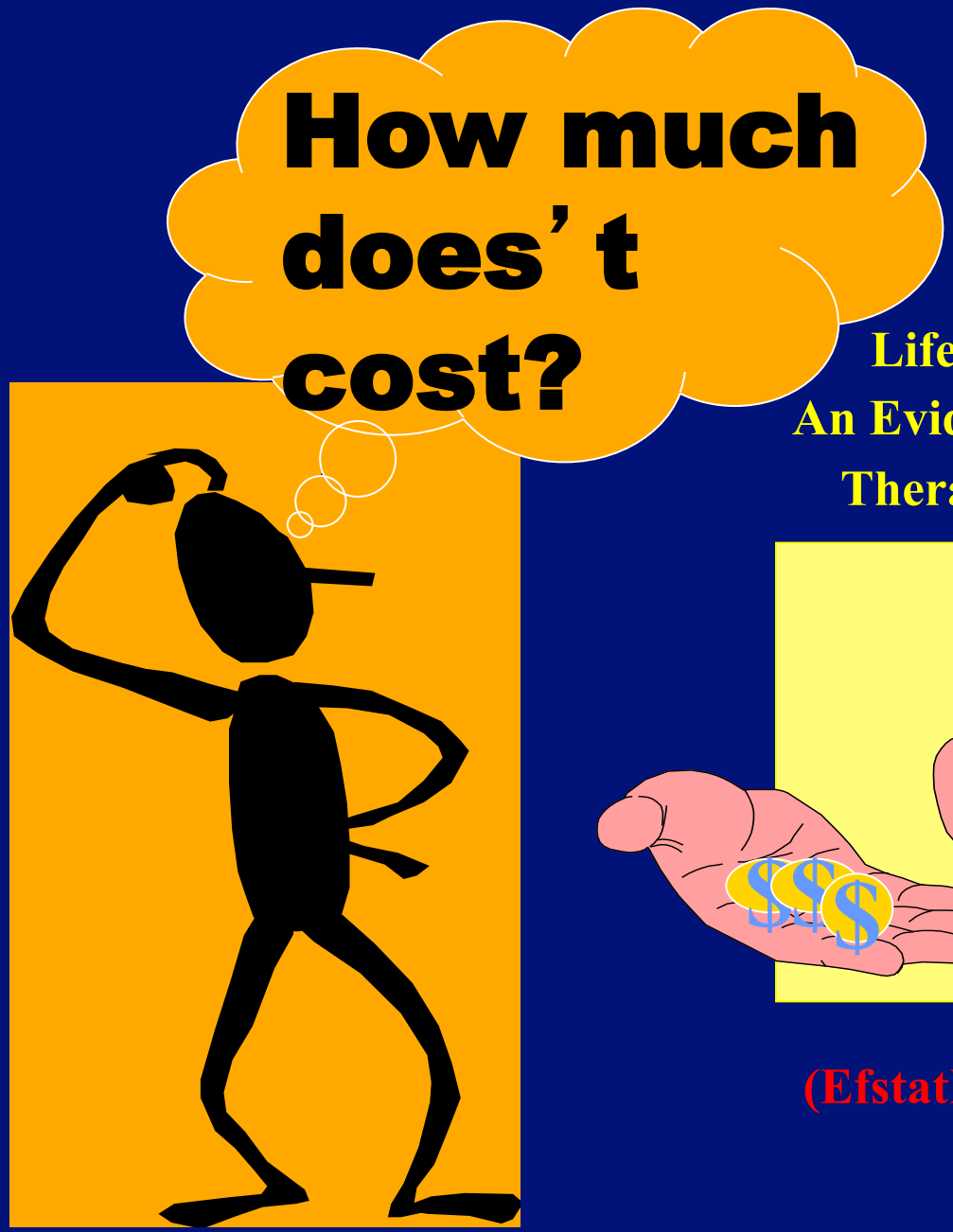
or

Brachytherapy

or

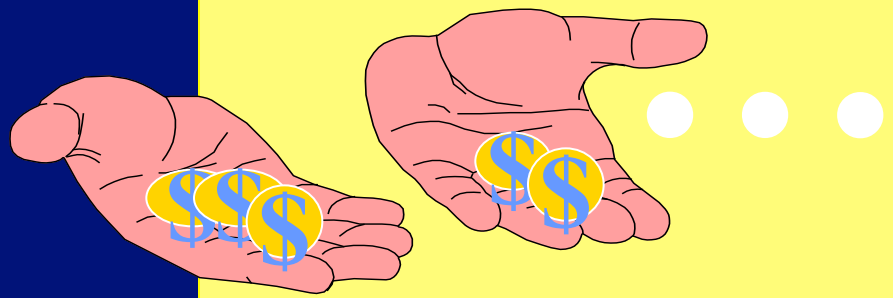
Brachytherapy/external beam


TODAY
Radical prostatectomy
Nerve sparing prostatectomy
Laparoscopic prostatectomy Robotic surgery
or
Conventional external beam
3-D
IMRT
Conformal external beam
Proton/Ion
IGRT
High-dose conformal
Dose escalation
High dose rate
Brachytherapy
Hypofractionation
Low dose rate
Brachytherapy/external beam
HIFU
RITA
Any of the above with androgen deprivation
Cryotherapy



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

Hadrons



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


TERA
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

fondazione CNAO

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:

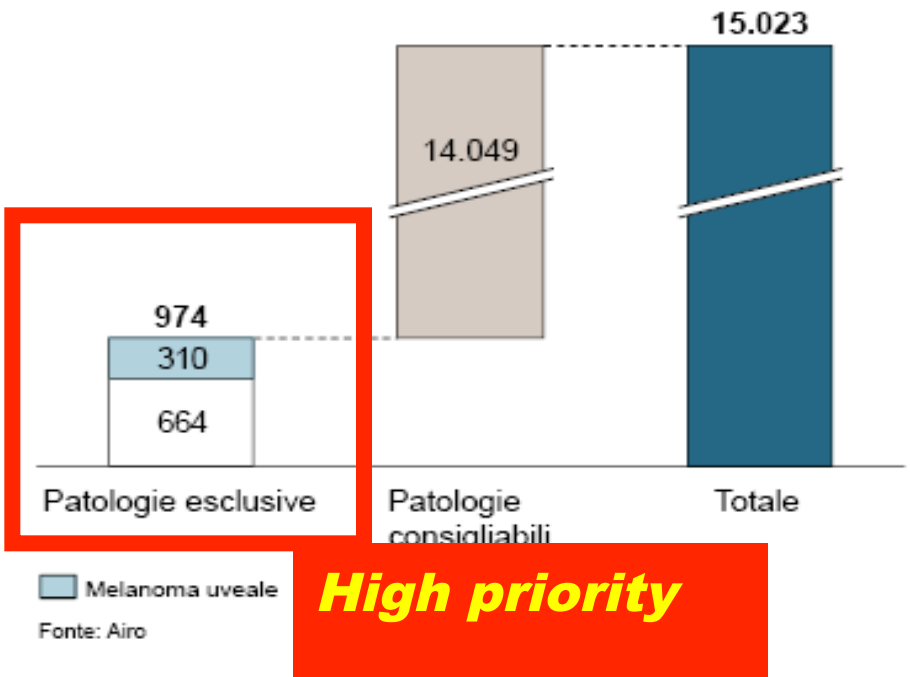
- To treat patients using hadrontherapy

- To perform clinical and radiobiological reasearch

Working Group 2003, 2008, 2009

Estimated 15.000 new eligible patients

in Italy for protons

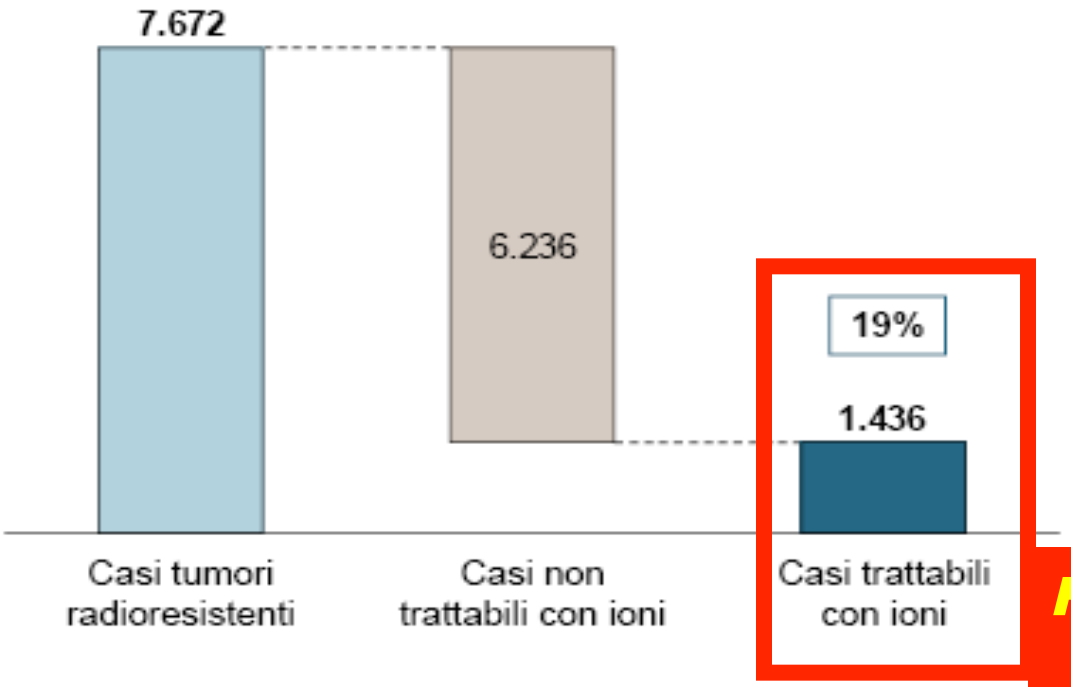


- Le principali patologie esclusive sono il melanoma uveale (corrispondendi al 47% delle patologie elettive), i cordomi della base cranica e della colonna vertebrale, i condrosarcomi dell'estremità cefalica e del tronco, i meningiomi della base cranica, i tumori paraspinali, gli schwannomi dei nervi 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 zione

High priority

Fonte: Airo

MIL-0101-08512-004-065-02

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

fondazione CNAO

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

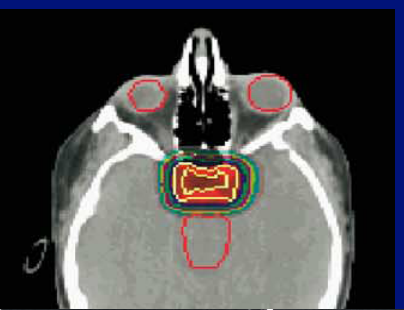
06/2011 Studio clinico di fase II: su boost di radioterapia mediante protoni (adroterapia) di neoplasie localmente avanzate del distretto cervico-cefalico

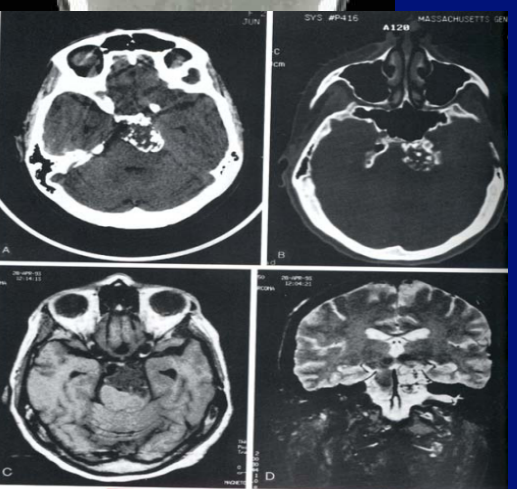
22 September 2011

Chordoma/ low grade chondrosarcoma
Skull base and spine

- Post op, Recurrent, Inoperable
- M0N0

- Contouring based on CT and MR fusion

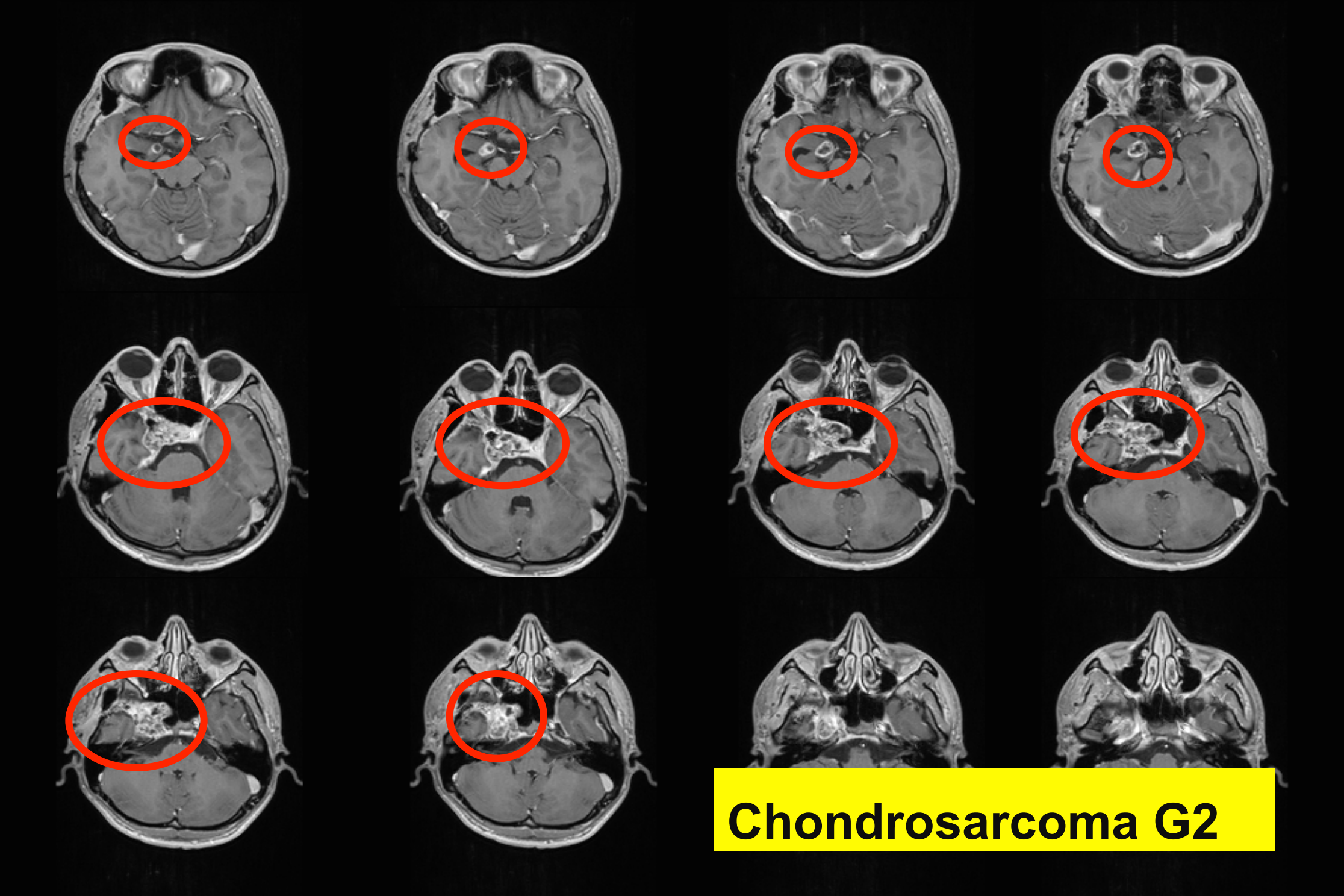




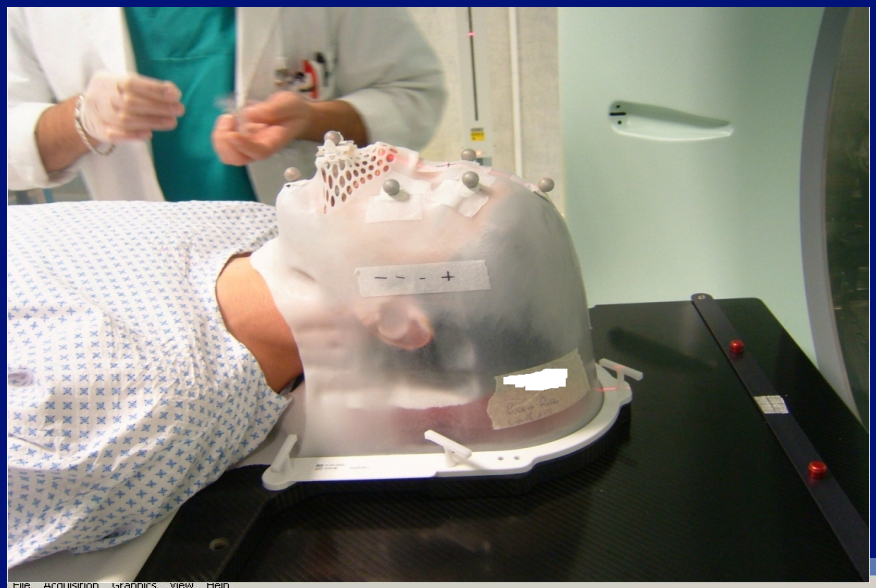
Dose chordoma: 74 GyE in 37 fractions,

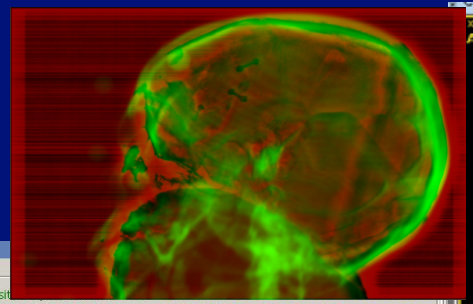
2 GyE per fraction, 5 fractions per week

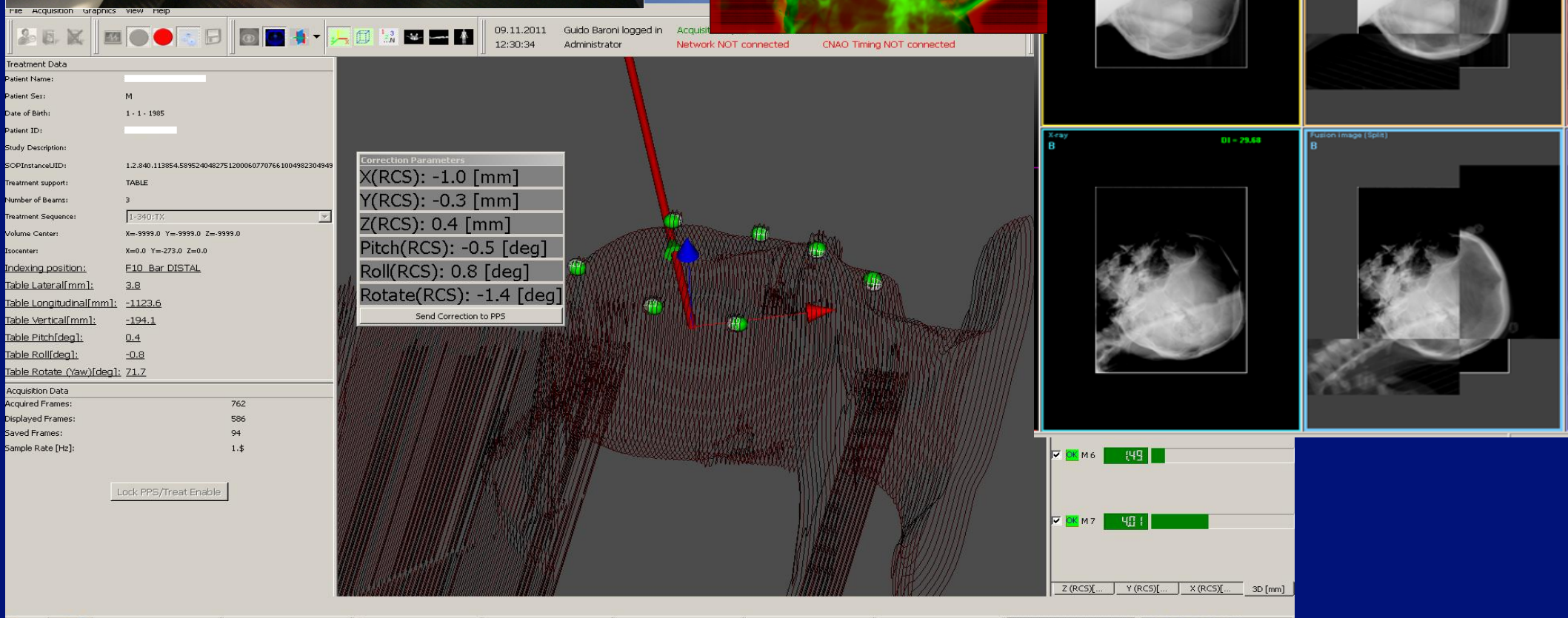
Dose chondrosarcoma: 70 GyE in 35 fractions, 2 GyE per fraction, 5 fractions per week

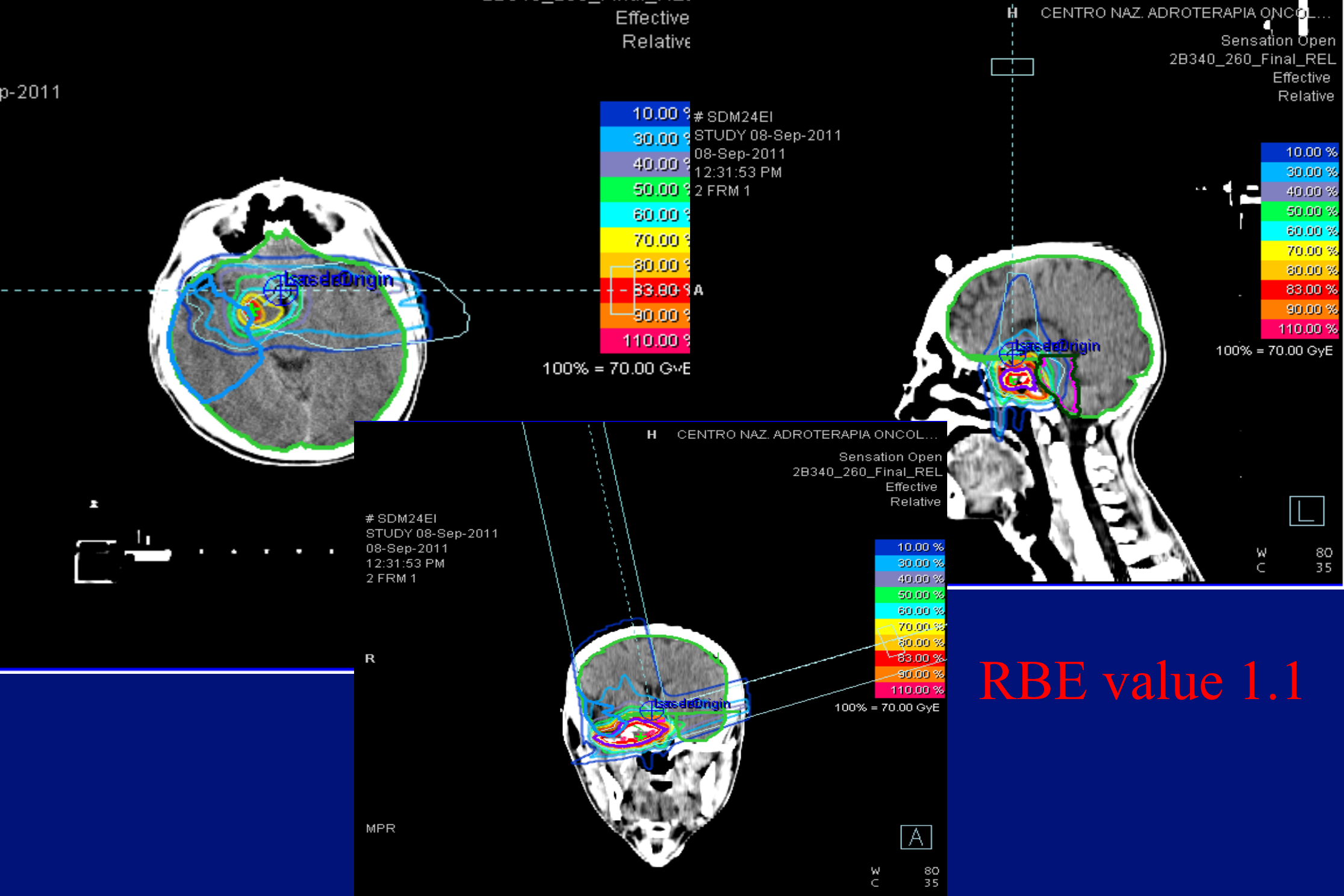

Chondrosarcoma G2

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

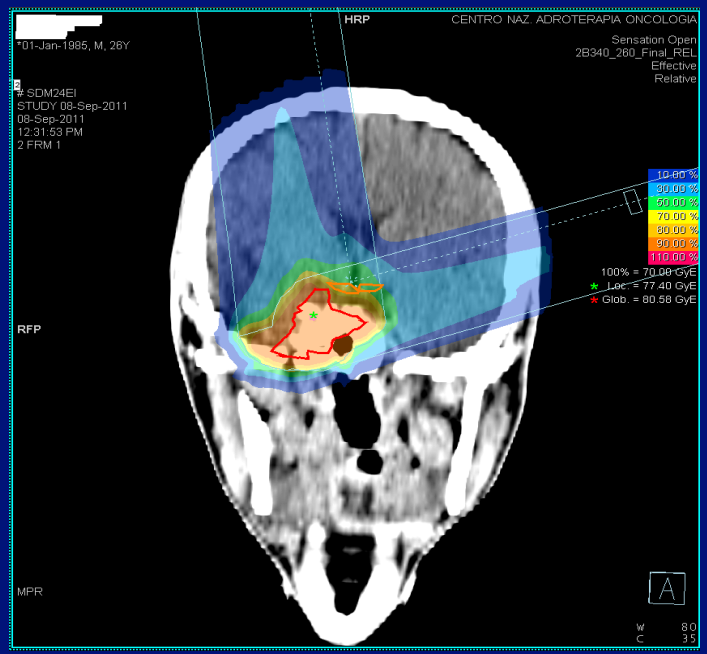


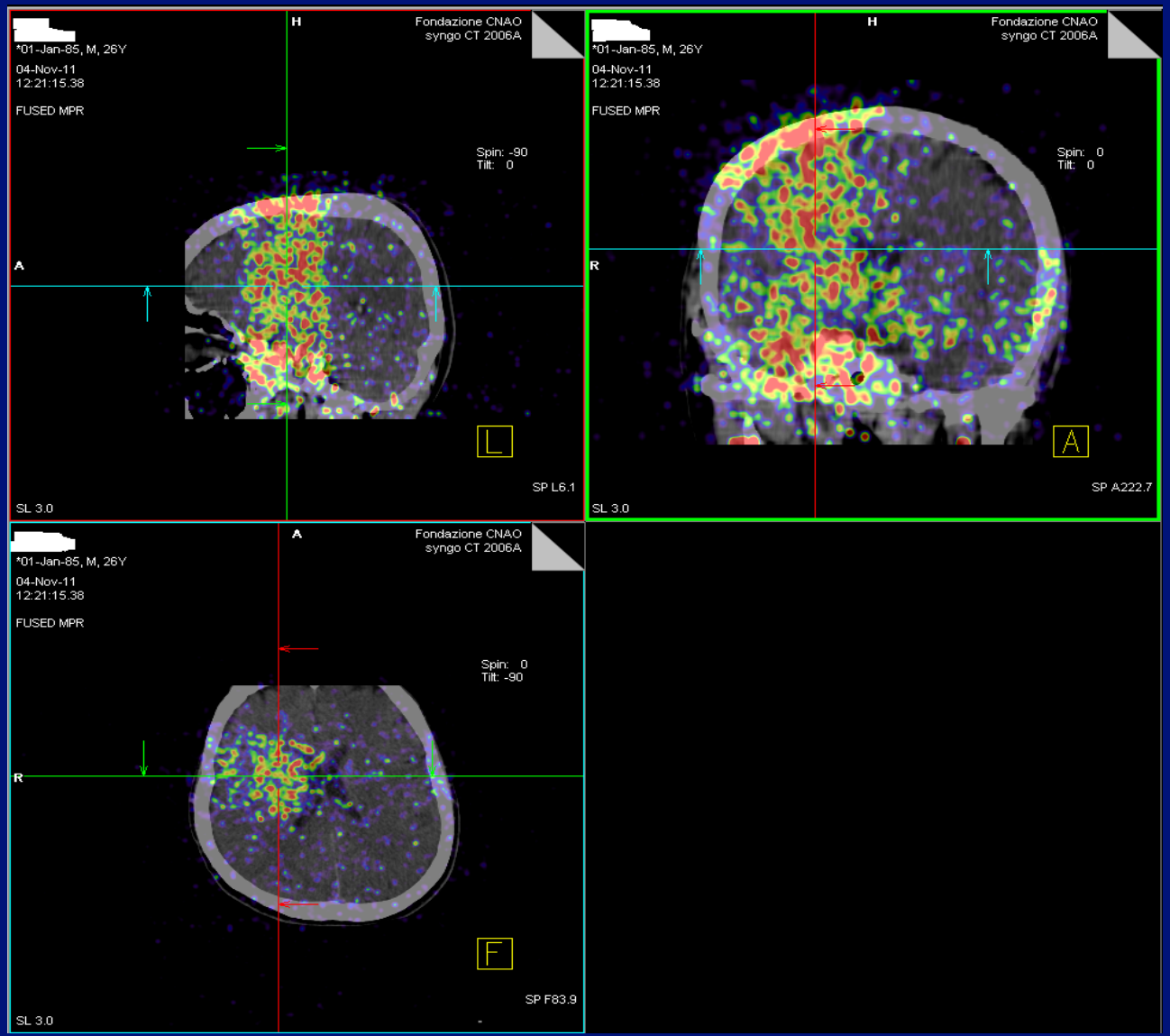





Effective
Relative
p-2011
10.00 %
30.00 %
40.00 %
50.00 %
60.00 %
70.00 %
80.00 %
83.00 %
90.00 %
110.00 %
SDM24EI
STUDY 08-Sep-2011
08-Sep-2011
12:31:53 PM
2 FRM 1
100% = 70.00 GyE
H
CENTRO NAZ. ADROTERAPIA ONCOL...
Sensation Open
2B340_260_Final_REL
Effective
Relative
MPR
R
A
L
W 80
C 35
RBE value 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

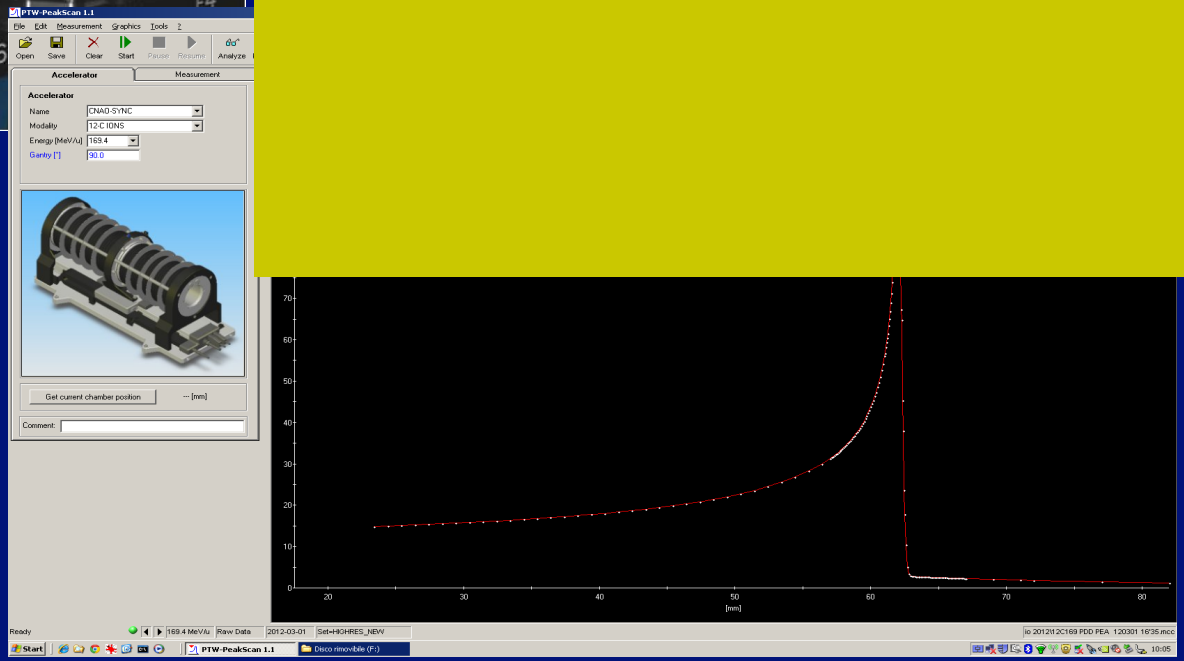
1 nasopharinx

Tumor type	
Chordoma	23
Condrosarcoma	5
Head & Neck carcinoma	2

10 under treatment

Carbon Ions

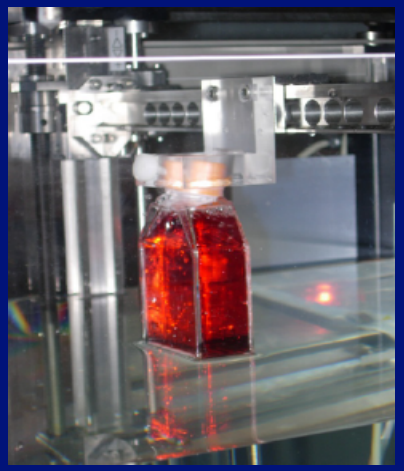
Physics



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

CNAO

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

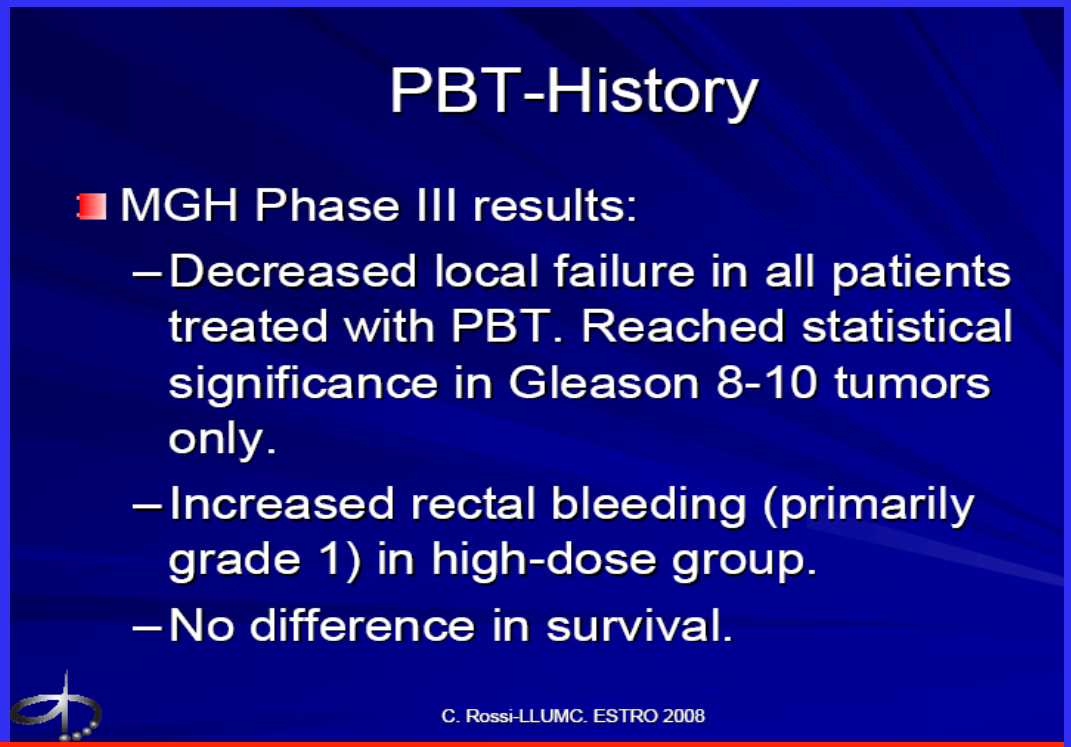
Proper design of clinical trial

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

Shipley, IJROBP, 1995

MGH

Boston



First Phase III randomized trial

MGH & LLUMC

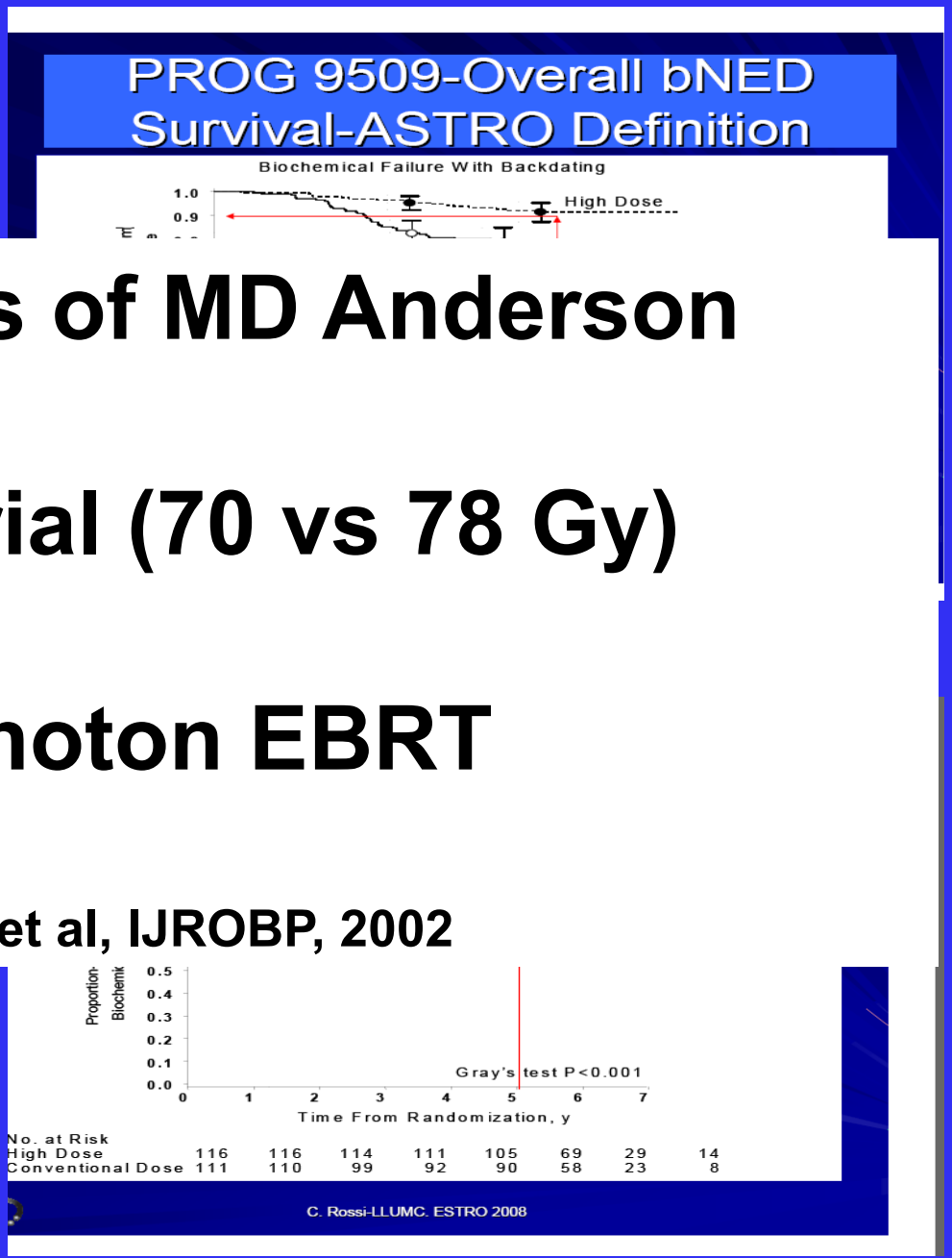
392 p… with early stag…

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)	

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

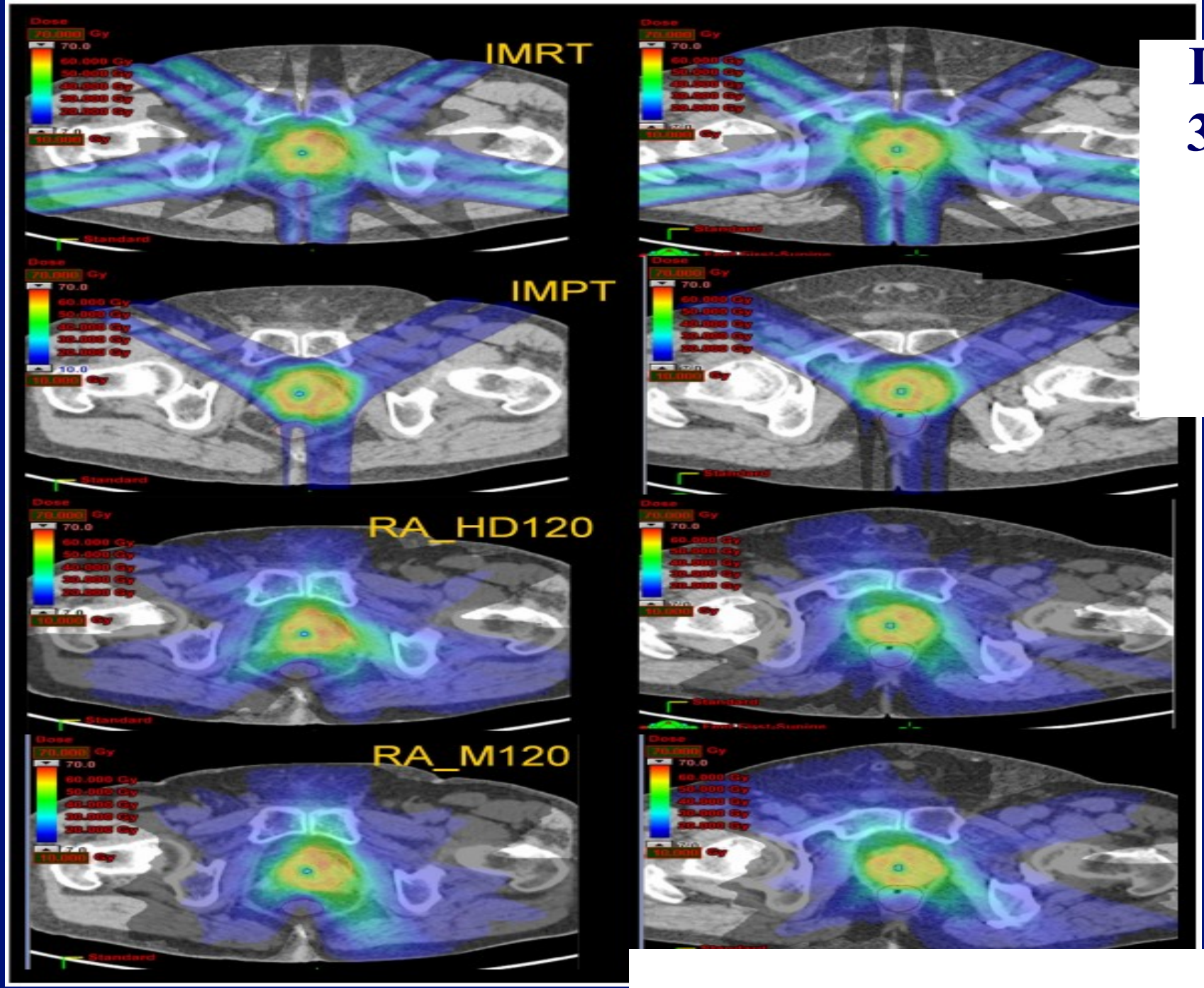
Primary endopoint *EPIC bowel scores at 6 months

350 patients randomized

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

Hadrontherapy

Which endpoint?



Integral Dose 3 times higher for all photon's techniques

Weber DC et al, Radiat Oncol, 2009; 4:34

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?

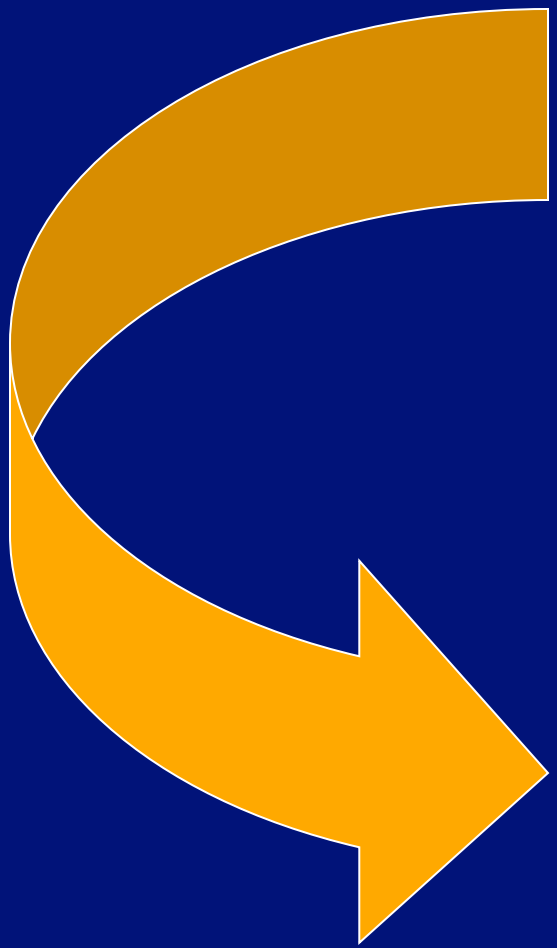
-Assume 60% decrease in 0.5% incidence at 15 y (NCI)

-For 80% power at p=0-05

	1-sides	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
- Al least equivalent results in almost all cancer, including radioresistant tumours
- Less morbibdity, 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-mesenchimal 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

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


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