Particle Radiation Therapy:
Current Status – Indications - Results

Eugen B. Hug
Center for Proton Therapy
Paul Scherrer Institute
and University of Zürich
Switzerland

Particle Radiation Therapy:

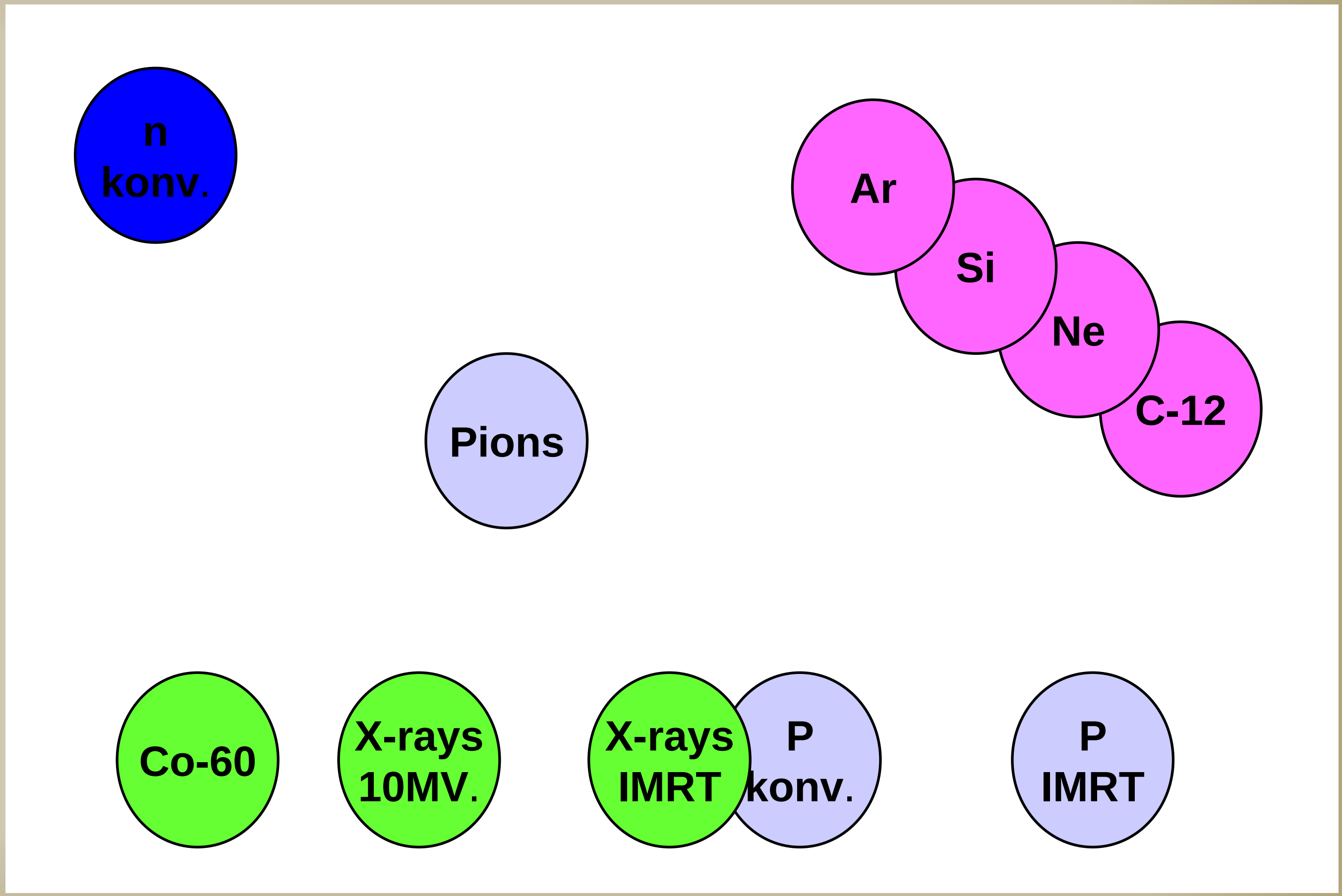
Selection of the optimum particle:

•*increased biologic effectiveness (selectively higher in tumor compared to normal, surrounding tisues)*

and / or

•*Improved dose conformity compared to photons*

Heavy ion therapy – A summary



Biological effectivity

Dose conformation

Universität Zürich

PAUL SCHERRER INSTITUT

Present Clinical Reality:

• > 55 000 patients have been treated with particles

•> 50 000 patients with protons

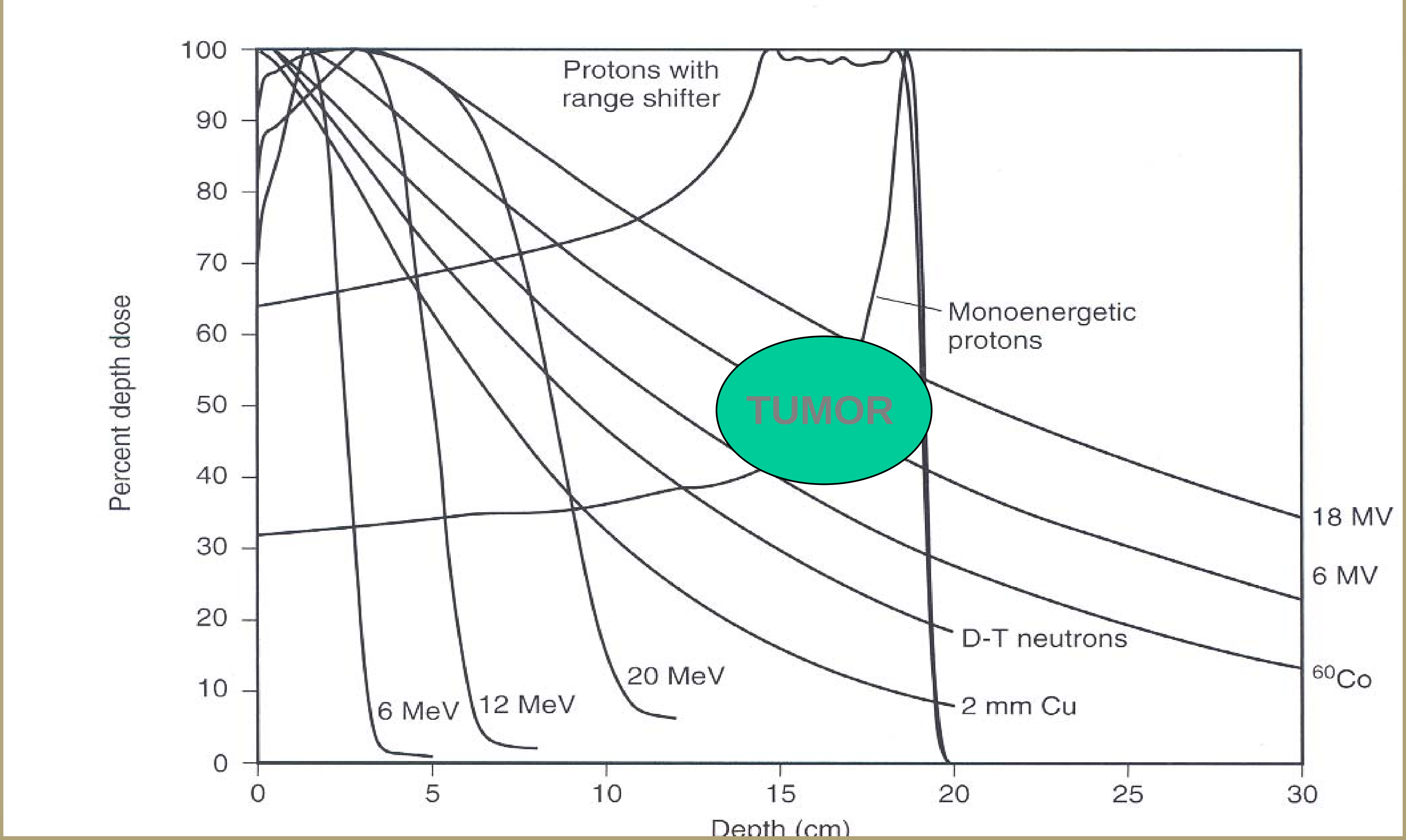
•> 4500 with Carbon Ions (< 10%) (> 90% at one facility (NIRS)

•>> proton facilities built world wide

• „Carbon Ion“ facilities permit use of multiple particles

Why Protons ?

Protons stop ………X-rays keep going*

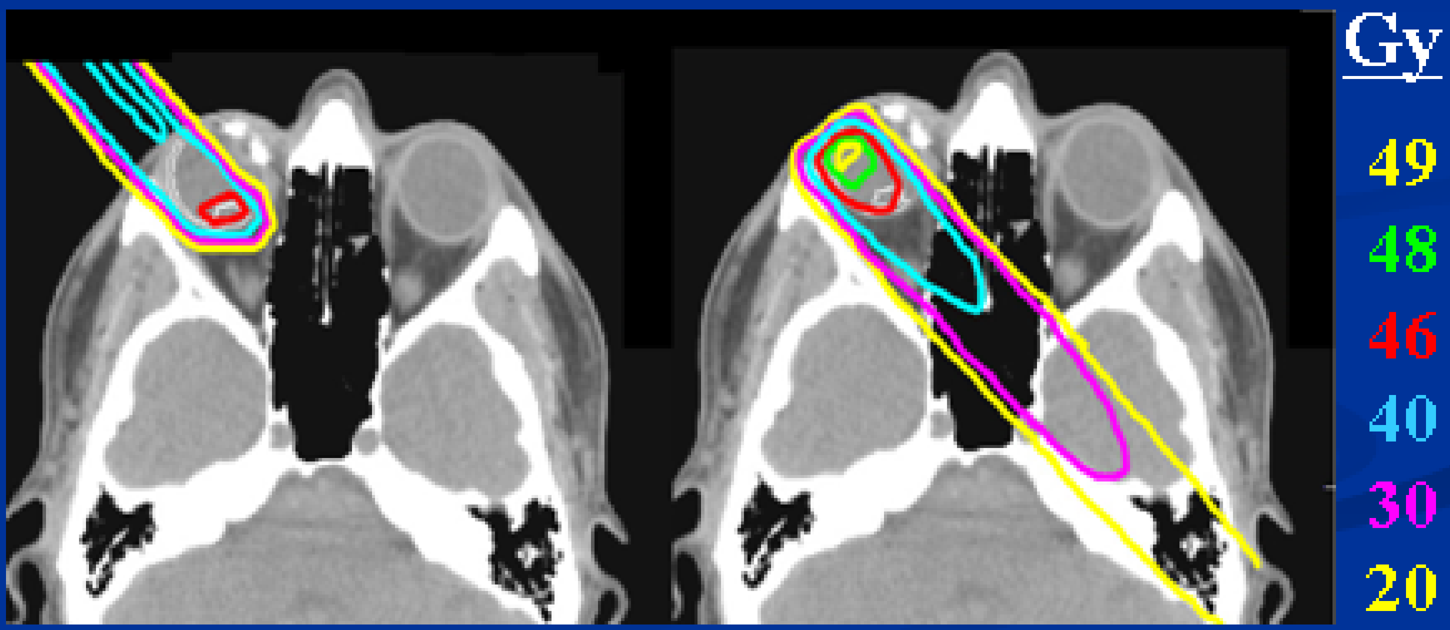


* Herman Suit, Michael Goitein

Why Protons ?

Comparison of single-beam proton and photons treatments for retinoblastoma

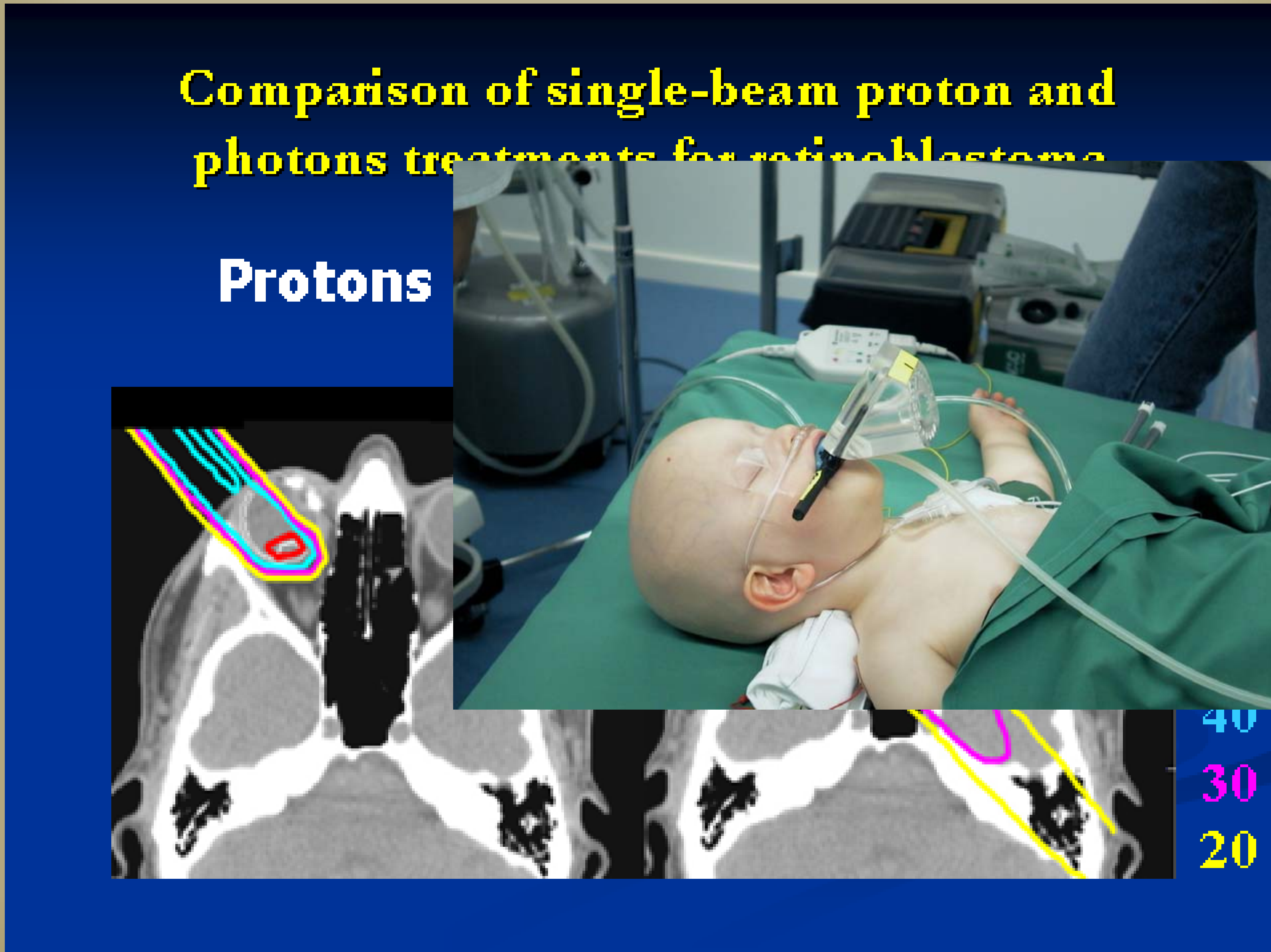
Protons **Photons**



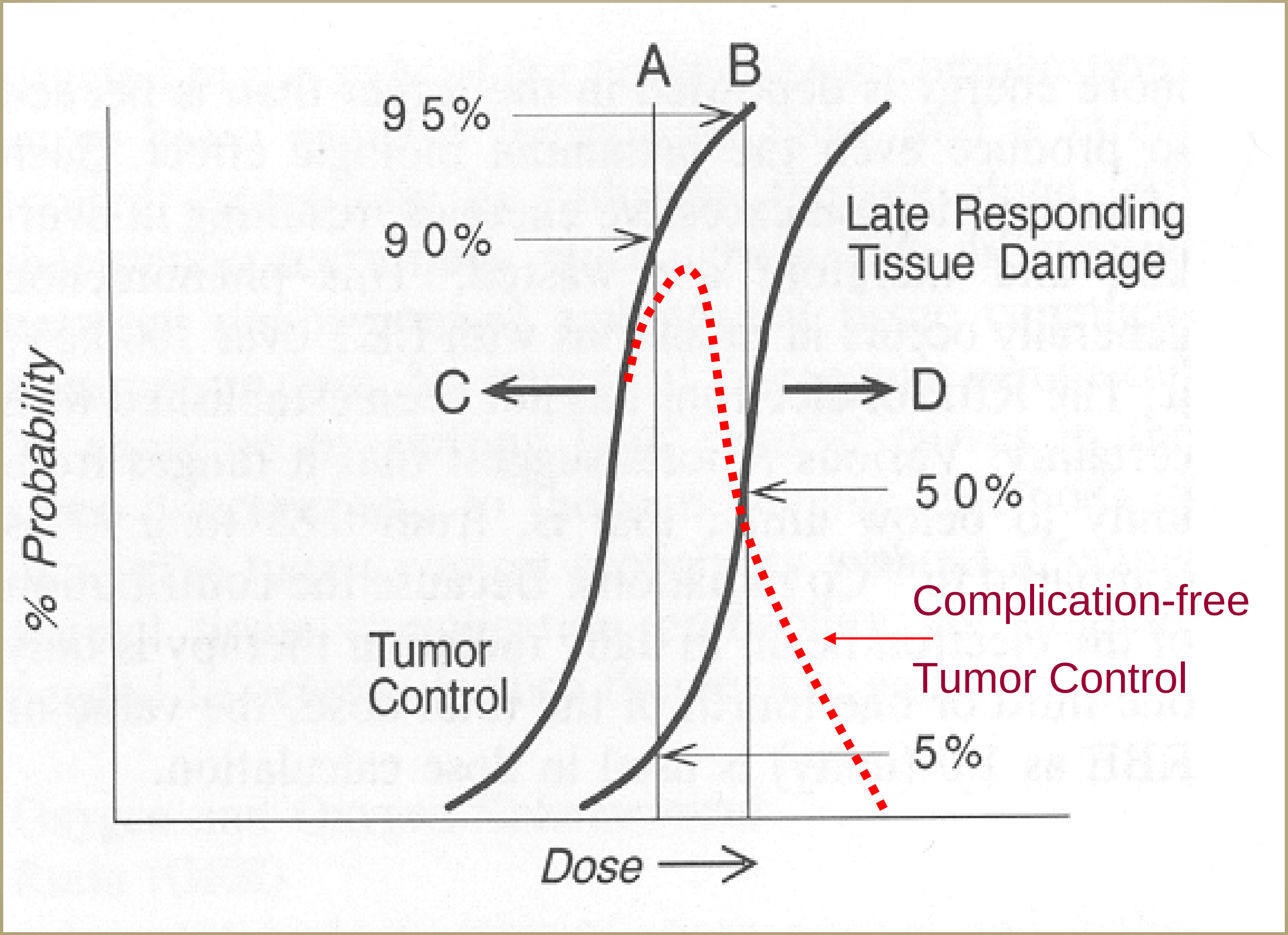
Universität Zürich

Why Protons ?

PAUL SCHERRER INSTITUT



The Ultimate Goals of *any* Cancer Therapy



The 2 legs

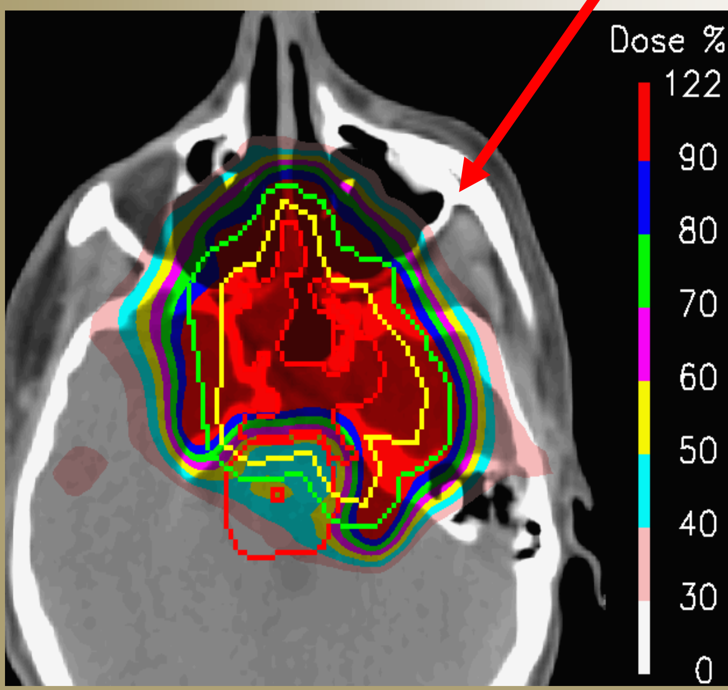
of Proton Radiotherapy

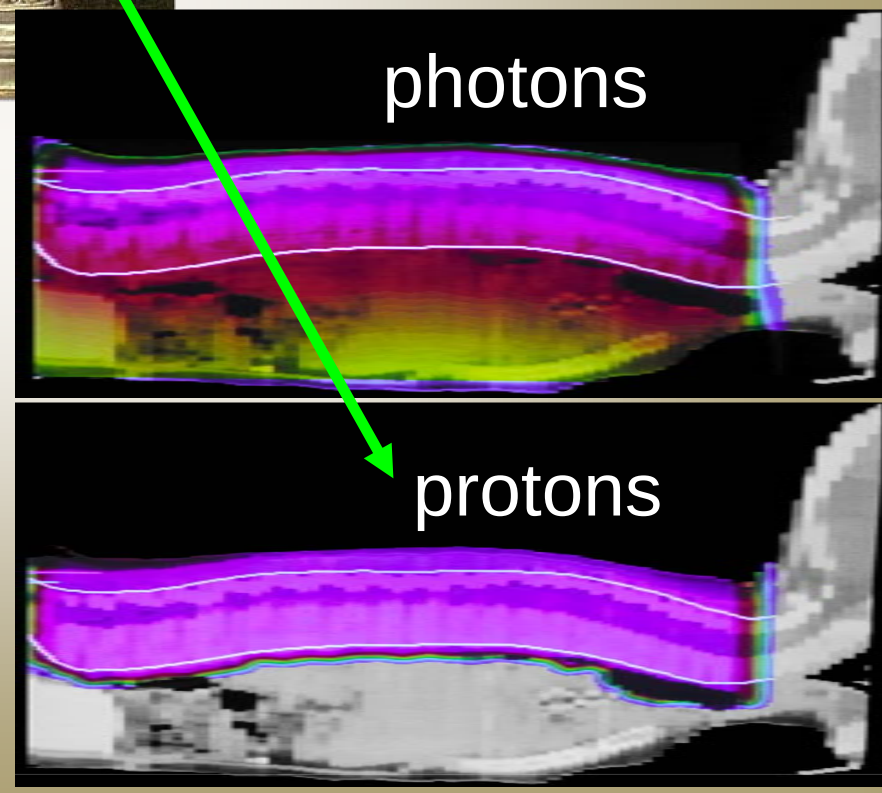
High-Dose Target coverage

Reduction of low-moderate dose volume

Universität Zürich

PAUL SCHERRER INSTITUT PSI





Universität Zürich

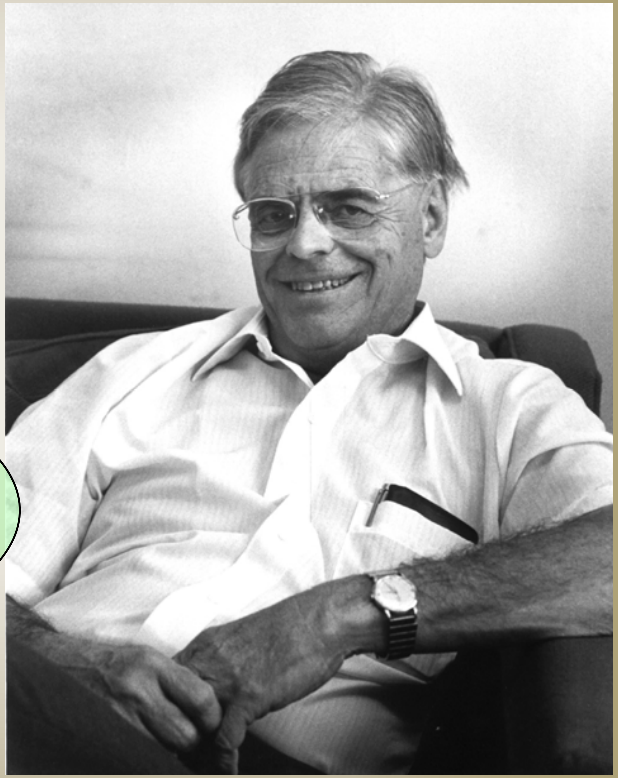
PAUL SCHERRER INSTITUT PSI

•Historic Milestones of Clinical Proton-Radiotherapy

Historic milestones of radiation therapy

20. century

1946 - Robert D. Wilson publishes the concept of PROTON-BASED therapy



Start of Proton Therapy:

- **1954 - Lawrence Berkeley Laboratory,USA**
- **1957 - Gustav Werner Institute, Uppsala, Schweden, *(first treatment of a cancer patient)***
- **1961 - Harvard Cyclotron Laboratory, USA**

Early clinical Phase: Proof of Safety and Efficacy

<u>1974</u> — Modern era of fractionated, „large field“ Proton Therapy Collaboration between Massachusetts General Hospital und Harvard Cyclotron, Boston und Cambridge, USA

Early Clinical Phase: Proof of Safety and Efficacy

Choice of clinical Indications and tumor entities

=

tumor models with highest chance to proof superiority of protons

Emphasis: increasing tumor dose in tumors with unsatisfactory cure rates by combining protons with 3D-treatment planning

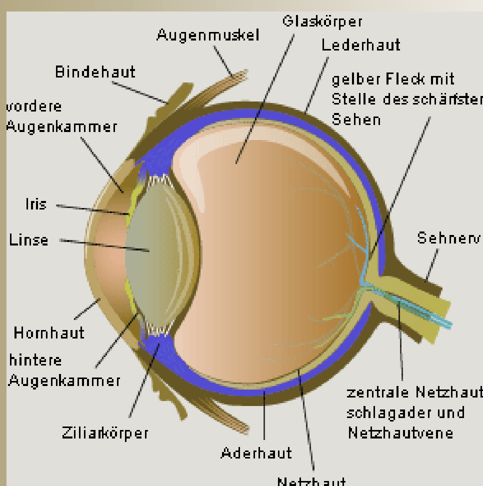
Universität Zürich

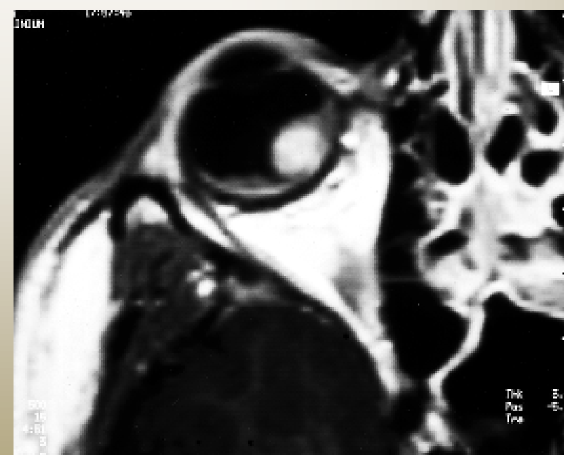
PAUL SCHERRER INSTITUT PSI

Proton-Radiotherapy:
Eye tumors

Start 1976 USA (MGH)
Start 1984 Europa (PSI)
- **15 000 patients treated world wide**

- **> 98% diagnosis: melanoma of the retina**





Proton-Radiotherapy:
Eye tumors

Fundus of the eye
PRIOR to therapy

Fundus of the eye
AFTER therapy

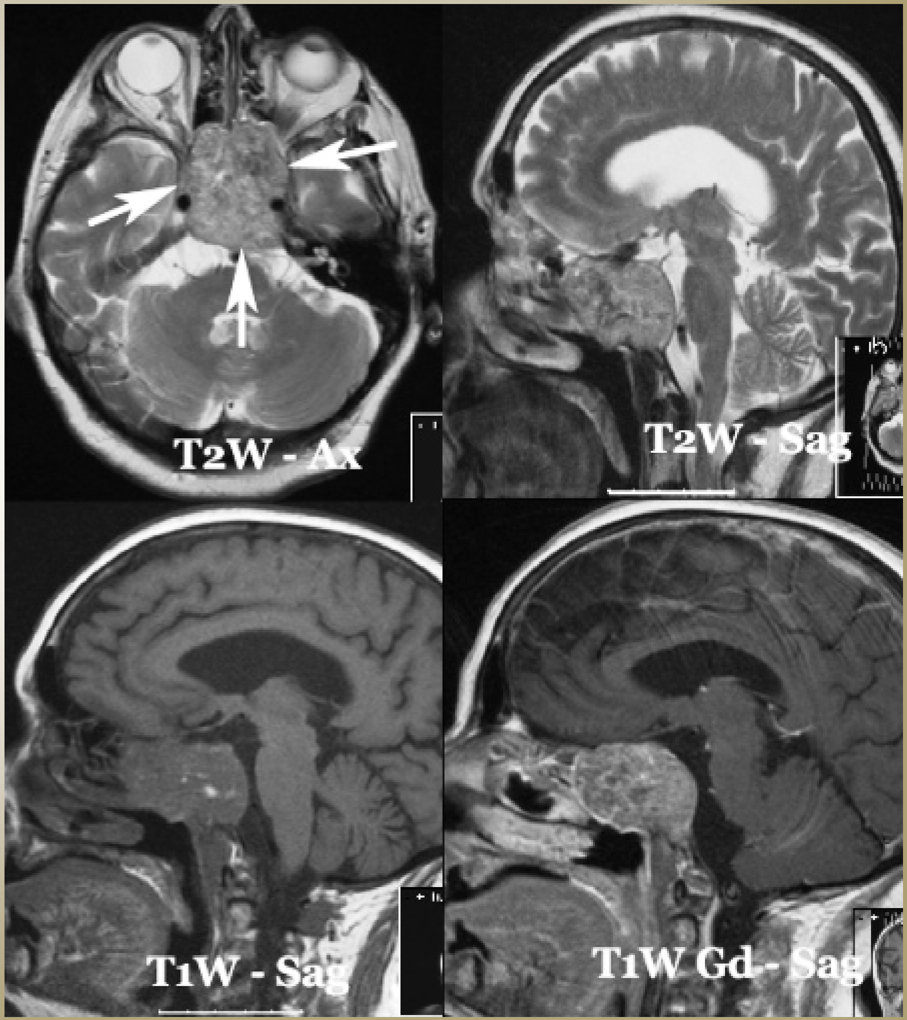
Local Tumor Control (at actuarial 10 years and depending in size and site)

- **96 % (PSI, > 5000 patients)**
- **95.7% (MGH/MEEI)**

Retention of the eye: depending on tumor size and location, about 70-97% (PSI)

Tumors of the base of skull (examples)

Chordoma

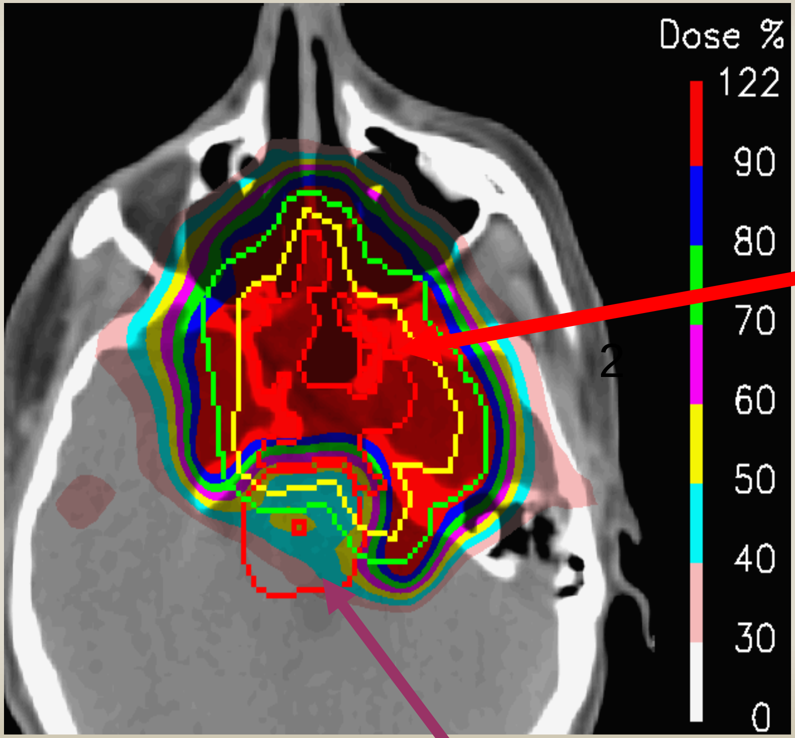


- **Primary skull base tumors:**
  - **Chordoma, Chondrosarcoma**
- **Secondary infiltration from intracranial tumors:**
  - **Meningioma**
- **Secondary infiltration from primary H&N tumors:**
  - **Nasopharynx CA,**
  - **Paranasale Sinus CA,**
  - **Adenoid-cystic CA**
  - **A.o.**

Universität Zürich

PAUL SCHERRER INSTITUT PSI

Proton-Radiotherapy for skull base tumors:



TUMOR
(TARGET VOLUME)

BRAINSTEM

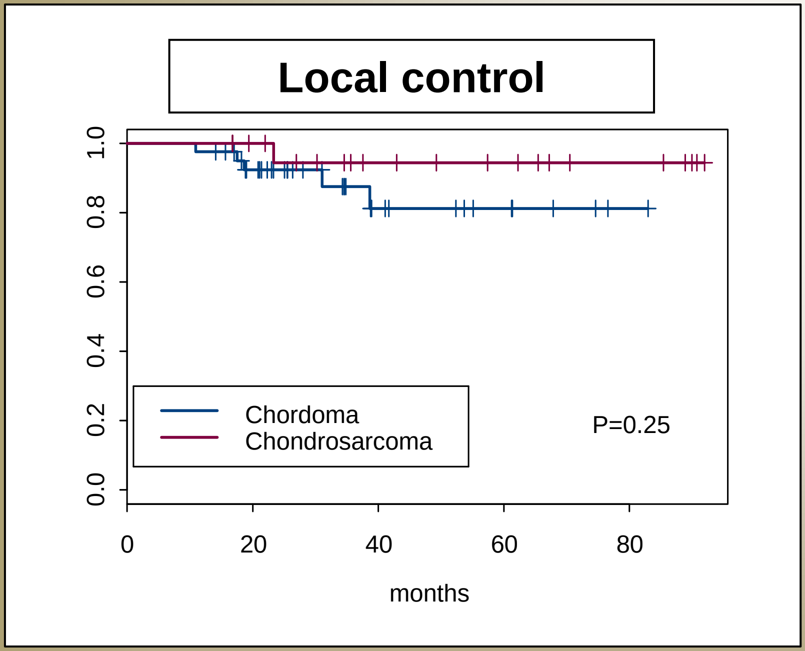
Lomax, *Phys. Med. Biol*. 44:185-205, 1999

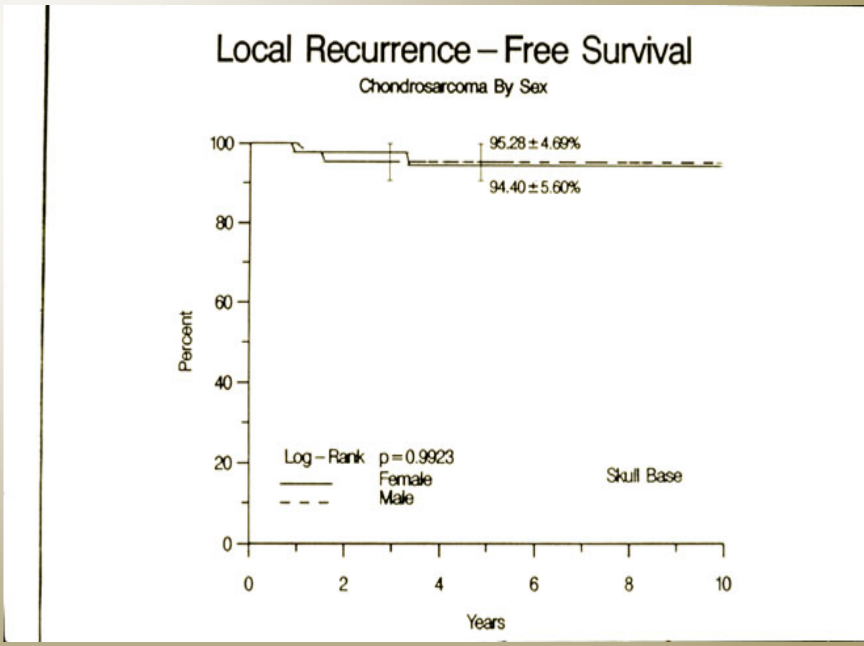
Paul Scherrer Institute (> 120 pts.):

Local control	5 years
Chordoma	81 %
Chondrosarcoma	94 %

Mass. General Hospital (> 500 pts.)

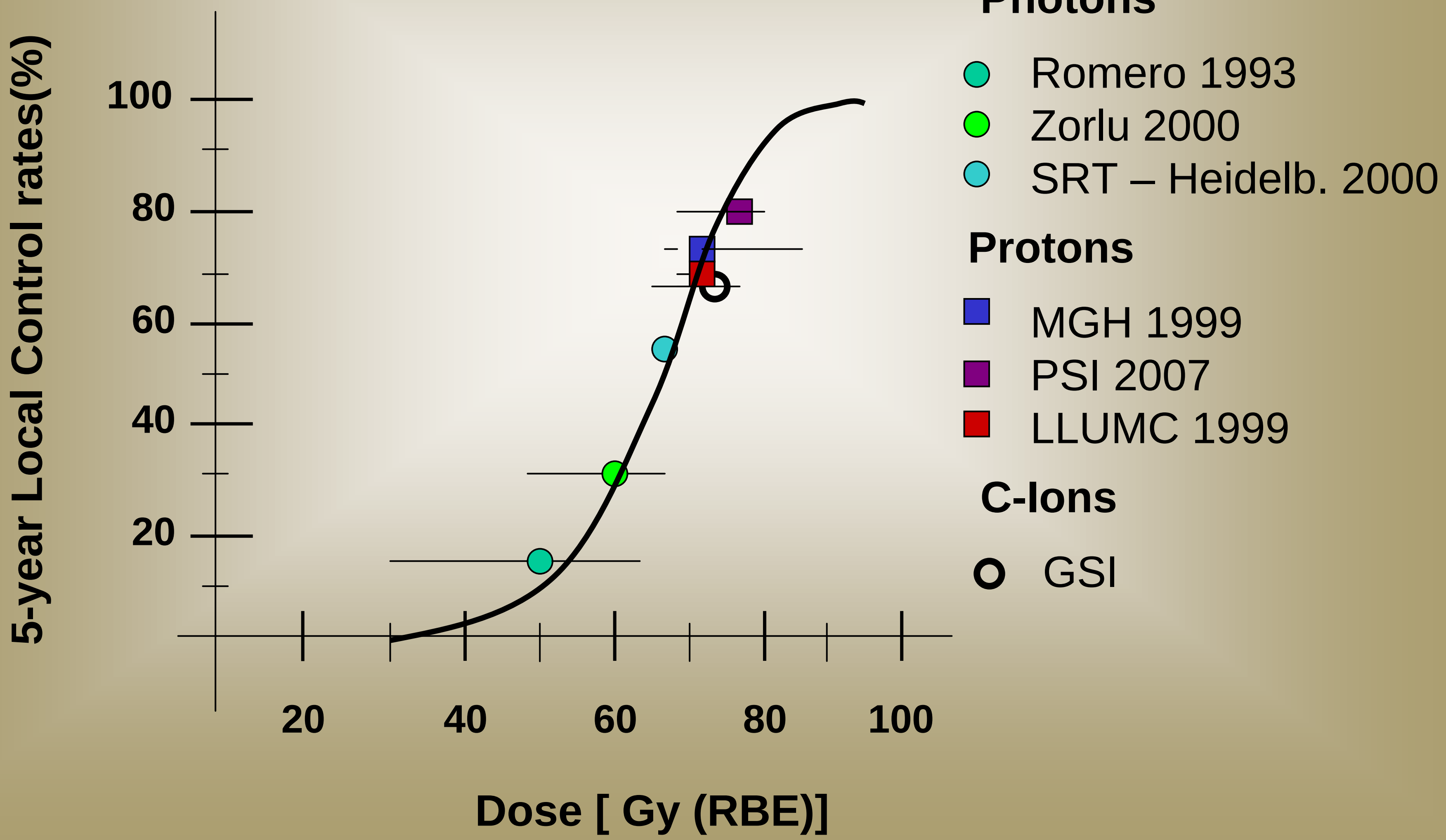
Local control	5 years
Chordoma	73 %
Chondrosarcoma	98 %



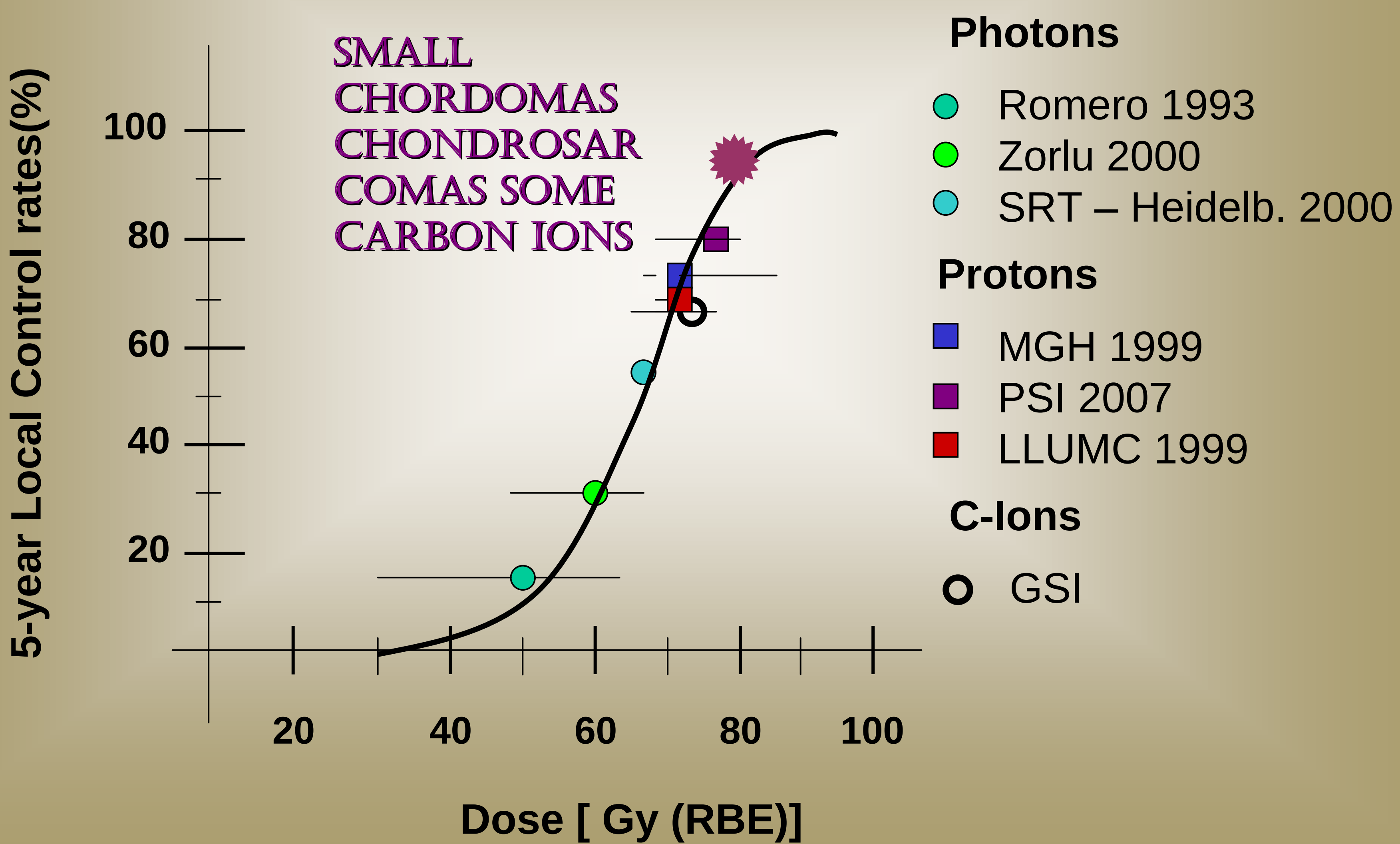


Severe Late Toxicities: 5 – 7 %

Chordomas of the Base of Skull



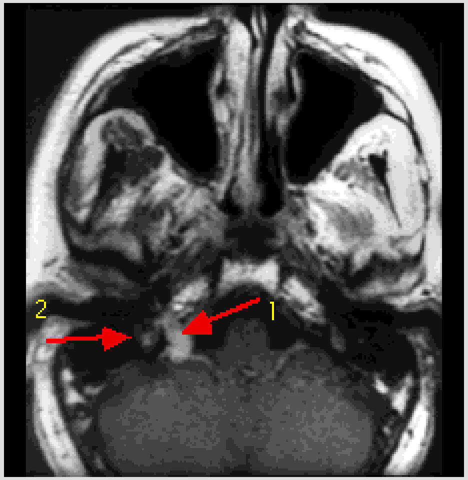
Chordomas of the Base of Skull

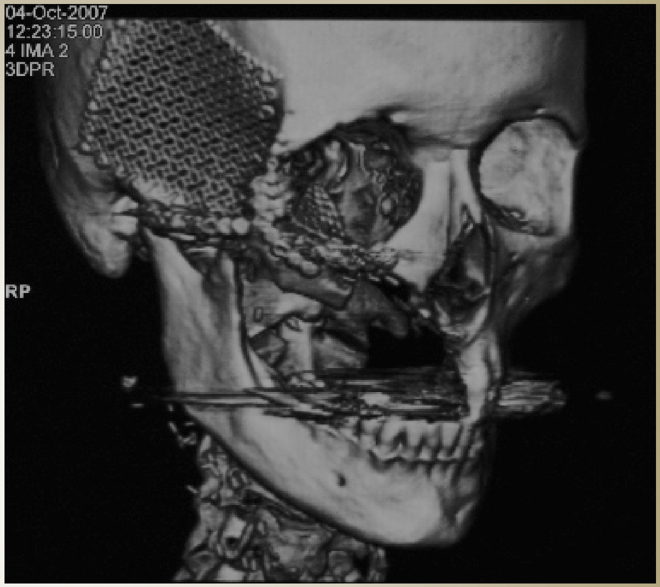


Proton-Radiotherapy for skull base tumors: *Adenoid Cystic Carcinoma of the H&N*

Primary tumor : tongue

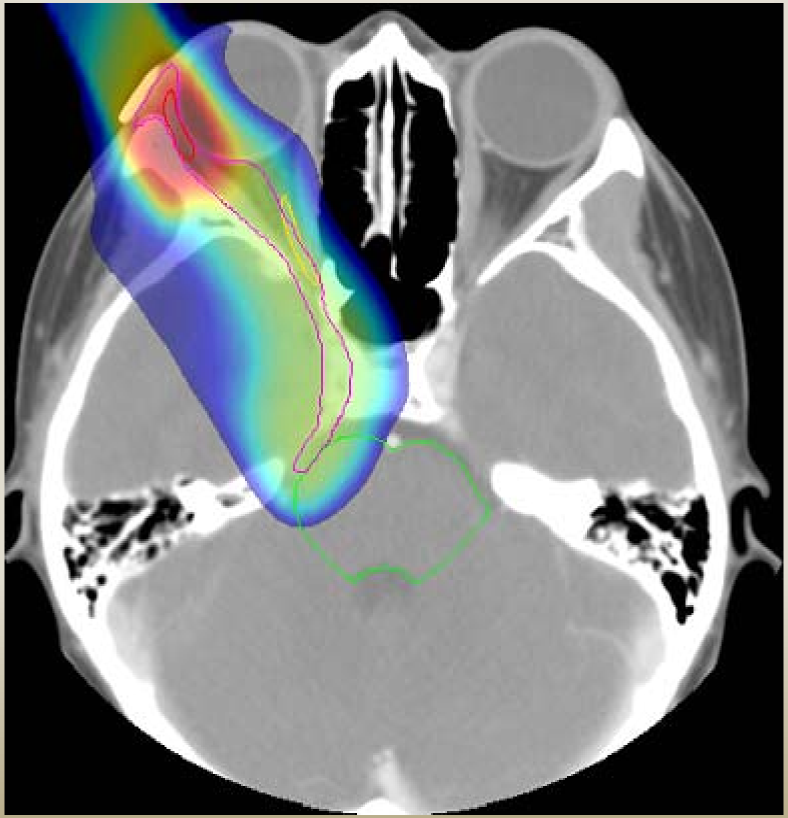
Recurrence at 6 yrs.: skull base





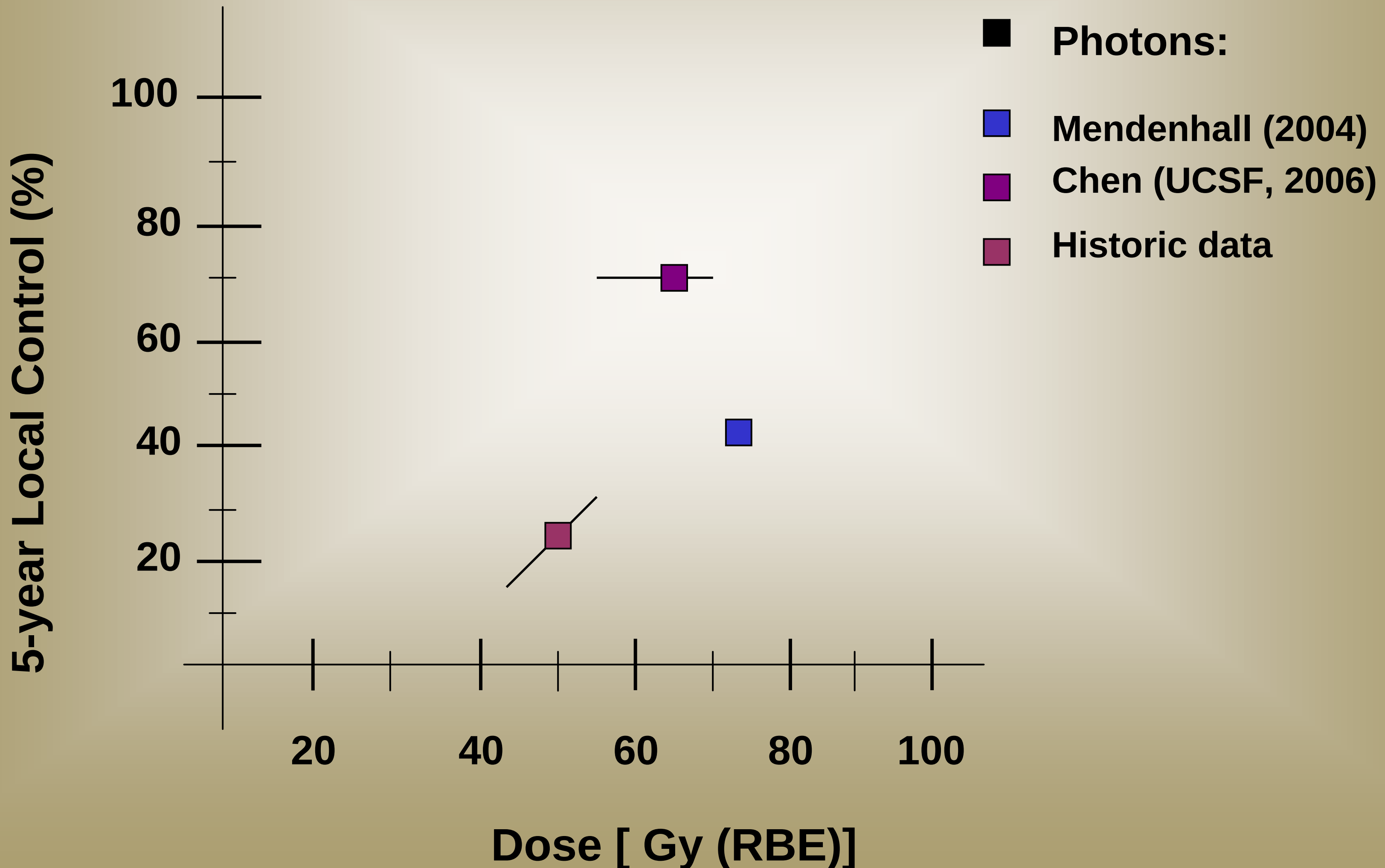
Adenoid-cystic Carcinoma of the Lacrimal gland

(treated at Massachusetts General Hospital)

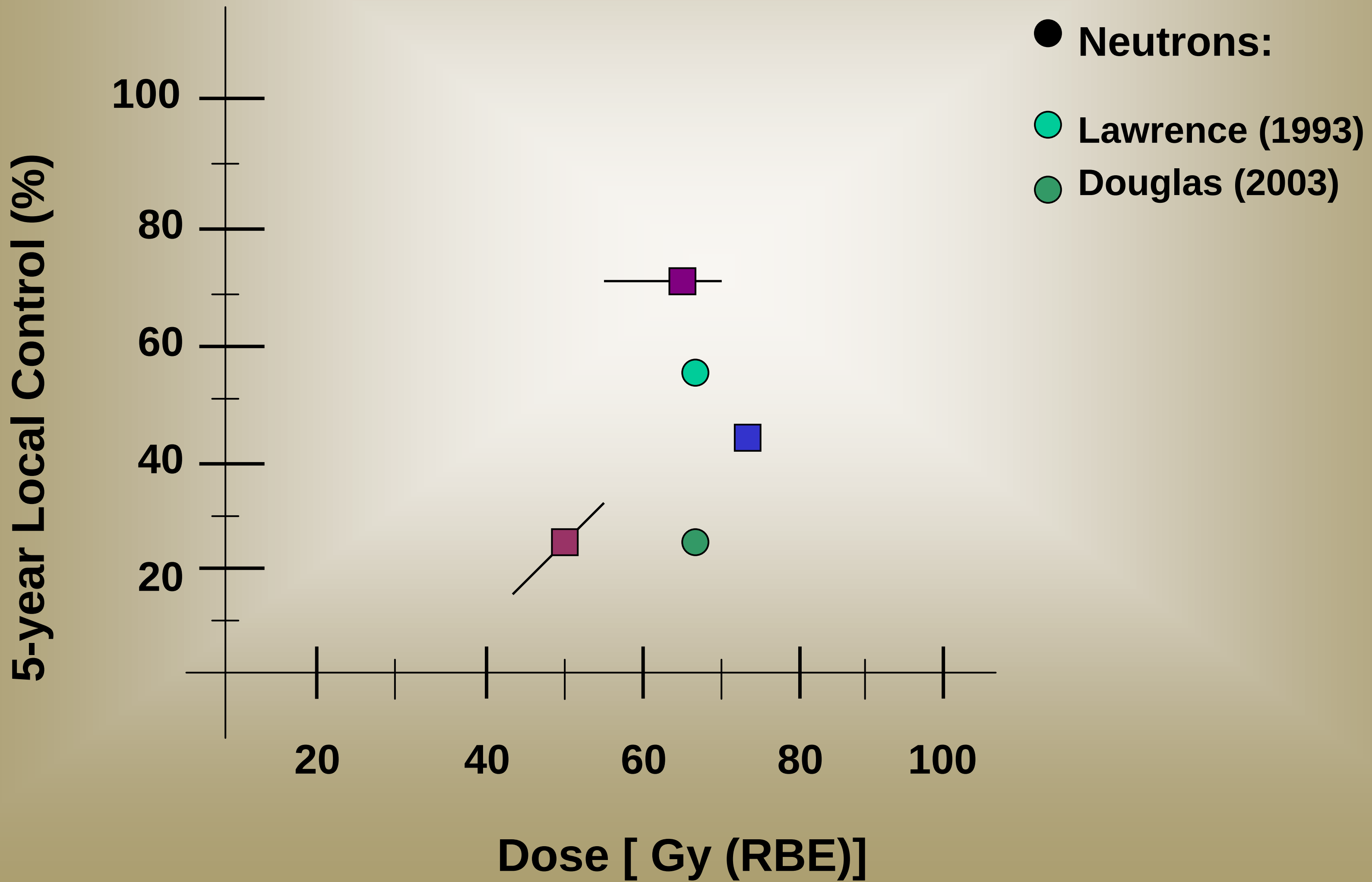


“Sculpting” of the dose distribution by protons

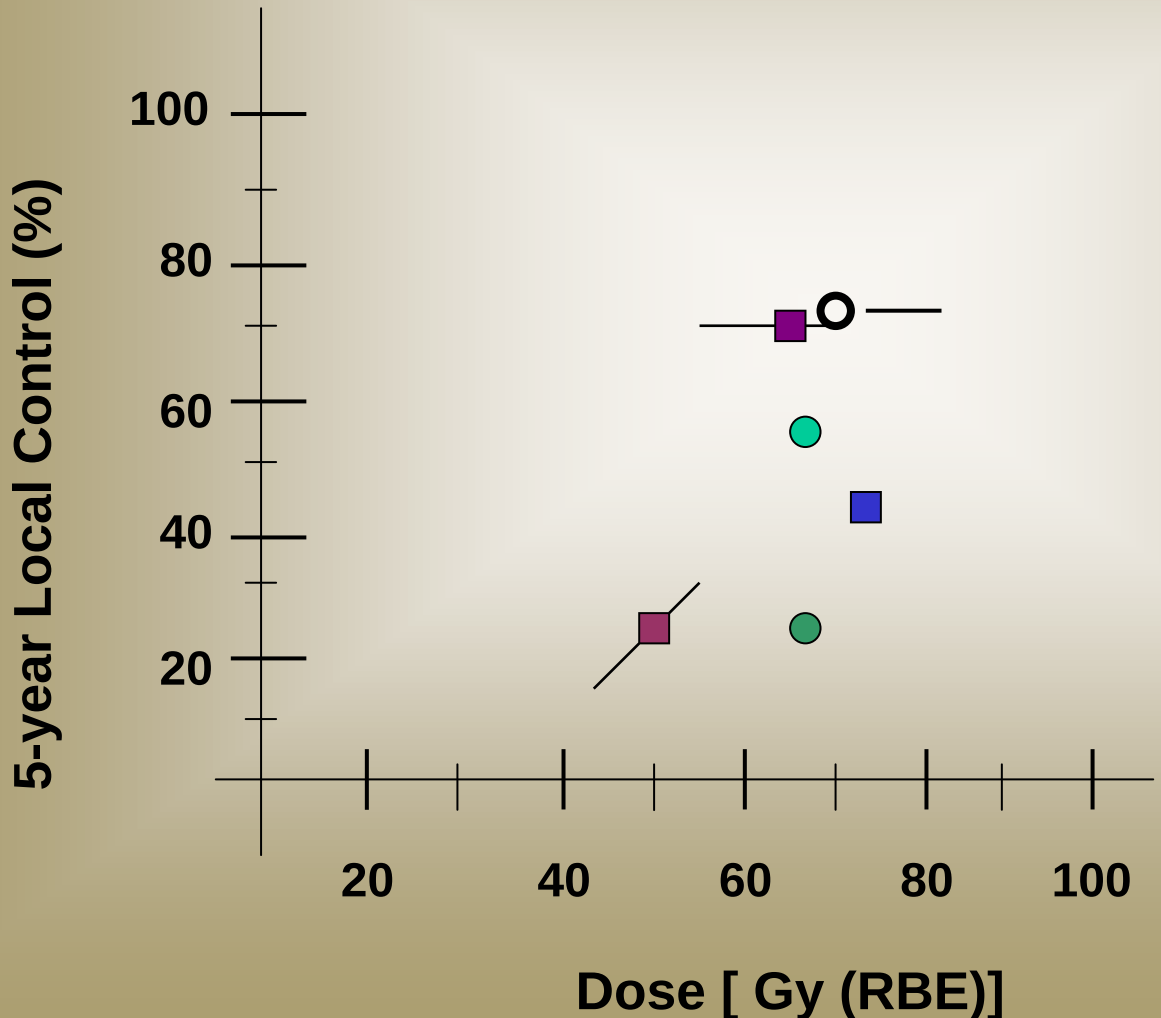
Adenoid-cystic Carcinomas with infiltration of the skull base



Adenoid-cystic Carcinomas with infiltration of the skull base



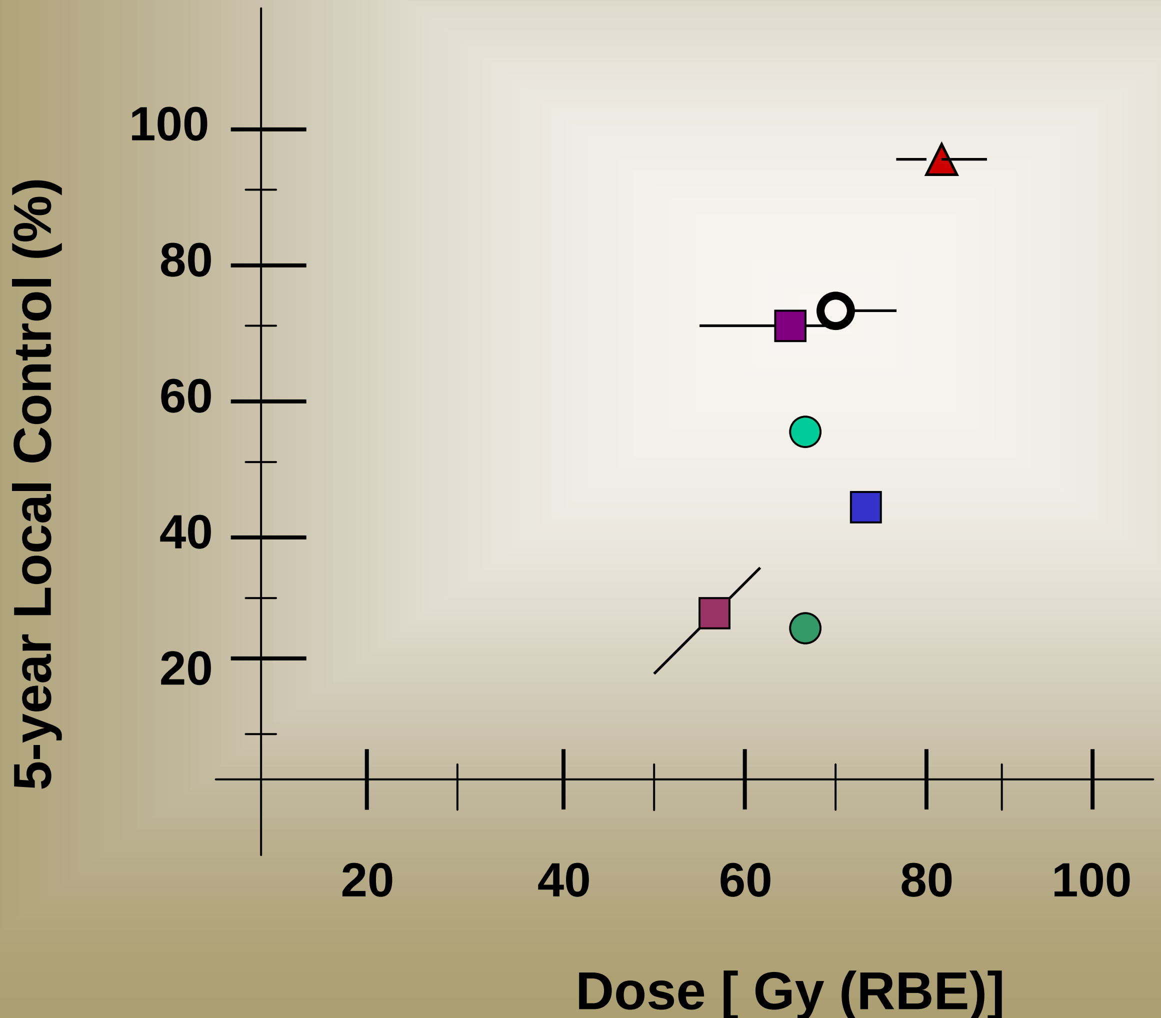
Adenoid-cystic Carcinomas with infiltration of the skull base



C-Ions:

Schulz-Ertner et al.
GSI – U Heidelberg

Adenoid-cystic Carcinomas with infiltration of the skull base



Protons:

Pommier et al.
MGH, 2006

Proton Radiotherapy:

High-dose and/or hypofractionated therapy concepts increased tumor control compared to conventional photon RT by

approx. 10 – 50 %

Examples: Skull Base Chordomas, Chondrosarcomas and adenoid cystic Carcinomas, Uveal Melanomas, Unresectable Sarcomas (paraspinal, sacral)

Clinical Phase of the 90‘s: Start of hospital-based Proton Radiotherapy Introduction of Gantry

Choice of clinical Indications

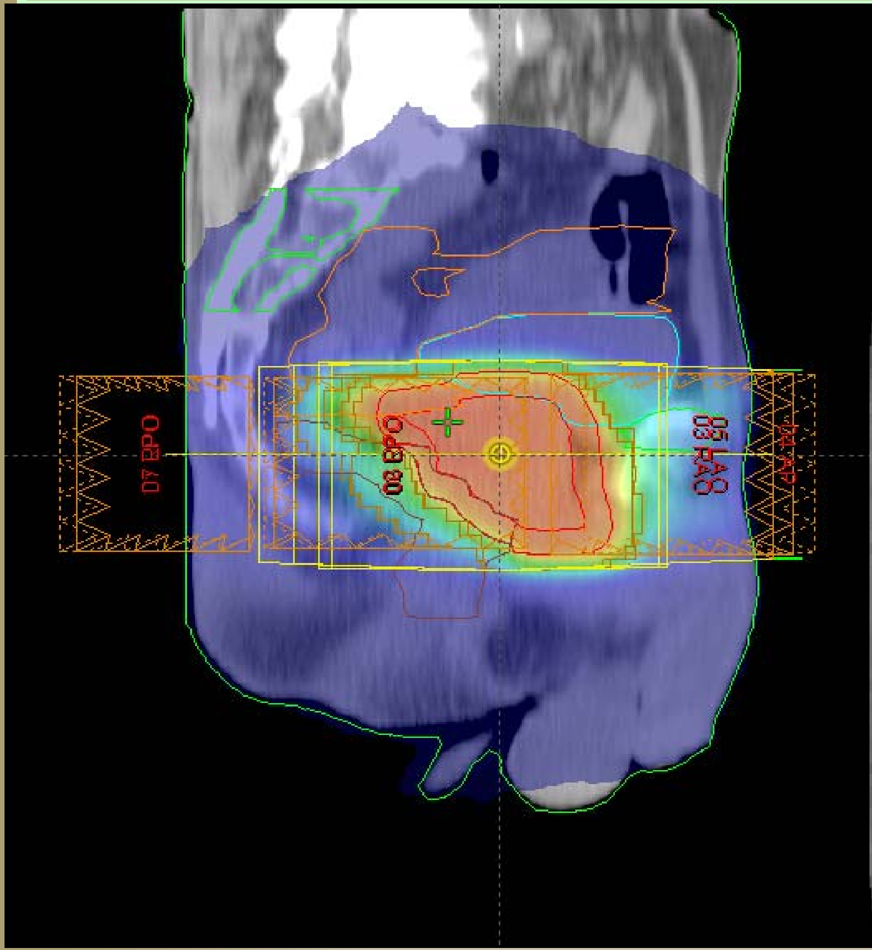
=

Exploring high-frequeny diseases:

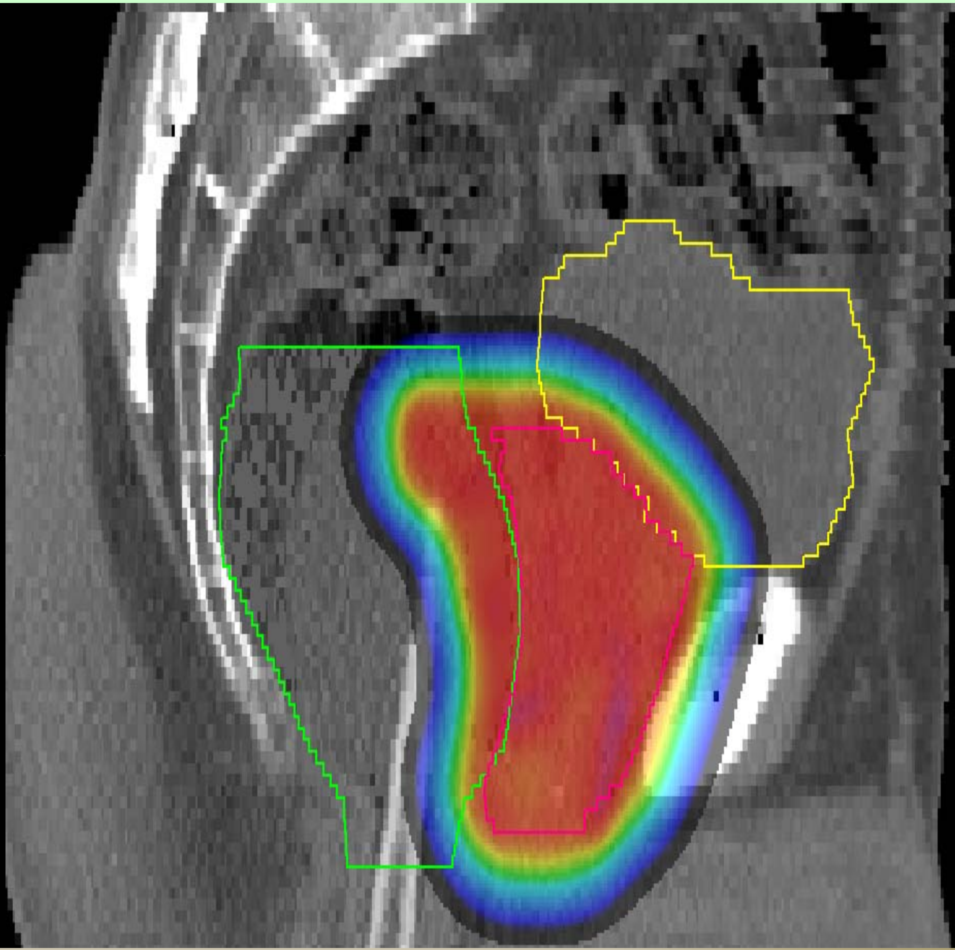
Prostate

lung

Prostate Cancer-80 Gy



IMRT



PROTONS

Universität Zürich

PAUL SCHERRER INSTITUT PSI

Prostate Ca

> 12 000 Patients (annually approx. 50% of all PT)

- Loma Linda University Medical Center (Drs. Rossi, Slater)

- 1255 patients treated between 10/91 and 12/97
- Patients had no prior surgery or hormonal therapy
- 74-75 CGE at 1.8 – 2.0 CGE per fraction
- Follow-up mean 63 mos., median 62 mos. (range 1-132)

Stage	Patients
1A/1B	35
1C	314
2A	291
2B	248
2C	283
3	50

Universität Zürich

PAUL SCHERRER INSTITUT PSI

Treatment Morbidity
RTOG Scale

	Grade 2	Grade 3 & 4
GI	3.5%	0
GU	5.4%	0.3%
Total	9%	**0.3%**

Universität Zürich

PAUL SCHERRER INSTITUT PSI

Randomized Trials:

protons versus protons

PROG 9509

T1b-2b prostate cancer
PSA <15ng/ml

randomization
ACR/RTOG

Proton boost
19.8 GyE

3-D conformal photons
50.4 Gy

Total prostate dose
70.2 GyE

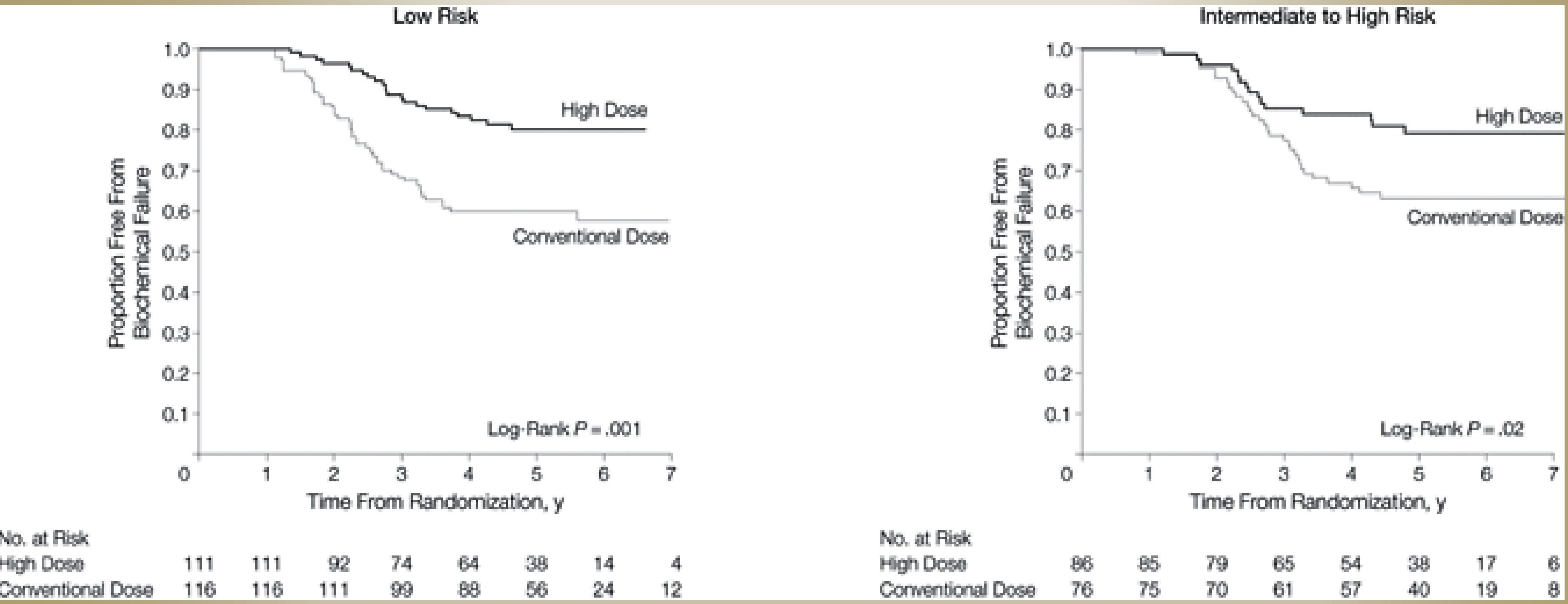
Proton boost
28.8GyE

3-D conformal photons
50.4 Gy

Total prostate dose
79.2 GyE

Zietman, A. L. et al. JAMA 2005;294:1233-1239.

Freedom From Biochemical Failure (ASTRO Definition) Following Either Conventional-Dose (70.2 GyE) or High-Dose (79.2 GyE) Conformal Proton / Photon Radiation Therapy



Zietman, A. L. et al.
JAMA 2005;294:1233-1239.

Acute and Late Genitourinary and Gastrointestinal (Rectal) Morbidity, by Assigned Radiation Therapy Dose and Toxicity Grade

Table 2. Acute and Late Genitourinary and Gastrointestinal (Rectal) Morbidity, by Assigned Radiation Therapy Dose and Toxicity Grade

	No. (%)							
	70.2 GyE (n = 196*)				79.2 GyE (n = 195)			
Morbidity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Acute								
GU	79 (40)	82 (42)	2 (1)	0	69 (35)	95 (49)	2 (1)	1 (1)
GI	62 (31)	81 (41)†	2 (1)	0	48 (25)	112 (57)†	0	0
Late								
GU	85 (43)	35 (18)	3 (2)	0	84 (43)	39 (20)	1 (1)	0
GI	71 (36)	15 (8)‡	1 (1)	0	84 (43)	33 (17)‡	1 (1)	0

Abbreviations: GI, gastrointestinal; GU, genitourinary.
*One patient underwent radical prostatectomy rather than radiation therapy because the bowel was too close to the prostate for safe administration of radiation. This patient was excluded from analysis of morbidity.
†$P = .004$ by χ^2 test.
‡$P = .005$ by χ^2 test.

Authors' conclusions: Men with clinically localized prostate cancer have a lower risk of biochemical failure if they receive high-dose rather than conventional-dose conformal radiation. This advantage was achieved without any associated increase in RTOG grade 3 acute or late urinary or rectal morbidity.

Proton-Radiotherapy for early Stage Lung Cancer

Hypofractionated Proton Radiotherapy for Stage I Lung Cancer.
Bush et al . Chest 126(4), 2004

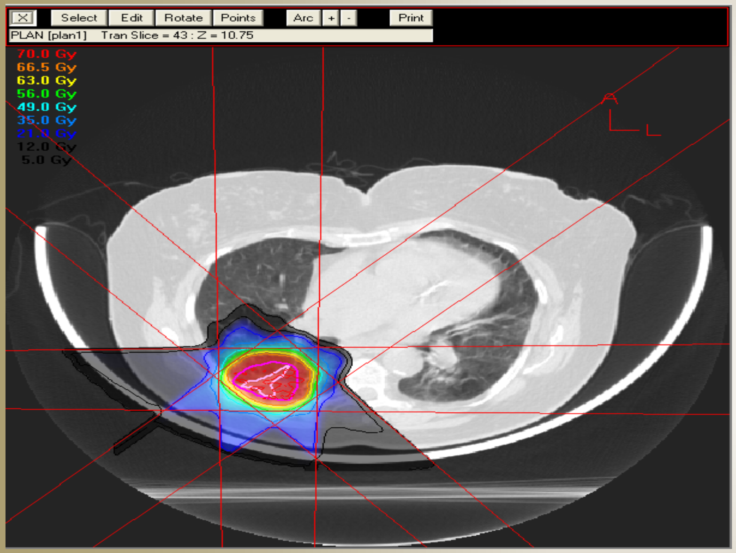
- •Proton radiotherapy only
- •68 patients,
- •T1 (29 patients) and T2 (39 patients), NO,MO
- • medically inoperable Non-small-cell Lung CA
- • Dose: 51 cobalt Gray equivalent (CGE) in 10 fractions over 2 weeks. Subsequently 60 CGE in 10 fractions.
- •Median follow-up time 30 months

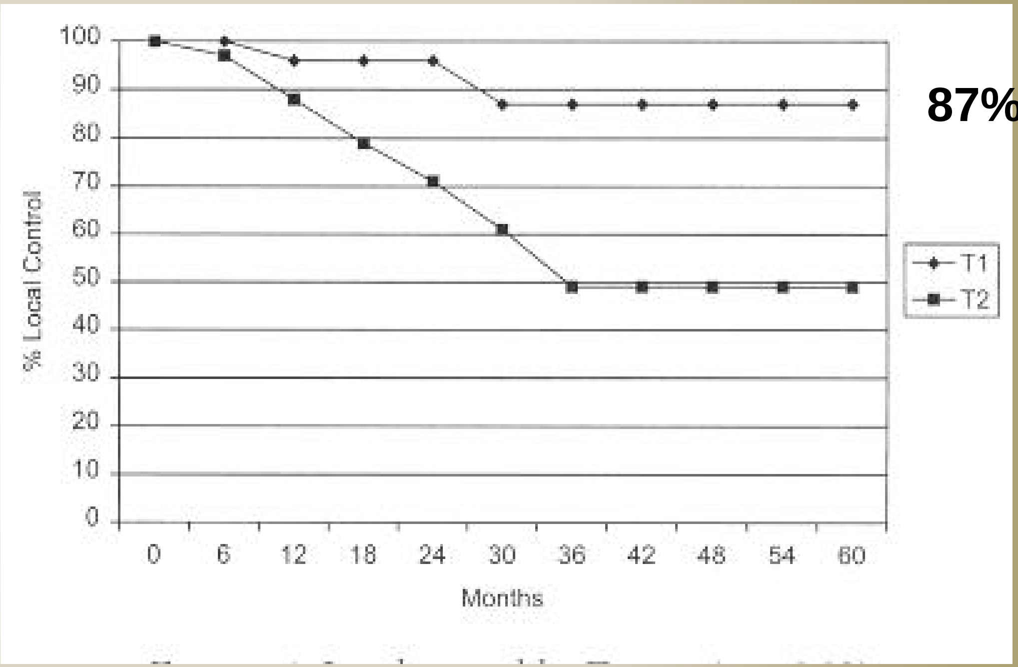
Universität Zürich

PAUL SCHERRER INSTITUT PSI

Hypofractionated Proton Beam Radiotherapy for Stage I Lung Cancer.

Bush et al . Chest 126(4), 2004





- No symptomatic pneumonitis or late esophageal or cardiac toxicity
- 3-year local control: 74%; 3-year disease-specific survival: 72%
- Local tumor control T1 vs T2 tumors = 87% vs 49%
- Trend toward improved survival.

Status of Proton-Radiotherapy for Carcinoma of Prostate and inoperable Lung-CA:

- **Thus far a conservative approach**
- **Similar dose levels and fractionation regimen compared to modern photon RT (IMRT, SBRT etc.)**
- **Similar rates of tumor control – <u>as had to be expected</u>**
- **indications of decreasing rates of severe side effects for protons.**
- **URGENTLY NEEDED: IDENTIFY SUBGROUPS OF PATIENTS THAT WILL LIKELY BENEFIT MOST FROM PROTONS. DOSE-ESCALATION STUDIES.**

Universität Zürich

PAUL SCHERRER INSTITUT PSI

Carbon Ion Therapy for Lung Cancer:

The NIRS experience

Universität Zürich

Clinical Study on Carbon Beam Therapy for Stage I Non-Small Cell Lung Cancer

PAUL SCHERRER INSTITUT PSI

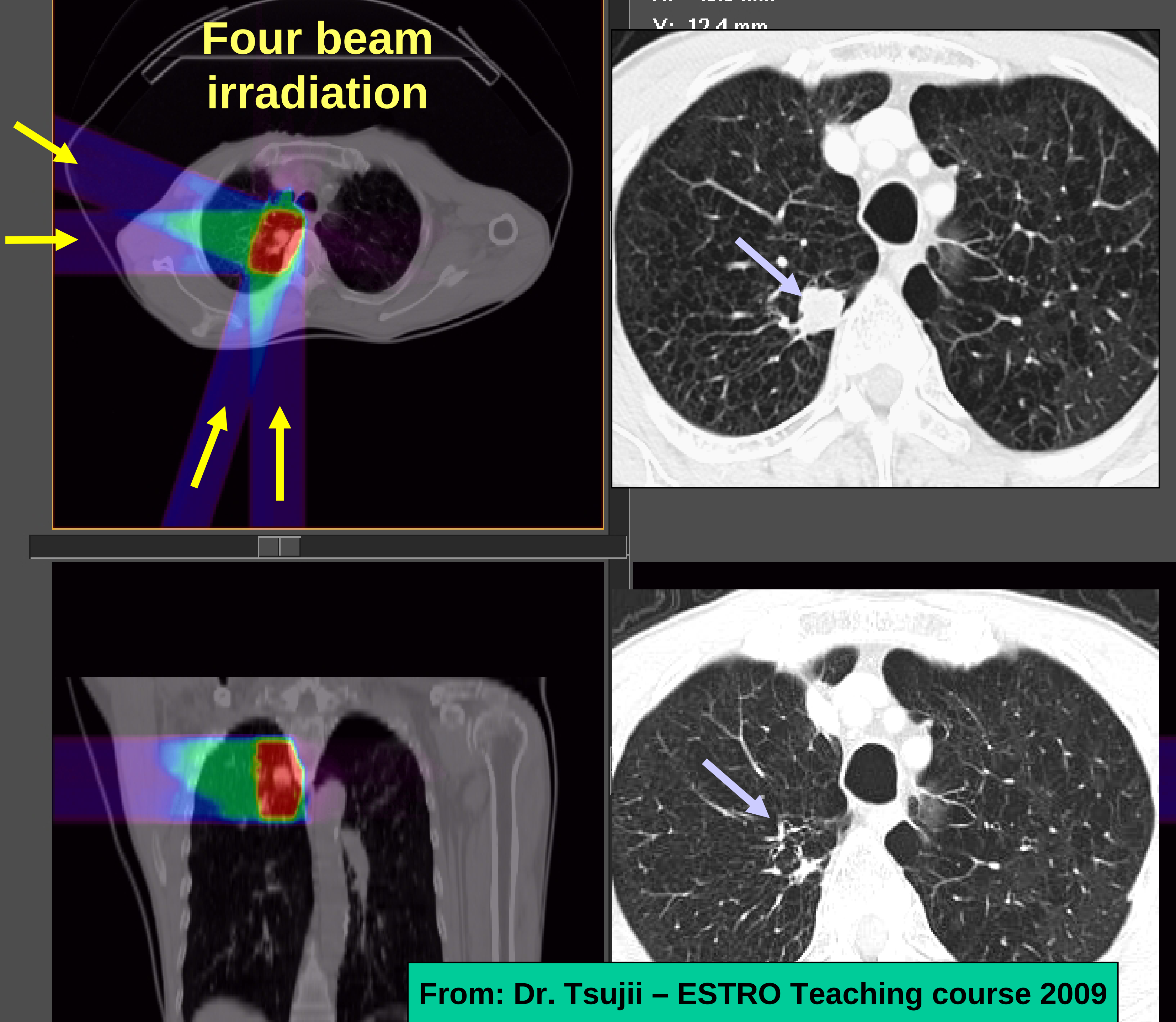
9303	9701	9802	0001	0201
Phase I/III (1994)	Phase I/II (1997)	Phase Ⅱ (4/99 - 11/00)	Phase I/II (12/00 - 11/03)	Phase I/II (12/03 ~)
18 fr / 6 wks 47 pats	9 fr / 3 wks 34 pts	9 fr / 3 wks 50 pats	4 fr / 1 wk 79 pats	Single-dose 84 pats
Dose-escalation: 59.4GyE 64.8 72.0 79.2 86.4 90.0 95.4	68.4GyE 72.0 75.6 79.2	72GyE	52.8GyE for stage IA 60.0GyE for stage IB	28GyE 30 34 36 38 40 42 44

Total 129 pats

Dose recommended

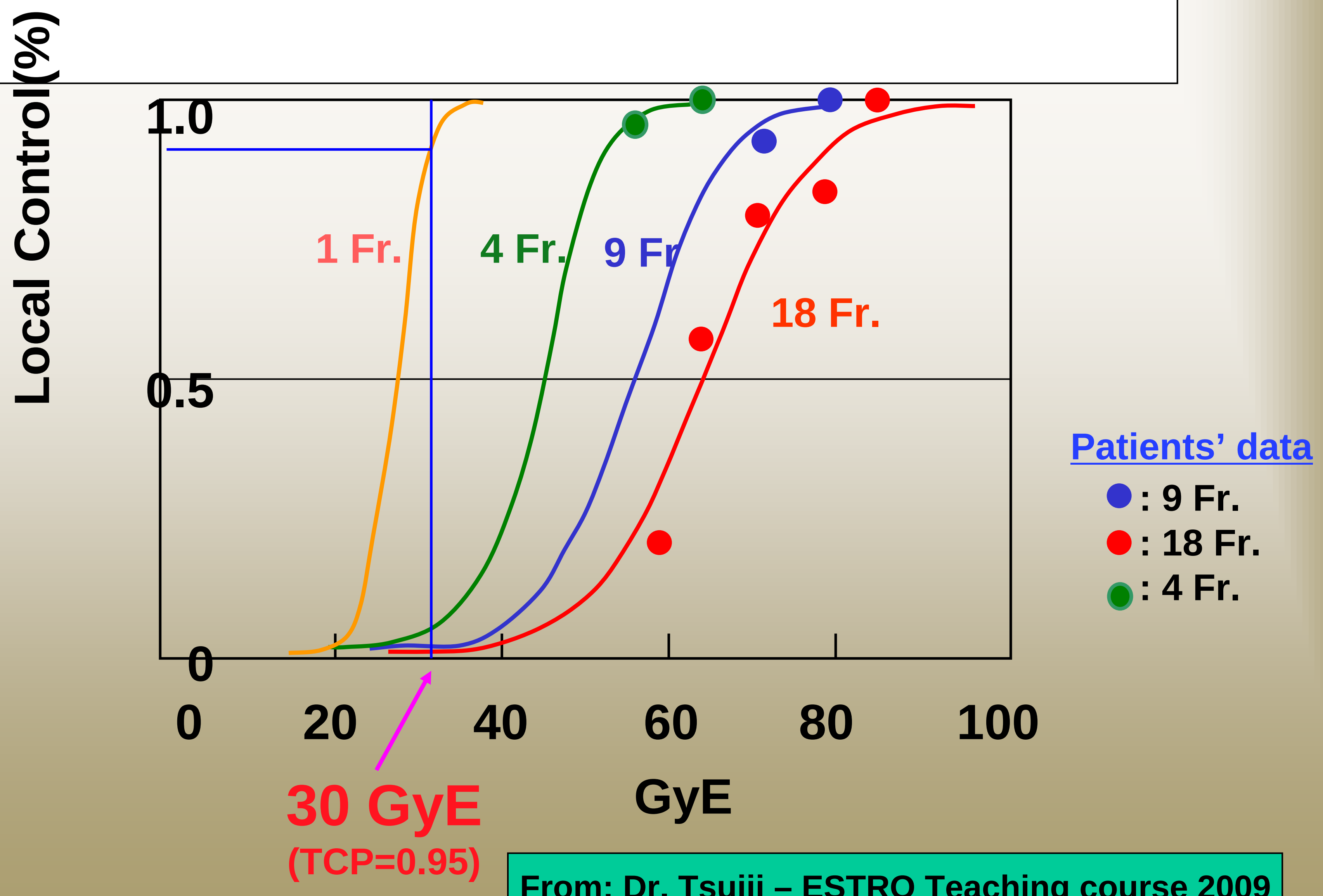
90GyE 72 GyE

From: Dr. Tsujii – ESTRO Teaching course 2009



From: Dr. Tsujii – ESTRO Teaching course 2009

Local Control vs. Carbon Ion Dose for Different Fractionations in NSCLC

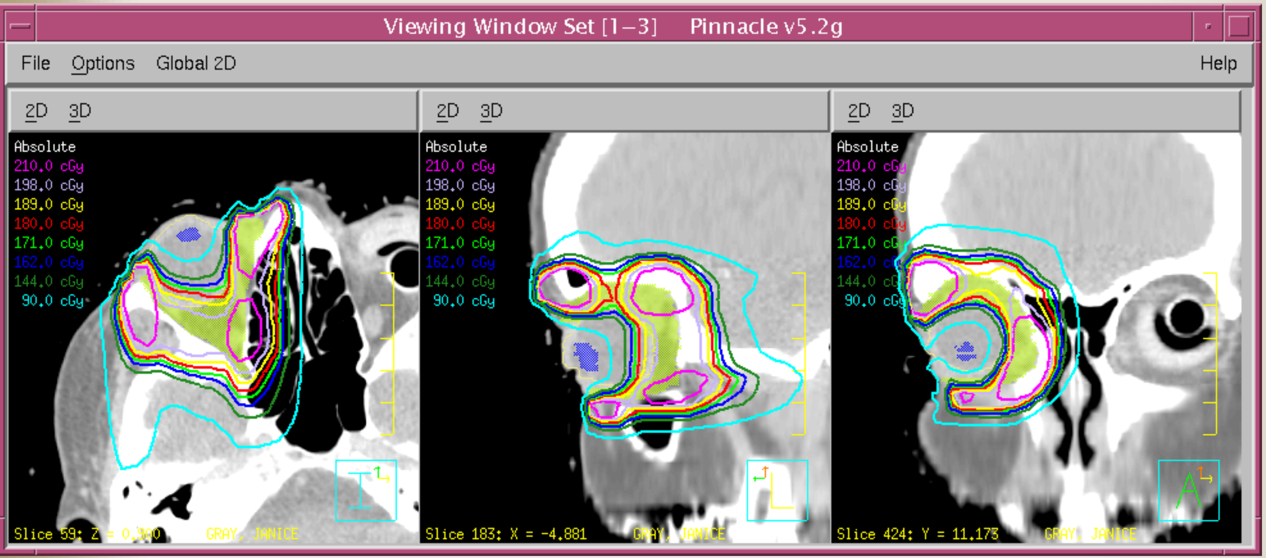


From: Dr. Tsujii – ESTRO Teaching course 2009

RadiationTherapy for Malignancies of the Childhood

- **The Issue:**
- **Cure**
- **Quality of Life for**
- **the Surviving Cancer Patient**

Orbitales Rhabdomyosarkom: Protonen versus Photonen

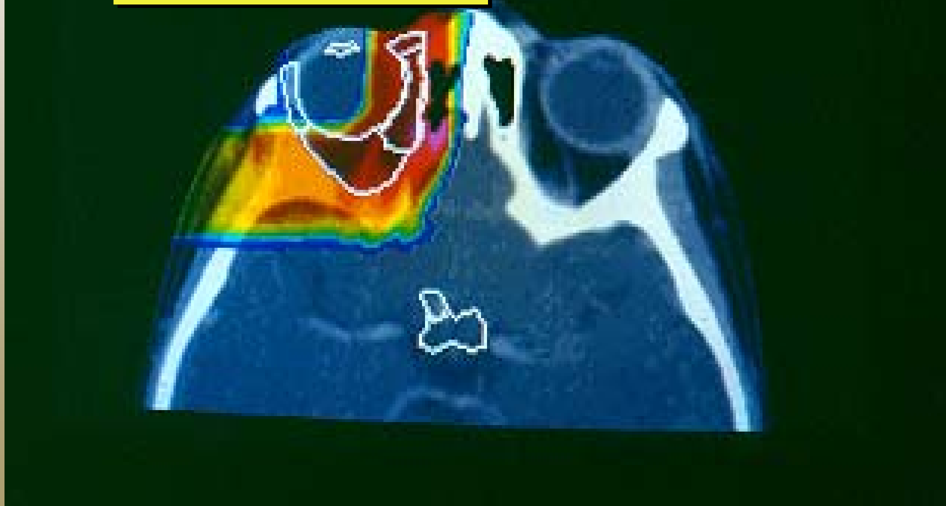


Hein, Hug et al. IJROBP 62, 2005

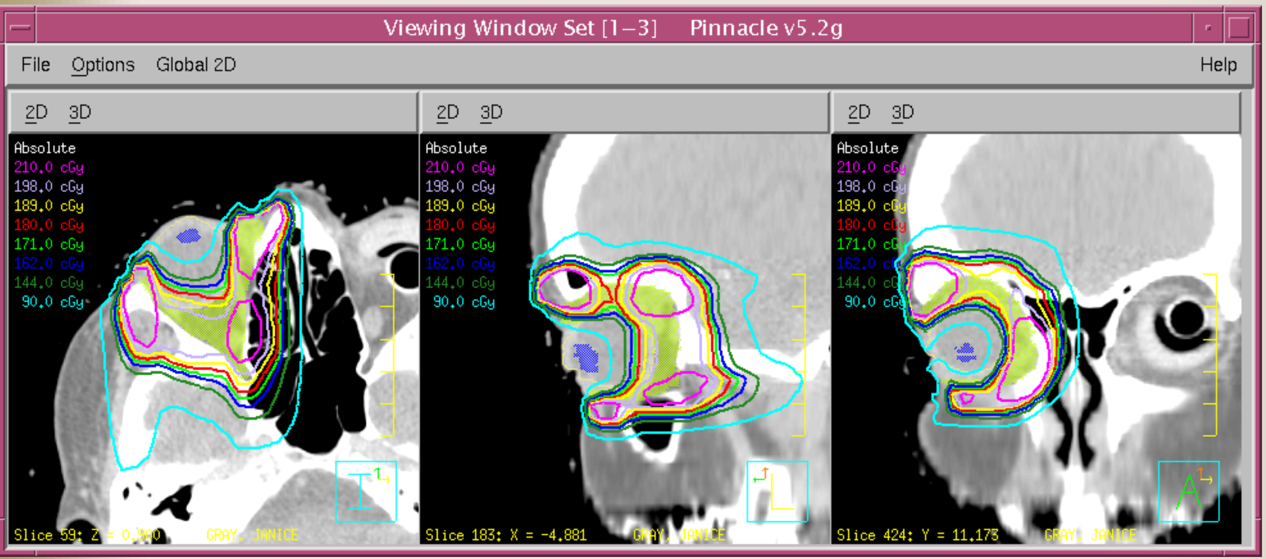
Hug, et al. IJROBP, 47, 2000

Photonen

Protonen



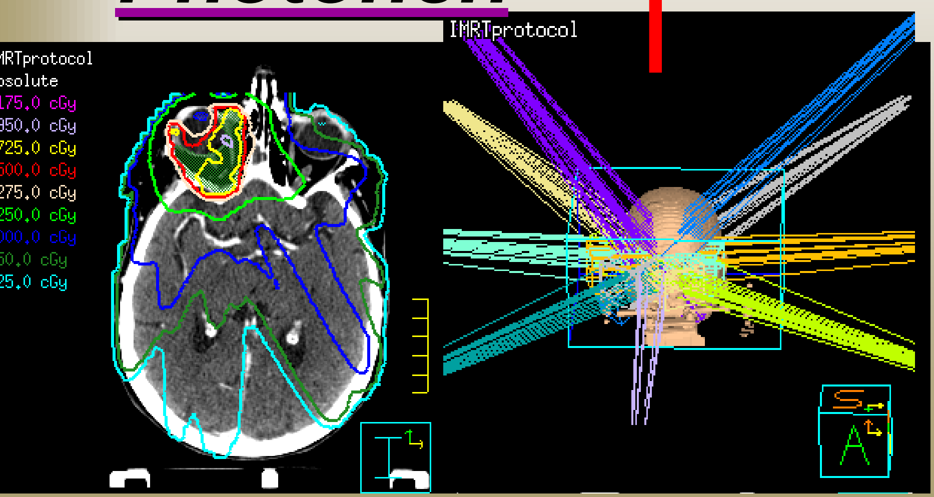
Orbitales Rhabdomyosarkom: Protonen versus Photonen



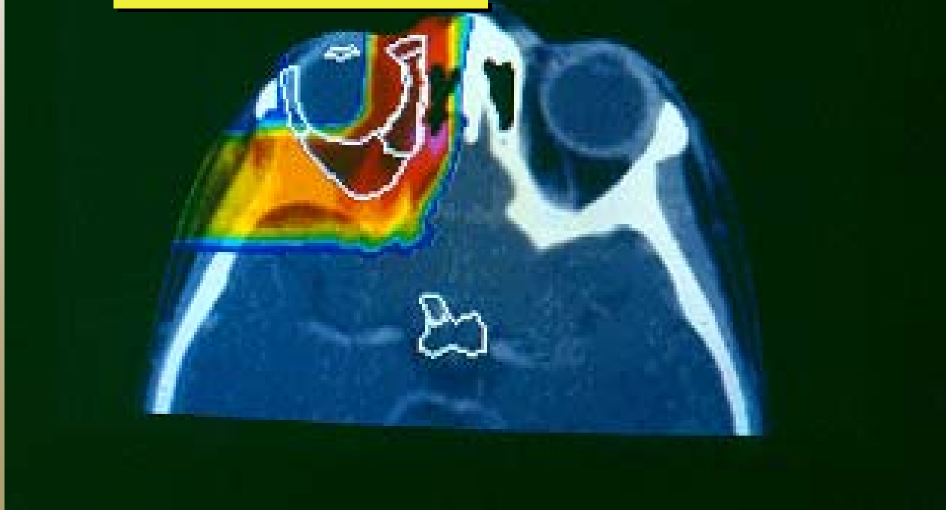
Hein, Hug et al.
IJROBP 62, 2005

Hug, et al. IJROBP, 47, 2000

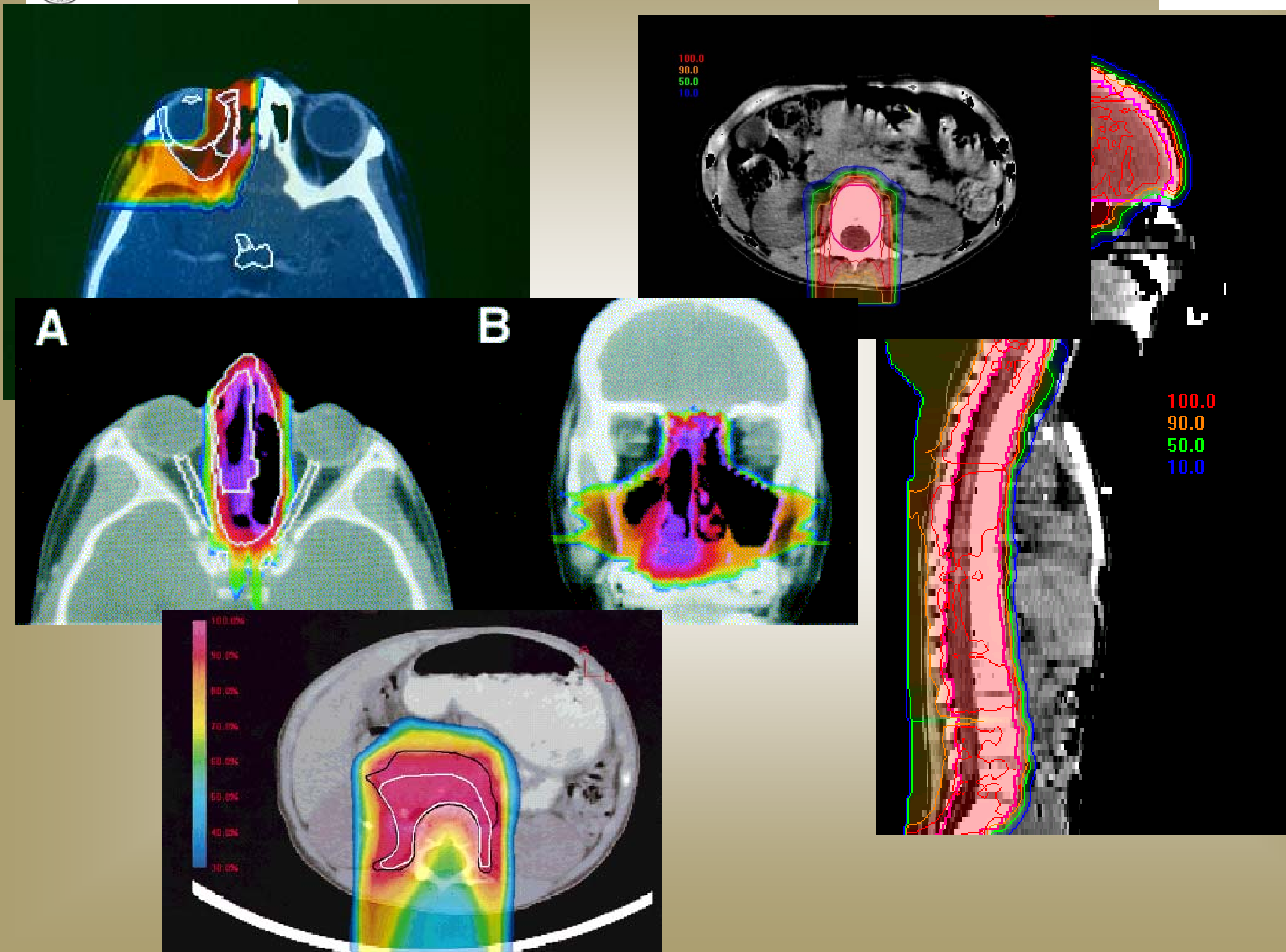
Photonen



Protonen



Pädiatrische Protonen- Radiatiotherapie



Universität Zürich

PAUL SCHERRER INSTITUT PSI

Proton-Radiotherapy for children and young adults:

REDUCTION OF THE „IRRADIATED VOLUME“

=

REDUCTION OF LATE EFFECTS

=

REDUCTION OF RISK FOR INDUCTION OF SECOND MALIGNANGY (SCANNING TECHNOLOGY)

Proton Therapy at PSI for children and infants:

Collaboration: PSI, University Hospital and Childrens' Hospital Zürich

Universität Zürich

PAUL SCHERRER INSTITUT PSI

Proton Radiation Therapy for pediatric indications:

- Established and accepted modality
- permitted in multi-institutional studies of Children’s Oncology Group (USA)
- growing acceptance in European studies
- At PSI: continously 5 children under treatment, 3-4 with general anesthesia
- Main focus at PSI: brain tumors, sarcomas

Proton RT

- after >35 years and > 50 000 patients treated no single disease entity ever treated with protons was later found unsuitable
- no publication has raised the issue of unexpected acute or late toxicity. Any incidence of late toxicity is related to high dose escalation rather than use of protons.
- The initial concept of physical dose distribution and effectiveness has not been called into question by clinical results
- HOWEVER: NO Phase III trials available comparing protons and photons. All data based on Phase I/II trials or retrospective reviews. Limited multi-institutional collaboration.

Universität Zürich

PAUL SCHERRER INSTITUT

Types (Modalities) of EXTERNAL beam Radiation Therapy (RT)

Single Fraction RT

(photons = x-rays)

↓

RADIOSURGERY (RS)

Gammaknife, Cyberknife, Tomotherapy Rapid Arc

Multiple Fraction RT

(photons= x-rays)

↓

2D- standard RT

3D-standard RT

Stereotactic RT

Intensity Modulated RT (IMRT), IGRT, adaptive RT

Particles

↓

Electrons

Neutrons

Carbon Ions

Protons

Planning-Comparison:

Tomotherapy versus IMPT

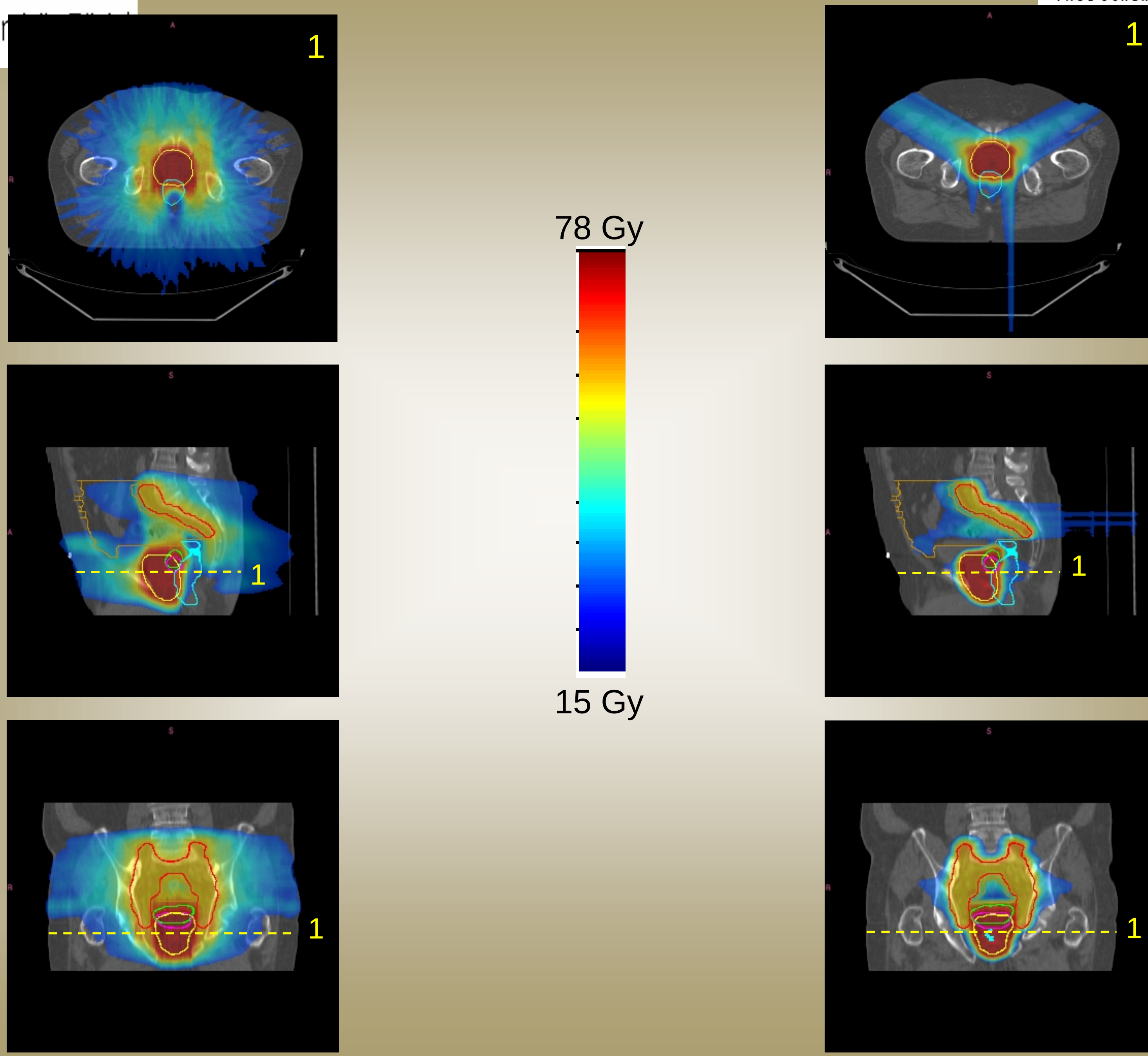
for high-risk Prostate CA –

RT to prostate, seminal vesicles and pelvic LN's

Lamberto Widesott, Claudio Fiorino, Ralf Schneider, Tony Lomax

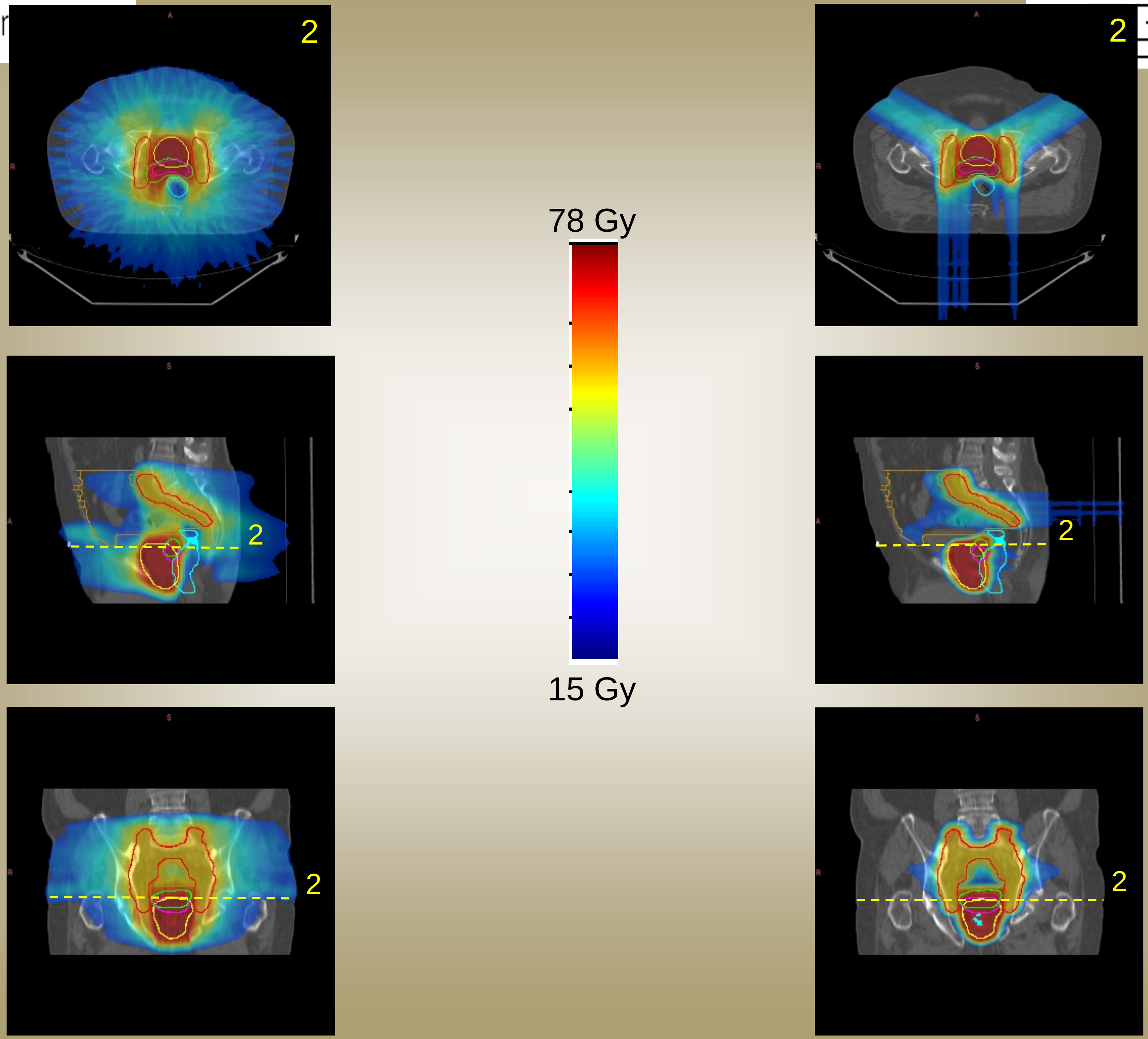
Tomotherapy

IMPT



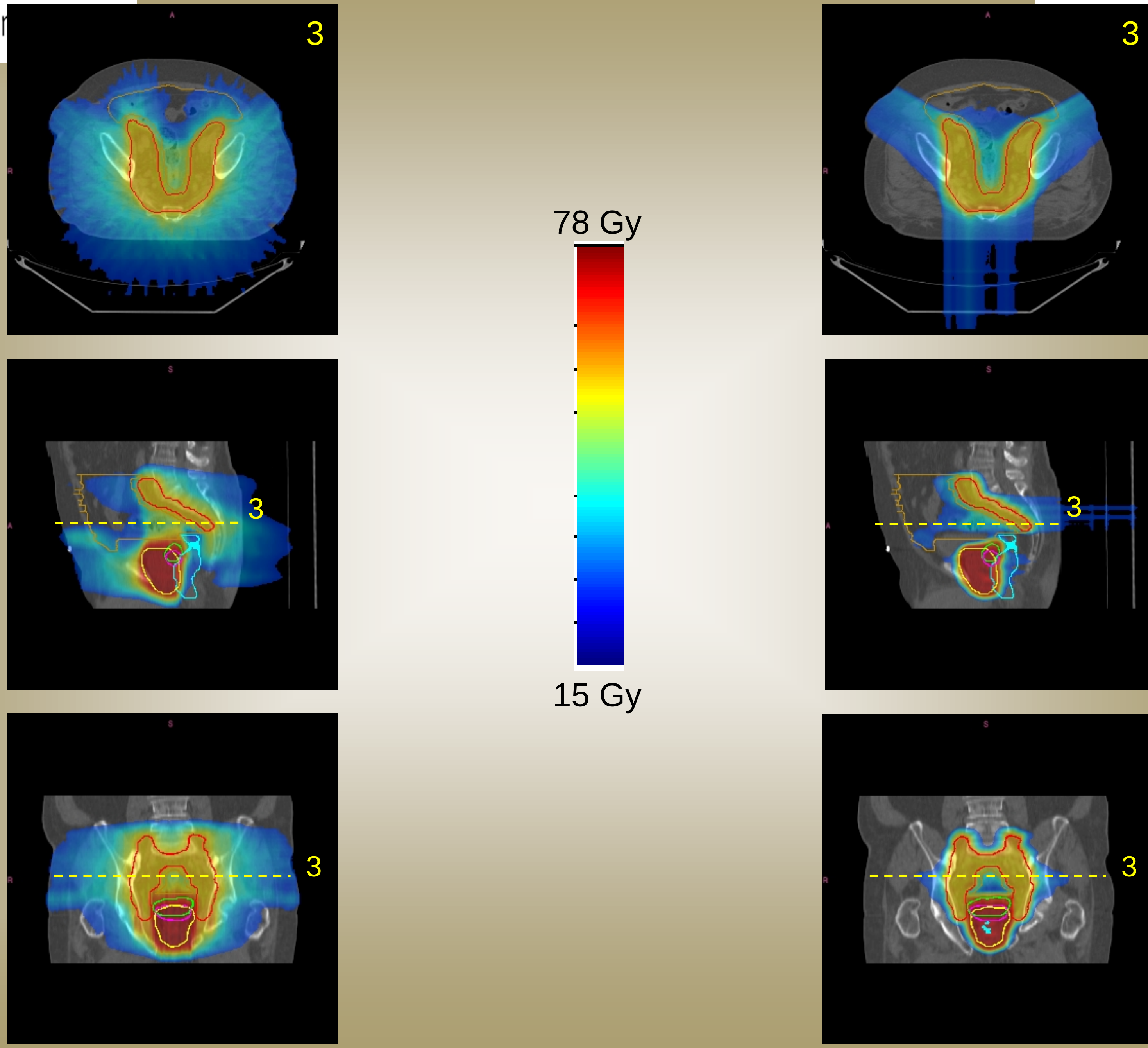
Tomotherapy IMPT

PAUL SCHERRER INSTITUT

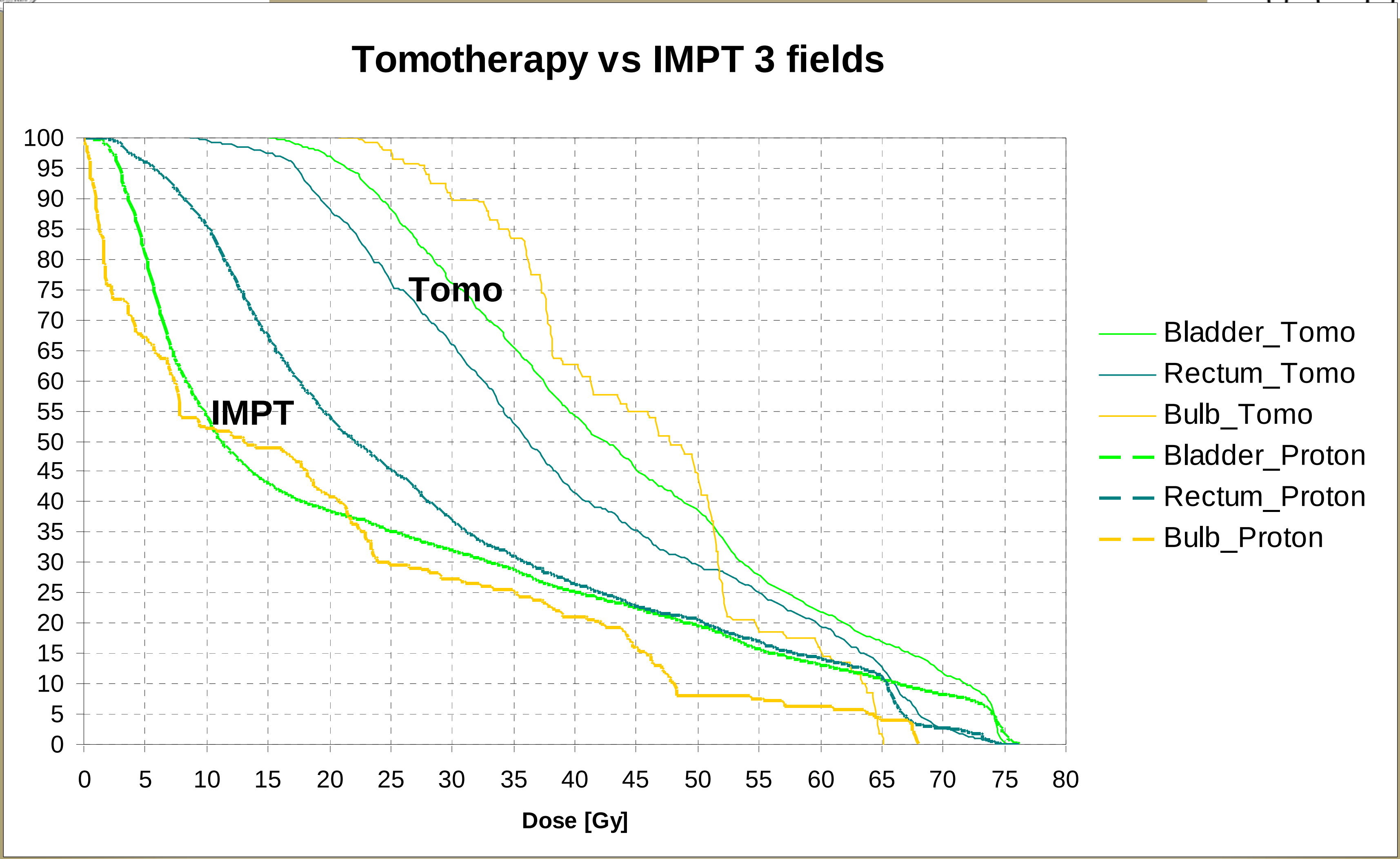


PAUL SCHERRER INSTITUT

Tomotherapy | IMPT

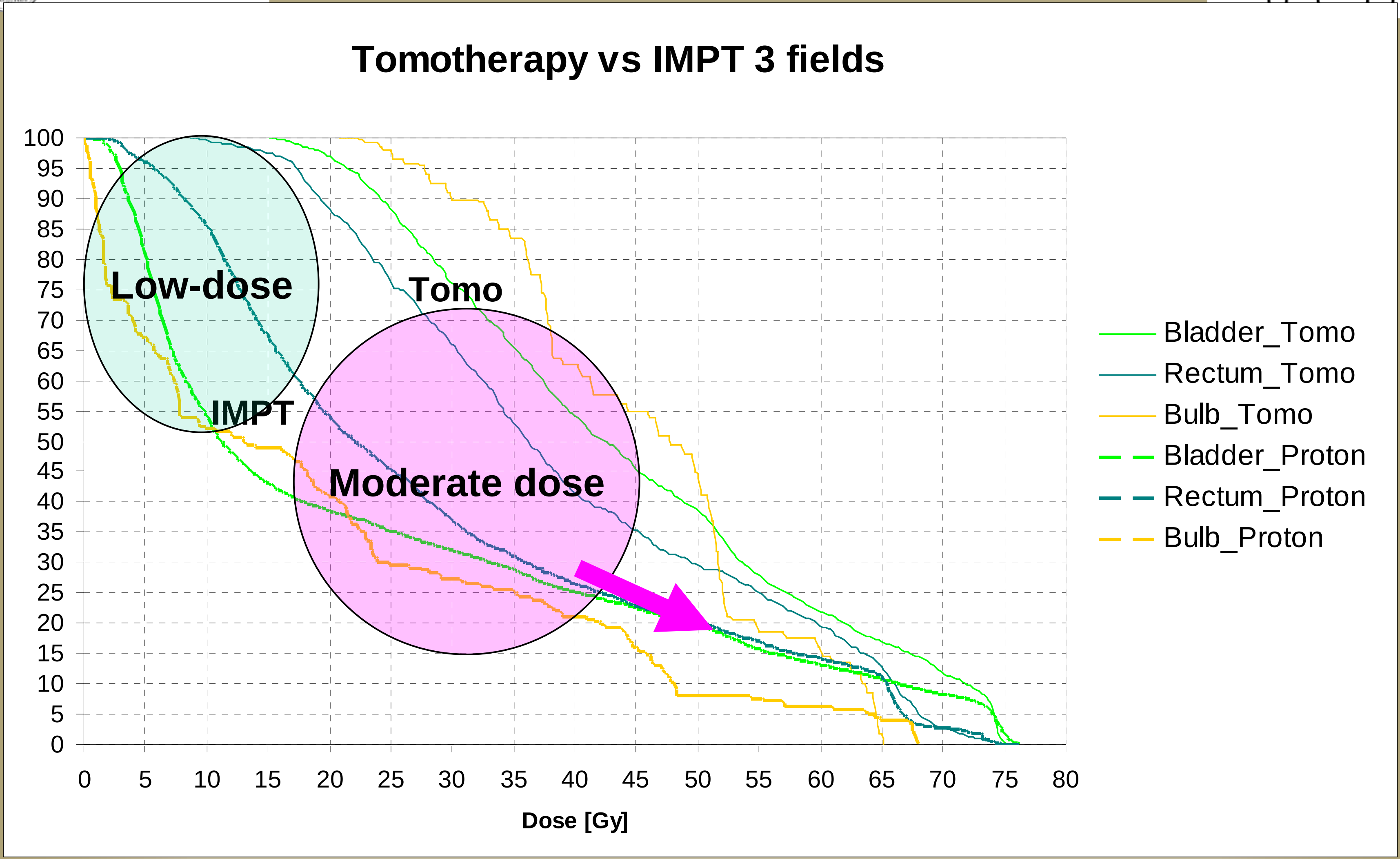


OARs



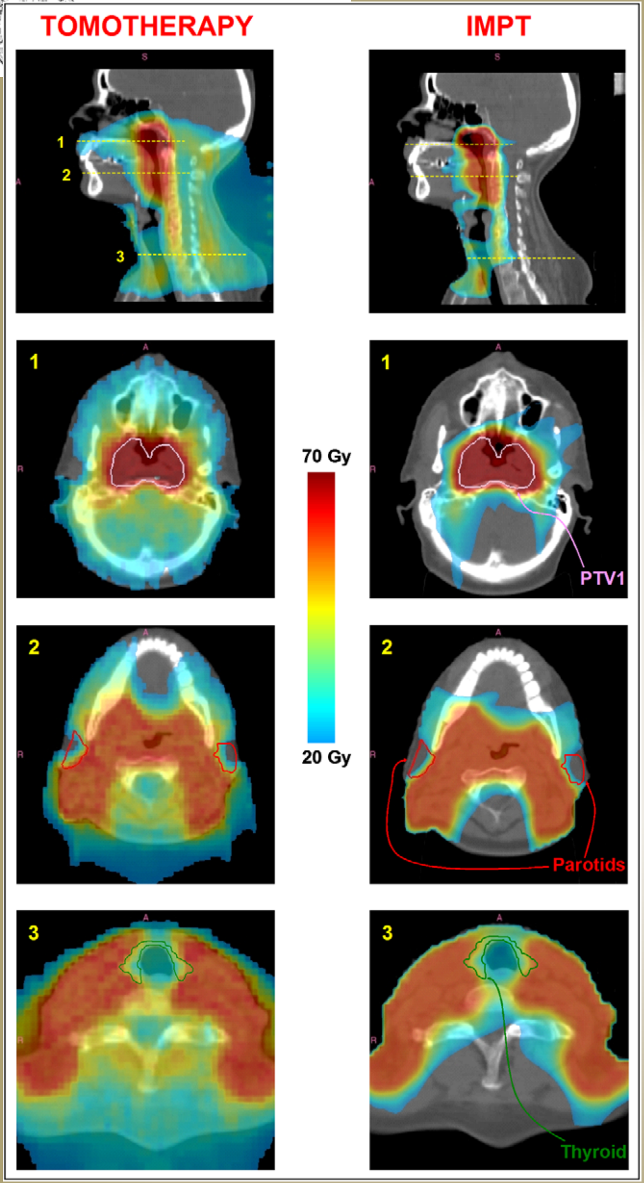
Tomotherapy vs IMPT 3 fields
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
Dose [Gy]
Tomo
IMPT
Bladder_Tomo
Rectum_Tomo
Bulb_Tomo
Bladder_Proton
Rectum_Proton
Bulb_Proton

OARs



Tomotherapy vs IMPT 3 fields
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
Dose [Gy]
Low-dose
Tomo
IMPT
Moderate dose
Bladder_Tomo
Rectum_Tomo
Bulb_Tomo
Bladder_Proton
Rectum_Proton
Bulb_Proton

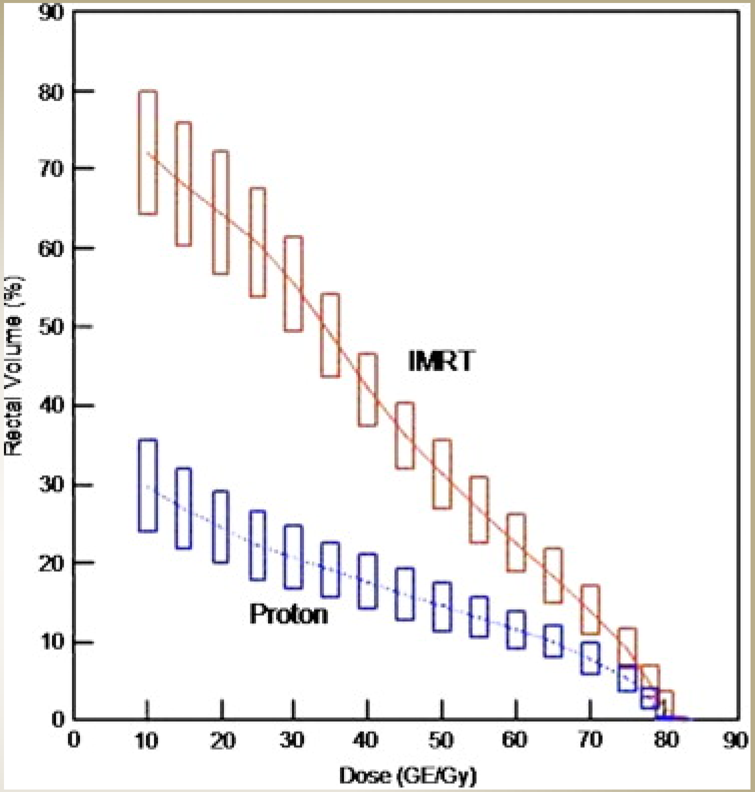
TOMO vs. IMPT



L. WIDESOTT, M. SCHWARZ.
IJROBP 72(2):589, Oct. 2008

IMRT v. Protons

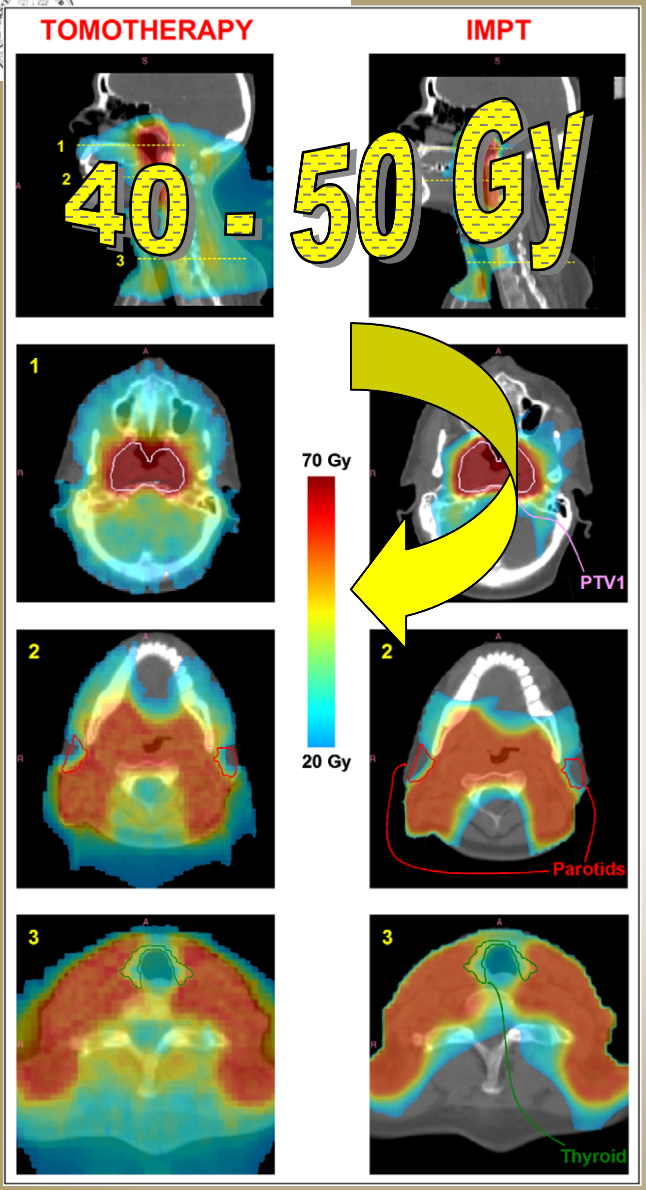
PAUL SCHERRER INSTITUT PSI



Combined rectal dose–volume curves for proton therapy and intensity-modulated radiotherapy (IMRT) (*n* = 20 plans)

Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer
Vargas et al, IJROBP 2008, 70(3):744

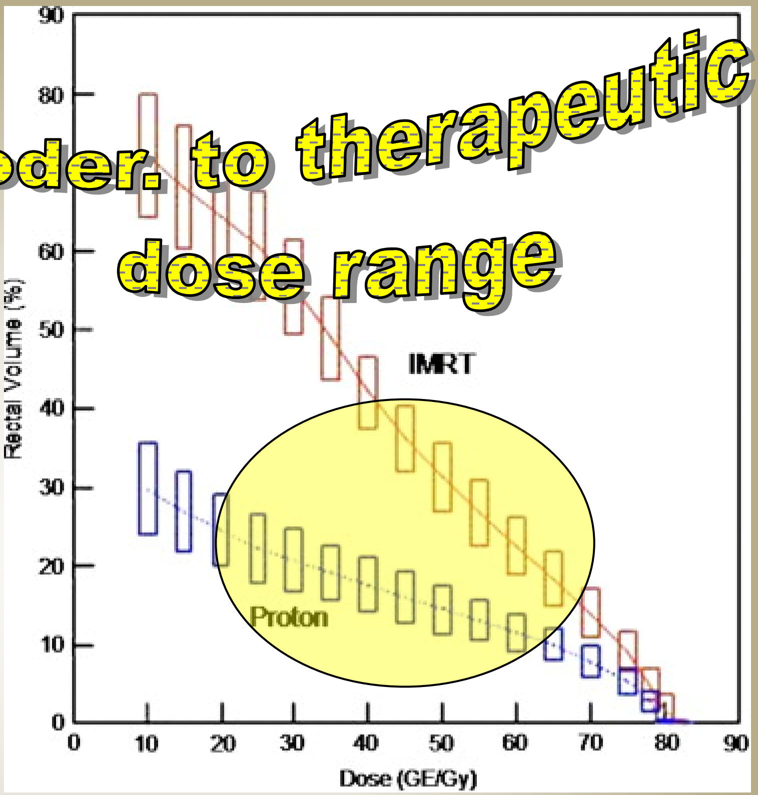
TOMO vs. IMPT



L. WIDESOTT, M. SCHWARZ. IJROBP 72(2):589, Oct. 2008

IMRT v. Protons

PAUL SCHERRER INSTITUT PSI



Combined rectal dose–volume curves for proton therapy and intensity-modulated radiotherapy (IMRT) (*n* = 20 plans)

Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer

Vargas et al,IJROBP 2008, 70(3):744

Conventional Wisdom *:

„low“ dose range

„moderate“ dose range

„high“ dose range

1 Gy ---- 10/15 Gy   ***15/20 ---35/45 Gy***   ***60/65 Gy and up***

50/55 Gy and up

„therapeutic“ dose range
(most solid tumors)

{Official definition of “low dose”

ICRU: < 5% isodose (report in progress)

BEIR IV Committee : < 0.1 Gy }

* = for use in radiooncology, not general public

Conventional Wisdom (i.e. my personal interpretation as clinician)*:

„low“ dose range

„moderate“ dose range

„high“ dose range

1 Gy ---- 10/15 Gy   15/20 ---35/45 Gy   60/65 Gy and up

50/55 Gy and up

„therapeutic“ dose range
(most solid tumors)

{Official definition of “low dose”

ICRU: < 5% isodose (report in progress)

BEIR IV Committee : < 0.1 Gy }

* = for use in radiooncology, not general public

Universität Zürich

PAUL SCHERRER INSTITUT

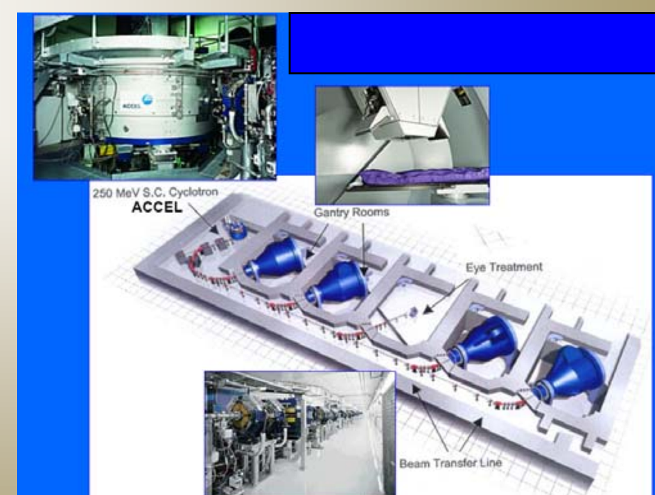
The Paradigm Shift

in proton therapy equipment and facility design

Proton-Radiotherapy facilities: the paradigm shift

Paradigm of 80's and 90's:

From research institute to hospital based large-scale facilities serving large geographic regions



Universität Zürich

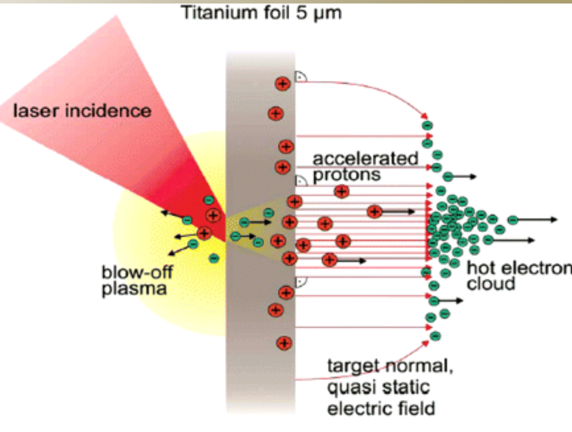
PAUL SCHERRER INSTITUT PSI

Proton-Radiotherapy facilities: the paradigm shift

Paradigm since 2000:

From large scale facilities to smaller facilities with few rooms or even single-room units serving populations of a mid-size Cancer Center

Prerequisite: Reduction of production costs, stable reimbursement system, established and accepted indications



Universität Zürich

The Future of Particle Therapy

PAUL SCHERRER INSTITUT PSI

„ Particles for everybody“

Proton accelerator and delivery technology are the furthest advanced amongst particles and will likely continue its success.

Wide-spread availability of protons is imminent.

The Future of Particle Therapy

„ *Cure without complications*“ will become a major paradigm for curable patients.

→ ***Protons (and other particles?) will become the „RT modality of choice“ for***

- ***pediatric malignancies,***
- ***in young adults,***
- ***patients with tumor-unrelated co-morbidities***
- ***for selected indications***

Carbon Ion Therapy:

Clinical results limited in number and institutions

- **„Safety and Efficacy“ phase successfully passed**
- **Majority of clinical outcomes data similar to protons.**
- **Hypothetical superiority to protons for „radioresistant“ tumors not generally demonstrated**
- **Promising data for large, unresectable tumors**
- **Exciting data on single/few fraction treatments of lung and liver CA**
- **Need more data before conclusions can be drawn**
- **Versatility to study different particles, combining particles etc. very promising**

What we clinicians need from particle researchers and developers:

- More compact (Carbon ions, Gantries)
- More precise, i.e. a „sharper“ beam (lateral penumbra)
- Faster (scanning of mobile tumors)
- Cheaper (particle therapy is the logical evolutionary next step of radiotherapy. The ONLY argument against particles are high costs)
- Continuation of creative solutions

Universität Zürich

PAUL SCHERRER INSTITUT PSI

Continue the search and quest for the „Holy Grail“ of particle therapy:

The illusive „ideal particle“ has yet to be found

Universität Zürich

PAUL SCHERRER INSTITUT PSI

THANK YOU !