WORKSHOP
Late Effects Studies

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Late effects

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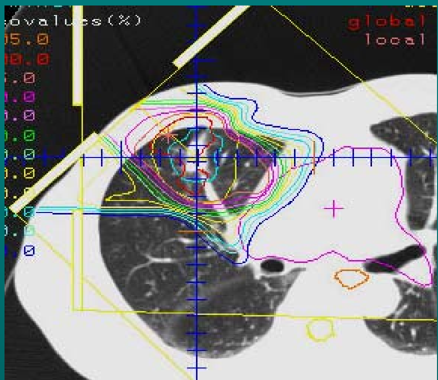
Lung Cancer *(AdenoCA.) : T1N0M0*

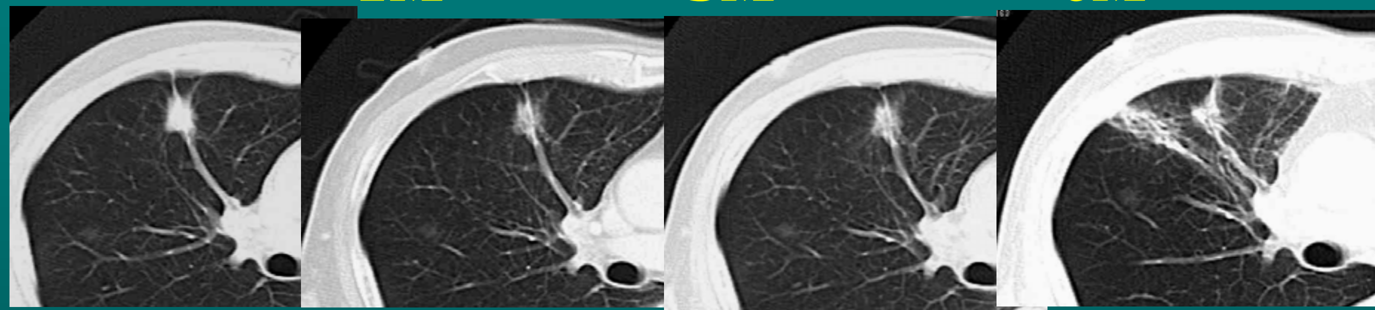
Proton

80GyE/20Fr/4W



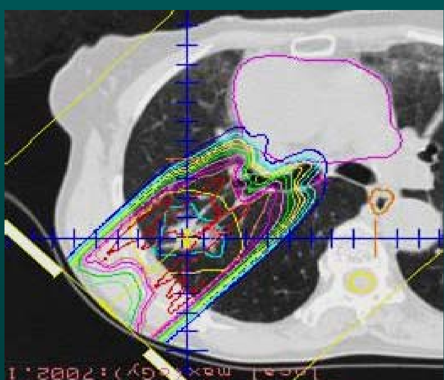
75M

Pre *1M* *3M* *6M*



Carbon

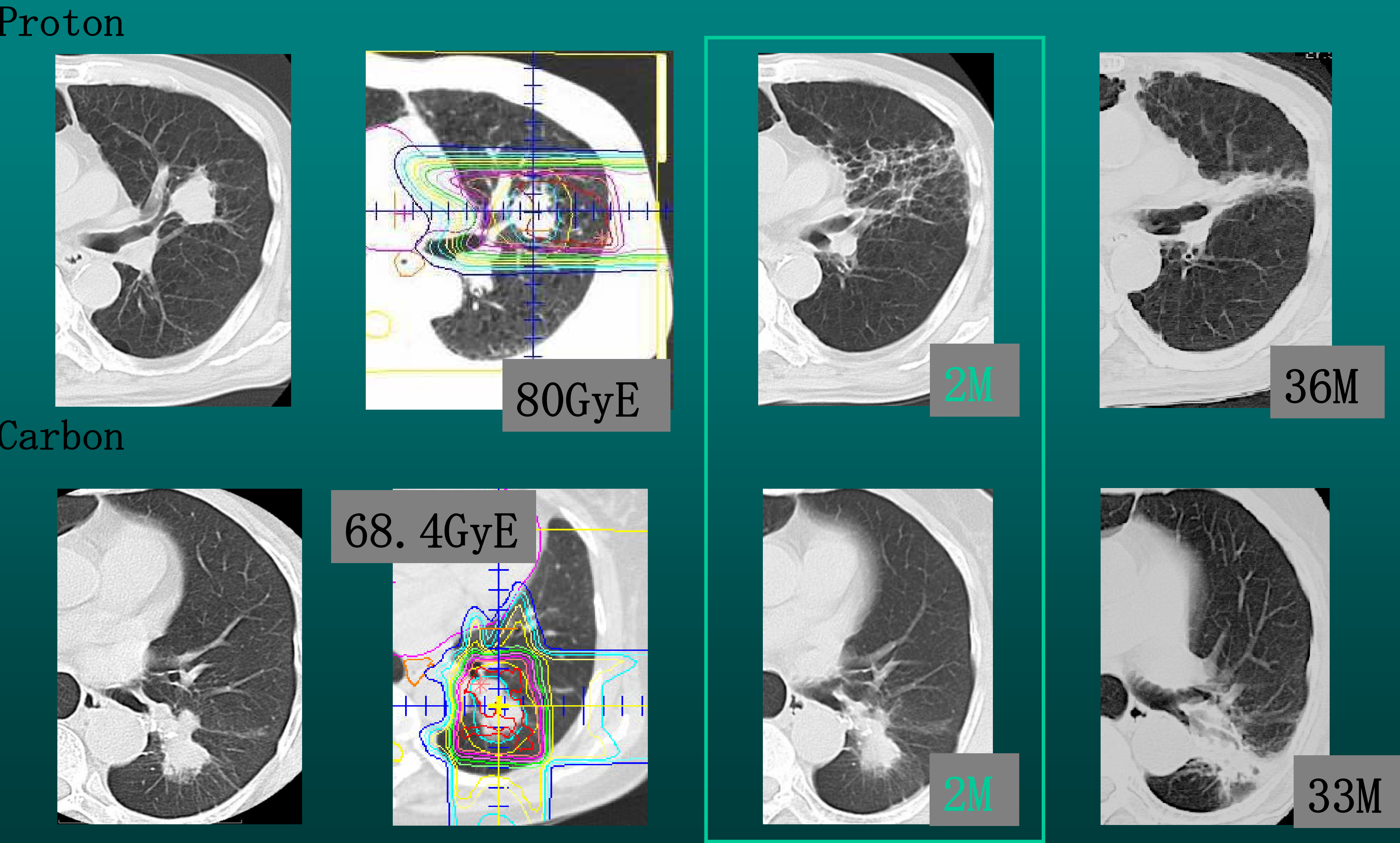
57.6GyE/16Fr/4W



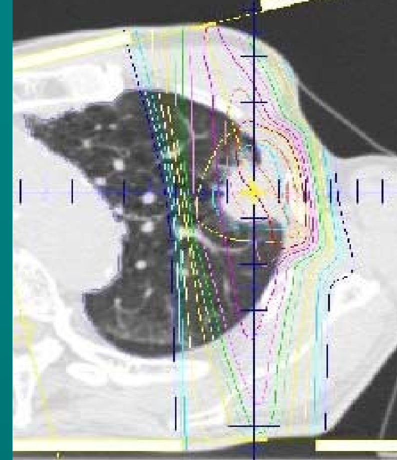
76M

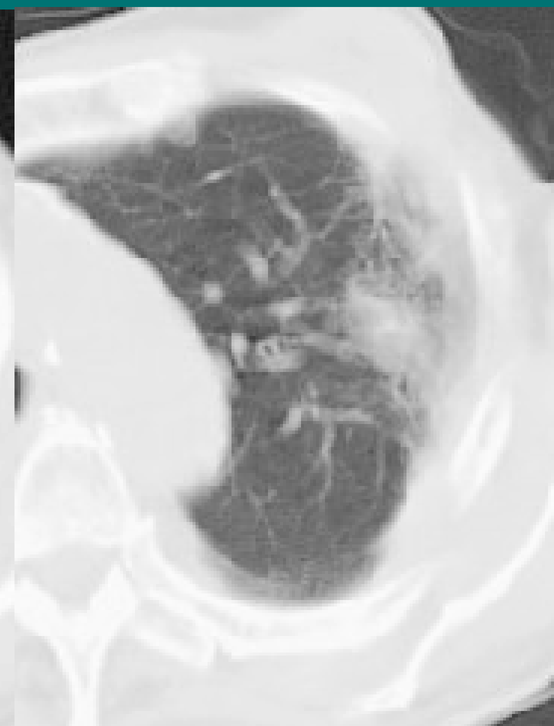
Pre *1M* *3M* *7M*

Lung ca. P vs. C



75y.o. Male
Lung　Ca
After r-lung resection





Before
28mm

6GyEx10
20mm

6M

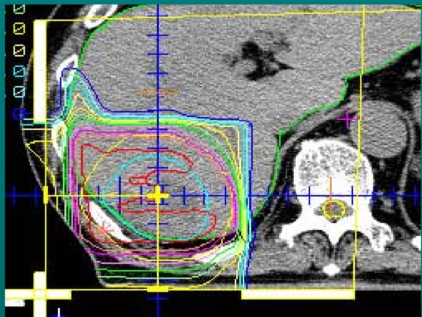
2Y

HCC : *T2N0M0*

Dynamic CE-CT

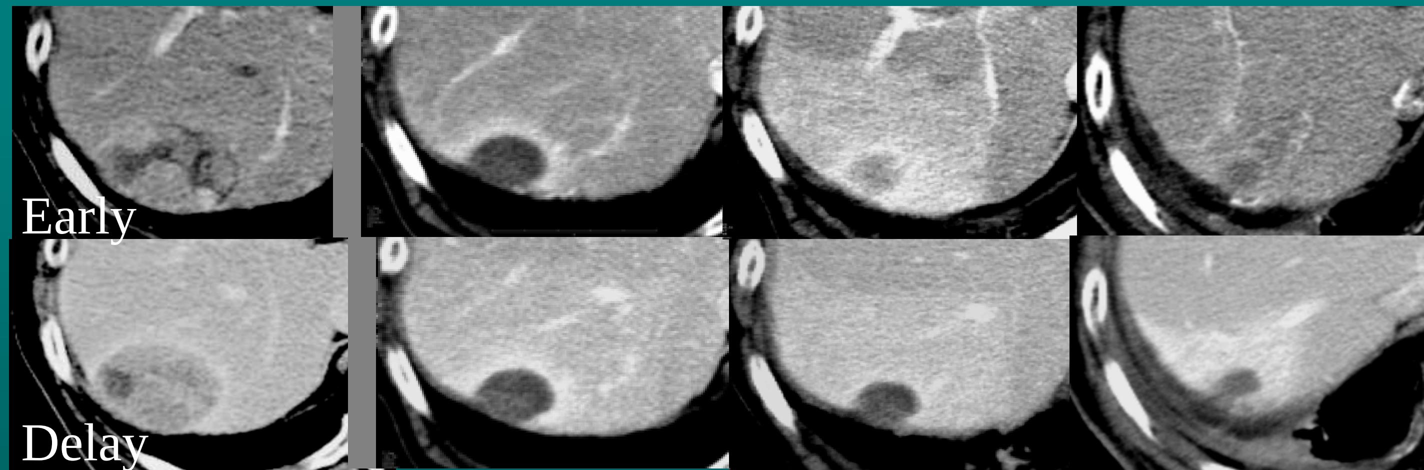
Proton

76GyE/20Fr/5W



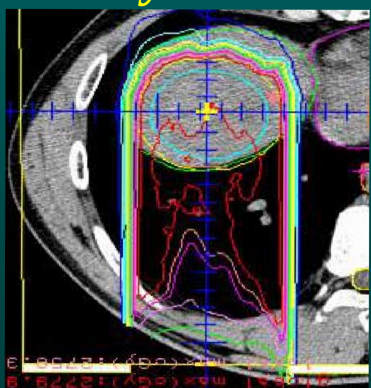
81M

Pre	*1M*	*2M*	*17M*



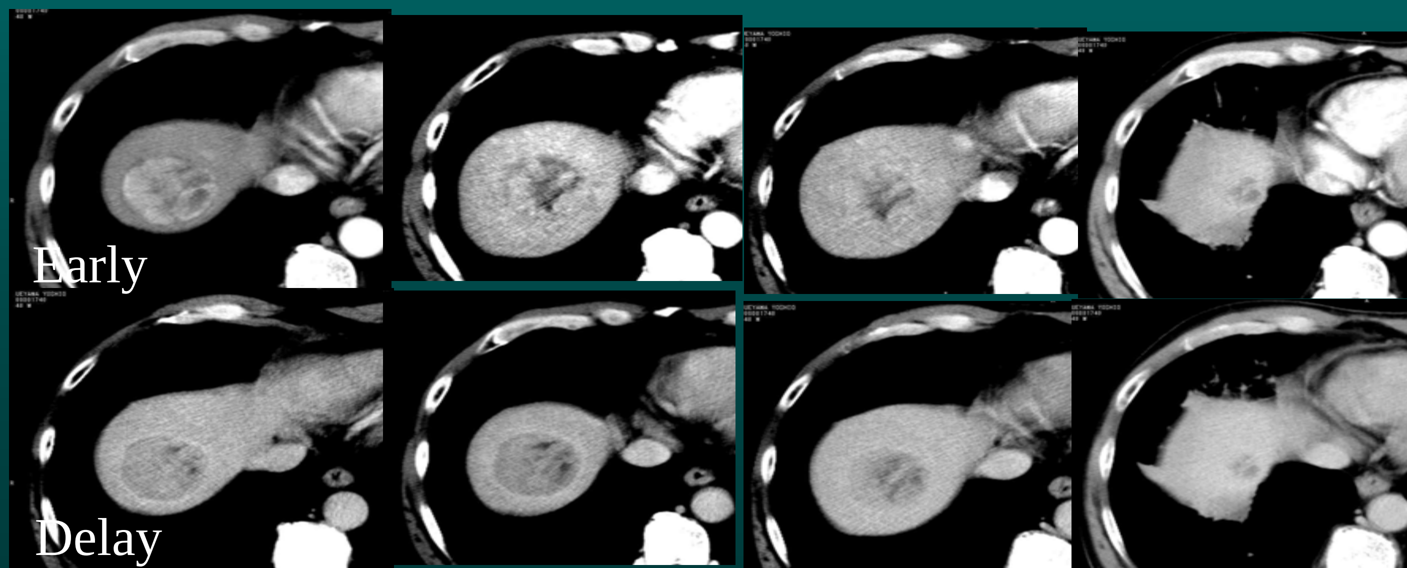
Carbon

52.8GyE/8Fr/2W

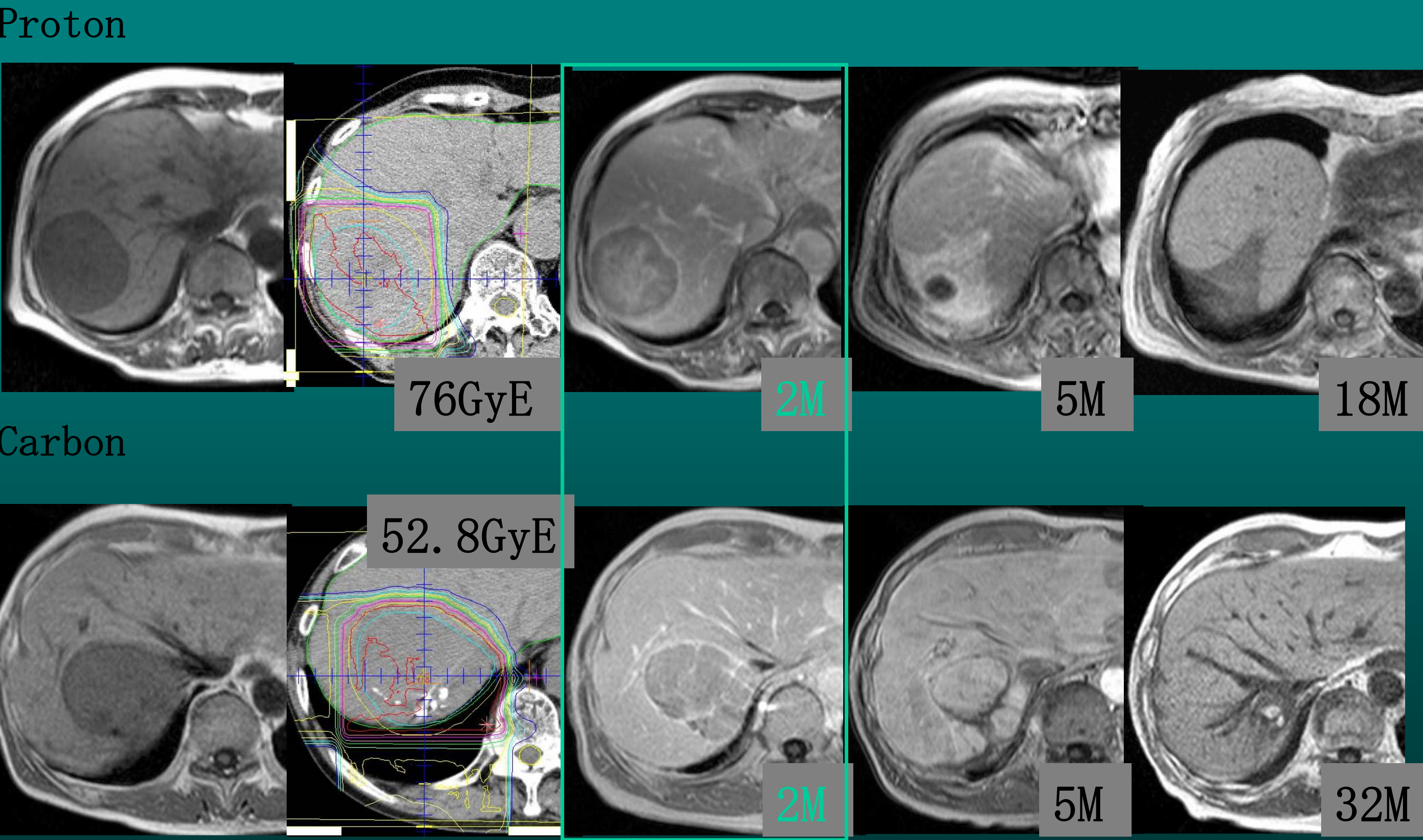


48M

Pre	*1M*	*3M*	*6M*



Liver ca. P vs. C








Thank you for your kind attention.

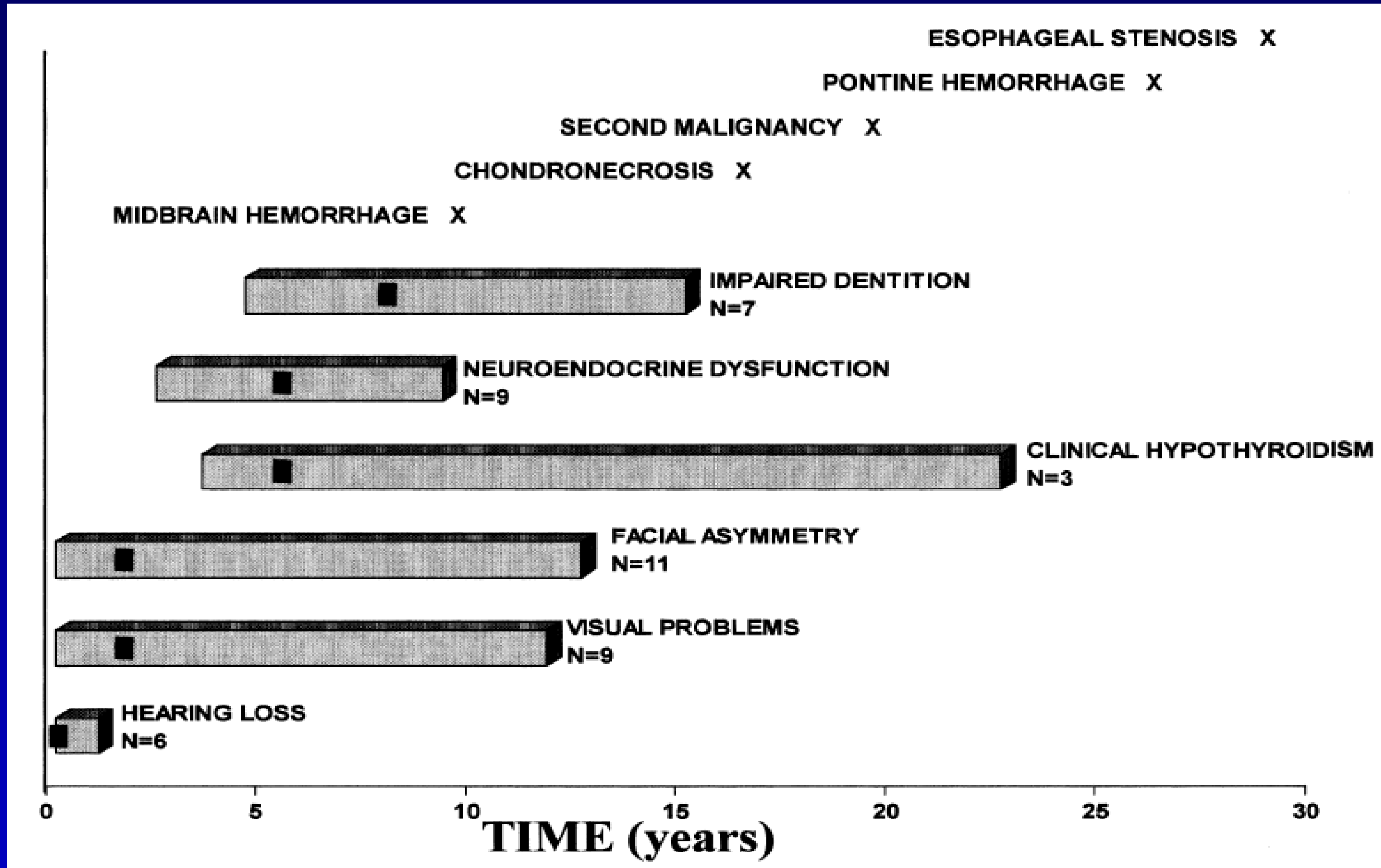
Late XRT Effects on Normal Tissue

- Central Nervous System
  - Neurocognitive and psychosocial deficits
  - Neuroendocrine
  - Auditory (cochlea) Visual (nerve, lens,lacrimal)
- Growth/Musculoskeletal
  - Atrophy Scoliosis/Kyphosis
  - Hypoplasia Length discrepancy
- Oral
  - Xerostomia Dental Radionecrosis

Late XRT Effects on Normal Tissue

- Cardiopulmonary
  - Myocardiopathy — Pericarditis
  - Arrhythmia — Valvular dysfunction
  - Coronary artery disease — Lung fibrosis
- Endocrine
  - Thyroid — Ovarian — Testicular
- GI
  - Small bowel — Hepatic — Proctitis
- Second malignancies

Timeline



Late Effects in 17 pts. with Head Neck Rhabdomyosarcoma

Paulino et al. IJROBP (2000) 48(5): 1489-1495

Late XRT Effects on Normal Tissue

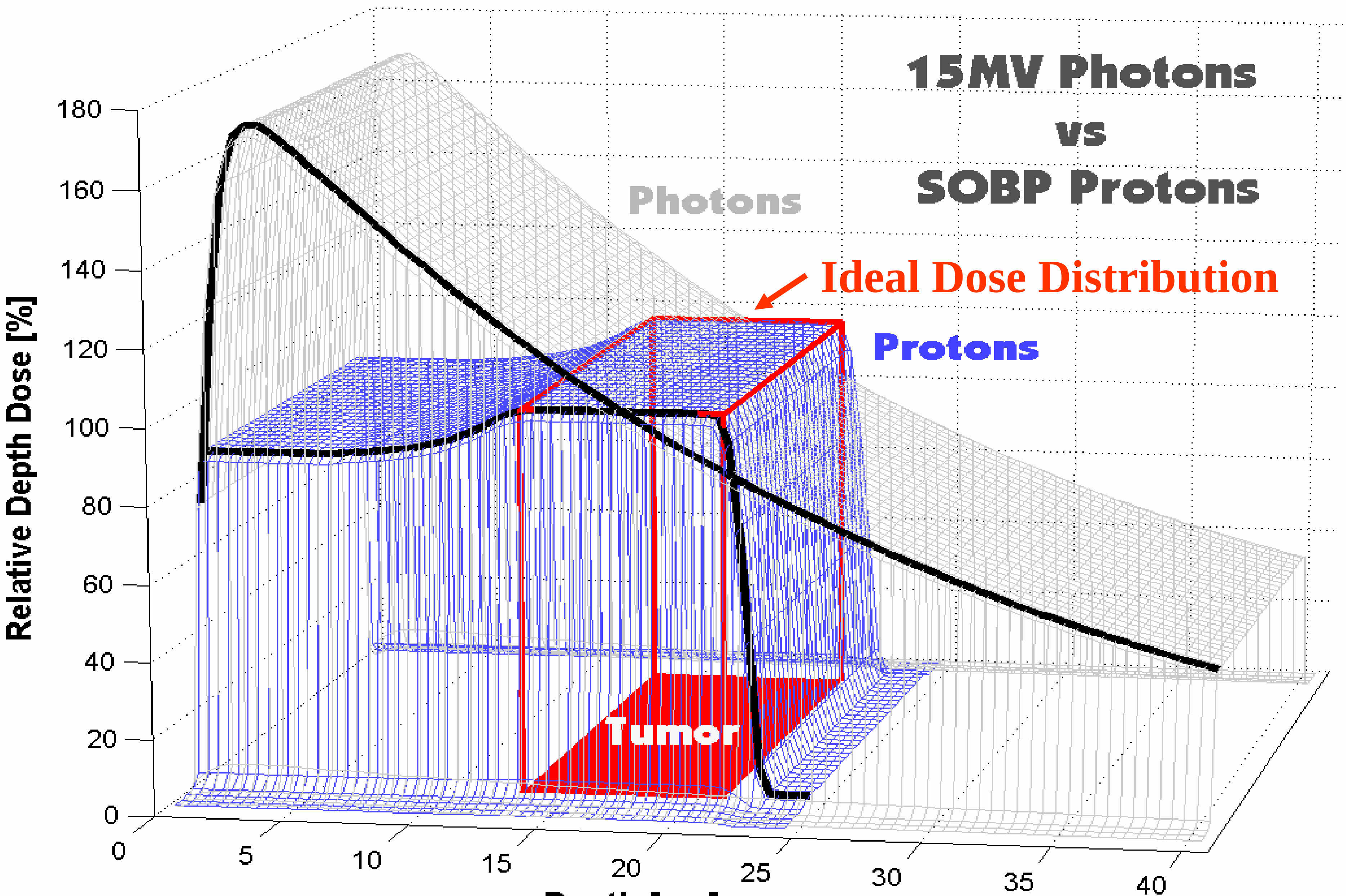
- Risk factors
  - Dose
    - Tolerance doses are described for normal tissues
  - Volume
    - Larger volumes are associated with substantially greater effects in general than smaller volumes
  - Dose distribution
    - Dose delivered to skin and other normal tissues can be technique dependent
  - **Tissues not in the primary beam at ↓↓ risk!**

Late XRT Effects on Normal Tissue

- Second malignancies
  - Breast cancers
  - Brain tumors
  - Myelodysplasia/AML
  - Thyroid Cancers
  - Sarcomas of bone/soft tissue
- Risk factors
  - Age at treatment
  - Radiation dose/volume
  - Genetic factors (Li-Fraumeni, Retinoblastoma)
  - Host factors: Smoking, alcohol, diet
  - **Tissues not in the primary beam at ↓↓ risk**

PROTONS

- Particles with charge and mass
  - Defined range in tissue
    - Proportional to energy
    - Unmodulated: deposit dose in sharp Bragg Peak
      - No dose delivered beyond that point
    - Bragg peak spread out toward surface to treat tumors
  - Contrast with photons (x-rays)
    - Continue to deposit dose beyond target in tissue
      - Unwanted dose to normal tissue


15MV Photons
vs
SOBP Protons
Photons
Ideal Dose Distribution
Protons
Tumor
Relative Depth Dose [%]
180
160
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40

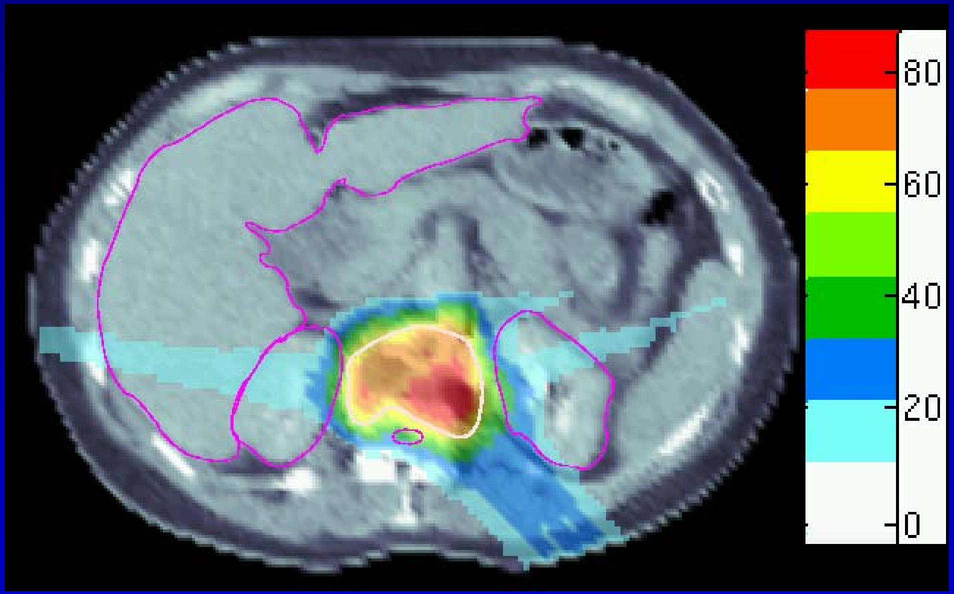
Protons: Physical Dose Advantage

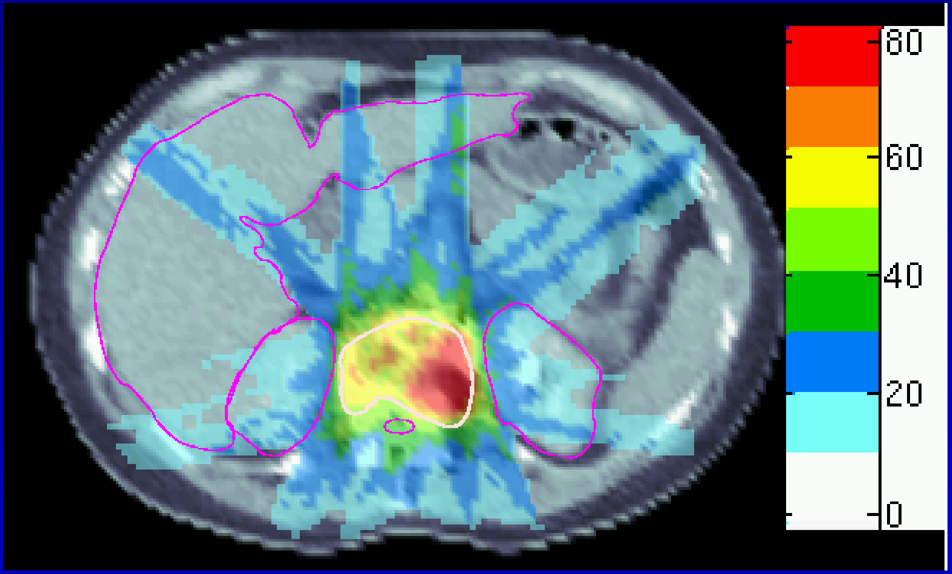
- Clinical advantage for protons over photons is a physical advantage based upon the superior dose distributions which can be achieved with protons
- i.e. Lower normal tissue doses for any tumor dose

Protons: Physical Dose Advantage

- Intensity modulated radiotherapy (IMRT)
  - Target dose distributions to the tumor are similar to what is achievable with protons
    - Integral dose is ALWAYS higher that with protons
    - Although selected normal tissues can be spared with IMRT, this is at the cost of INCREASED DOSE TO OTHER NORMAL TISSUES
- INTENSITY MODULATION IS APPLICABLE TO PROTONS

L1 Angiosarcoma





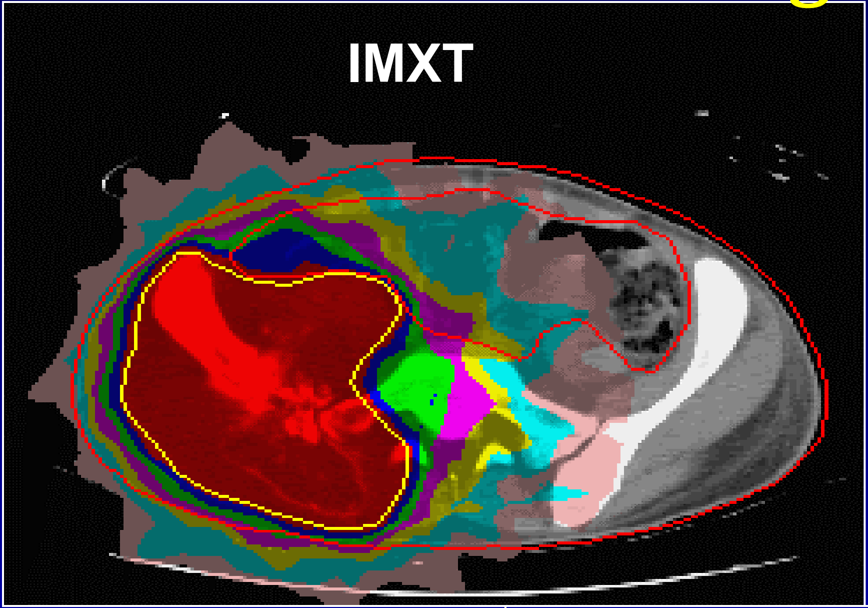
Proton

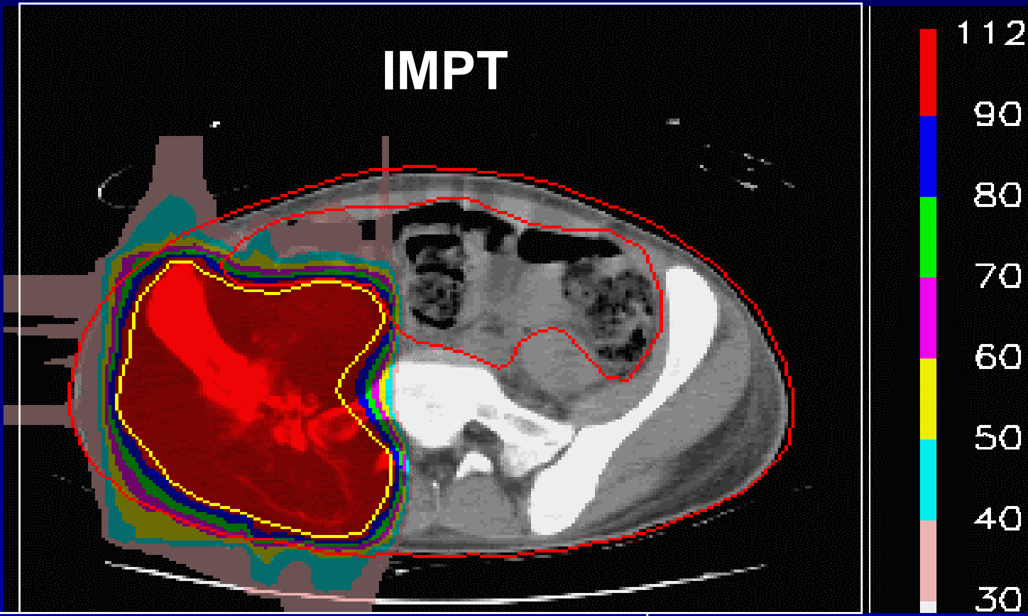
IMRT

Protons: Clinical Advantages

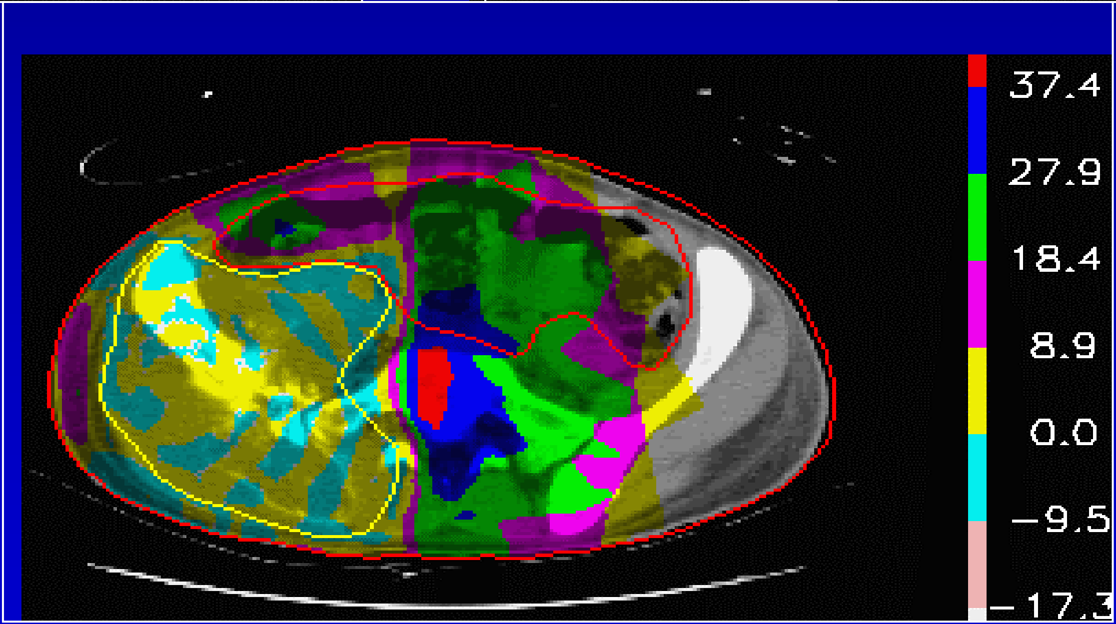
- Does this improved physical dose profile yield any clinical gain for the patient?
  - Dose escalation →? Improved local control
    - Improved survival?
  - Reduction in morbidity?
    - Acute
      - No interruptions in radiotherapy→Improved local control/survival
      - No interruptions in chemotherapy→Improved local control/survival
    - Late
      - Reduction in treatment related morbidity (i.e growth effects in children, normal tissue necrosis)
      - Reduction in second malignancies

Ewings Sarcoma





DIFFERENCE
(IMXT - IMPT)



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Protons: Reduction in Second Malignancies

- Comparative Treatment Plans
  - Protons vs. Photons (Conformal or IMRT)
    - Rhabdomyosarcoma
      - Protons reduce risk of 2nd malignancies by factor of $\geq$ 2
    - Medulloblastoma
      - Protons reduce risk of 2nd malignancies by factor of 8-15

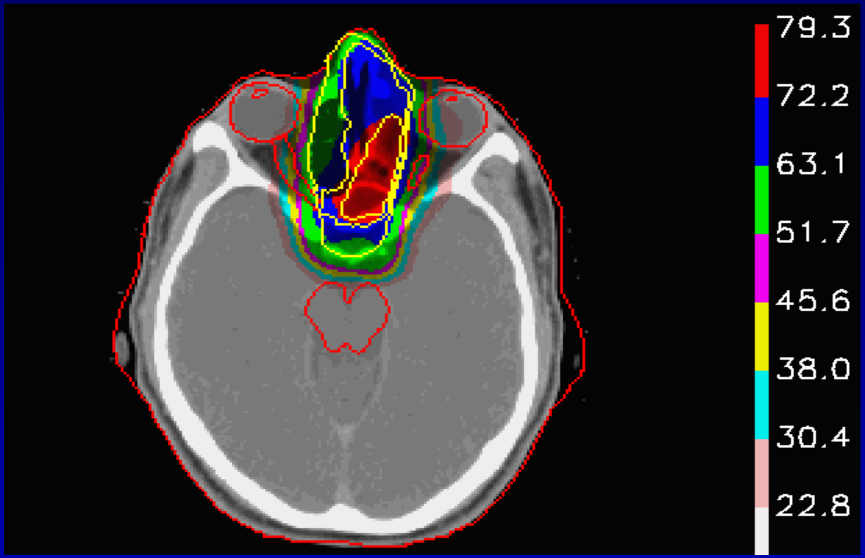
Miralbell, Lomax et al, Int J Radiat Oncol Biol Phys. 2002;54:284-9

Protons: Reduction in Late Effects

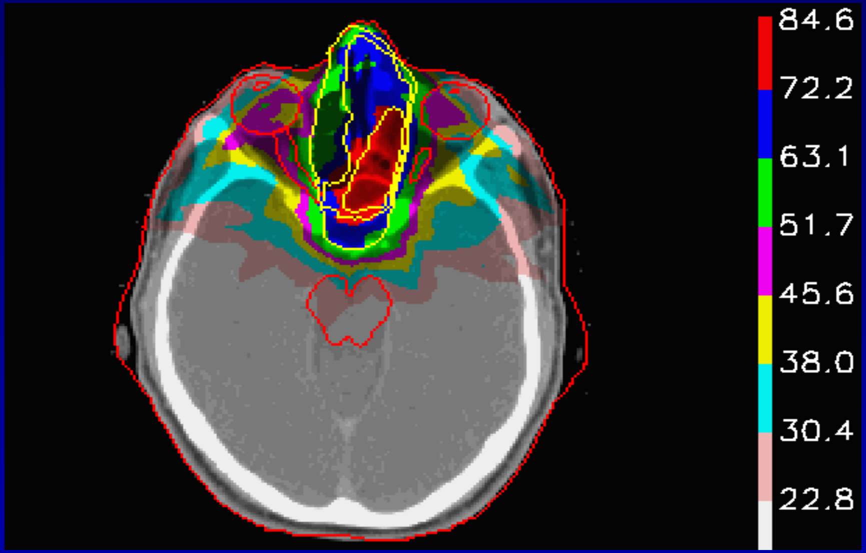
- Paranasal sinus carcinoma
  - Reduction in ocular sequelae
  - Less dose to brain, parotid glands
- Medulloblastoma
  - Reduction in auditory sequelae
  - Less dose to heart, lungs
- Pediatric malignancies
  - Less growth impairment

MAXILLARY SINUS

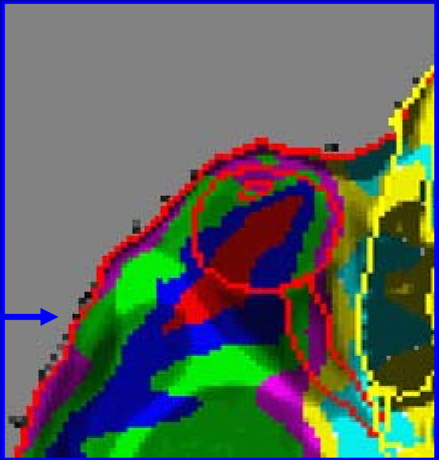
IMPT

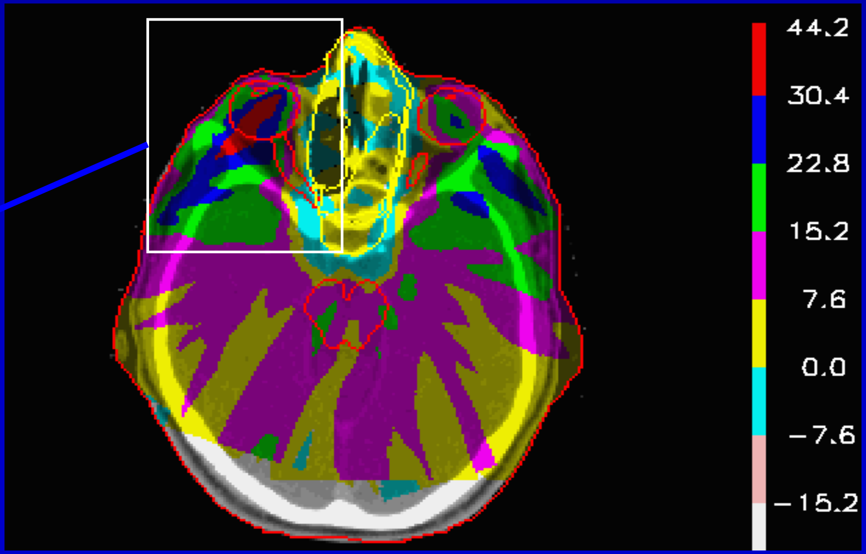


IMXT



Dose Difference





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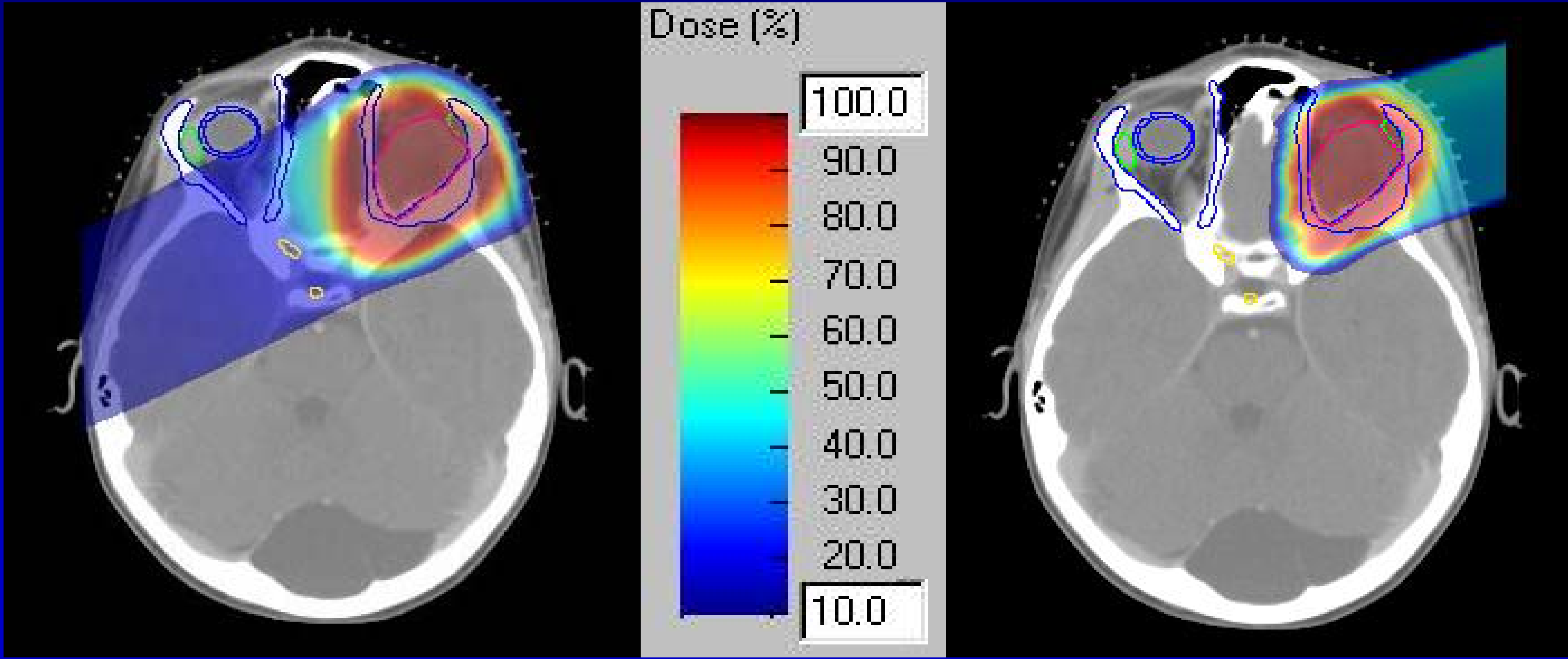
X-Rays

Protons



Cost of Proton Beam Radiotherapy

- Primary difference in cost is initial capital expenditure for cyclotron and gantries
  - ~$100 million for entire facility with 3 Rx rooms
    - Should run for ~40 years
- Goitein: Protons ~ 2.4 x cost of IMRT, but may come down to 1.7-2.1 in next 5 years
- Lundkvist: Protons cost 23,600 Euros less than photons for 5 year-old with medulloblastoma with an additional 0.68 QALY per patient.

Protons: Clinical Advantages

- Will need to be documented in a scientific fashion through carefully designed clinical trials
- Phase II studies may be the only ones that are clinically and ethically capable of being performed
  - Clinicians and patients aware of dose advantages for protons may refuse to participate in randomized phase III studies comparing photons versus protons
- Will likely require comparison with patients treated with photons: i.e. Children’s Oncology Group
  - Requires long and careful follow-up: $

Late Effects Scoring

- Documentation of late effects requires the use of late effects scoring systems
  - NCI Common Toxicity Criteria (CTC v.3)
  - RTOG/EORTC Late Effects Scoring Scale
  - Musculoskeletal Tumor Society Functional Rating Scale
- Increasingly studies are incorporating formal Quality of Life assessments
  - Quality of Life instruments

Pediatric Quality of Life

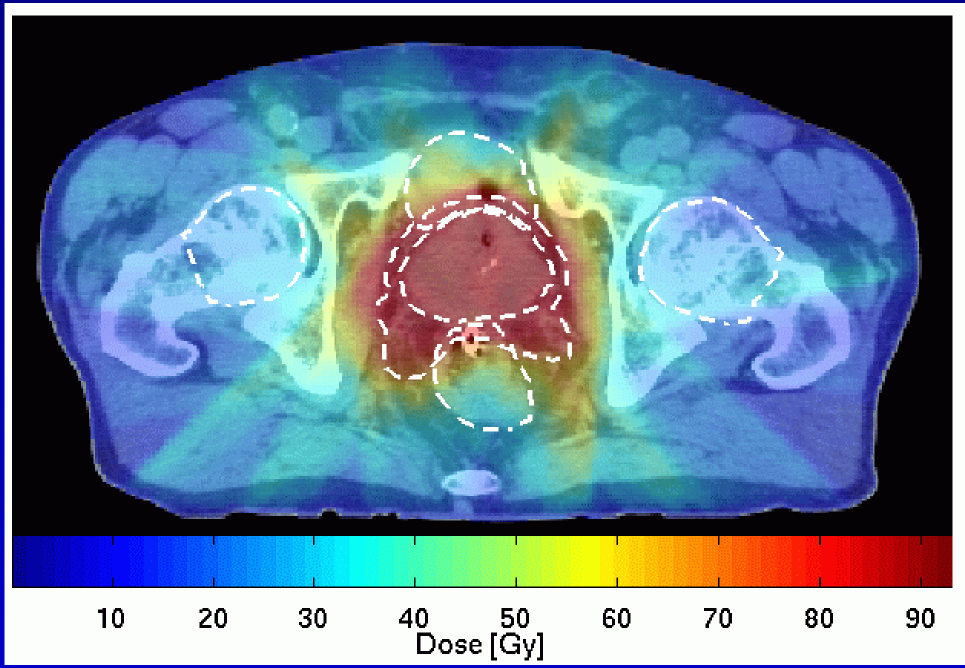
- PedsQL Generic Core
  - 23 item measure that examines a child's physical, emotional, social and school functioning.
    - (Varni, Seid, and Rode 1999)
- PedsQL Cancer Module (Varni 2002)
  - Cancer related HRQOL issues such as pain and procedural anxiety
- Good psychometric properties
  - Offered for a wide range of ages
  - Child self report
  - Parent proxy reporting function
  - Take approximately 10 minutes to complete.

Quality of Life

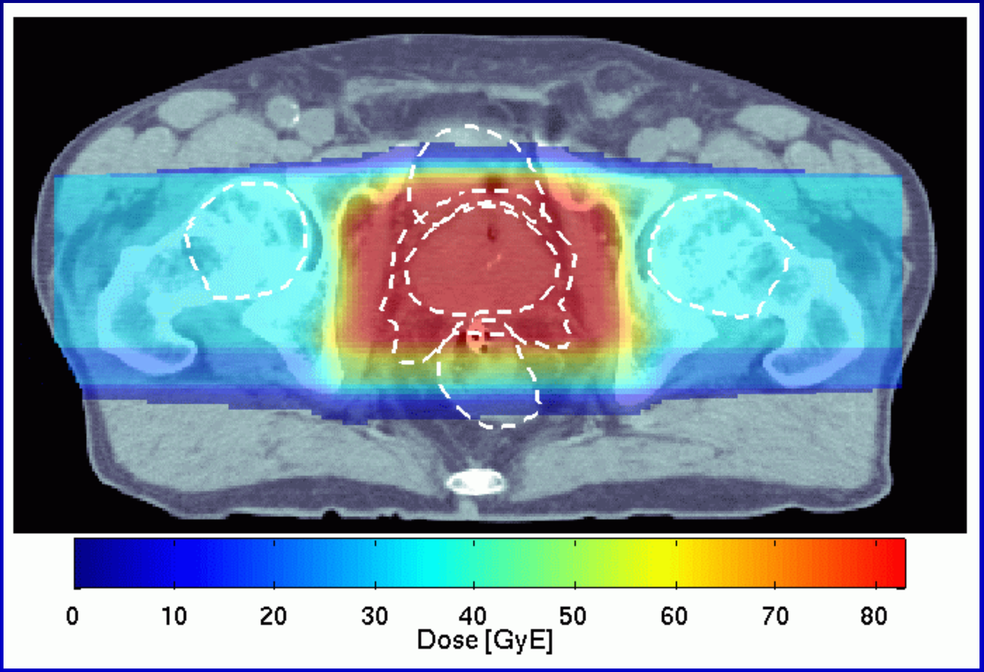
- Prostate and Rectal Cancer
  - Validated indexes measuring urinary, bowel and sexual function
  - Defined 3 levels of function
    - Normal- no abnormal symptom,
    - Intermediate—any abnormal symptom but none severely abnormal and
    - Poor—any severely abnormal symptom
      - Talcott et al, J Urol 2006; 176: 1558.

Quality of Life

- Prostate Cancer



IMRT

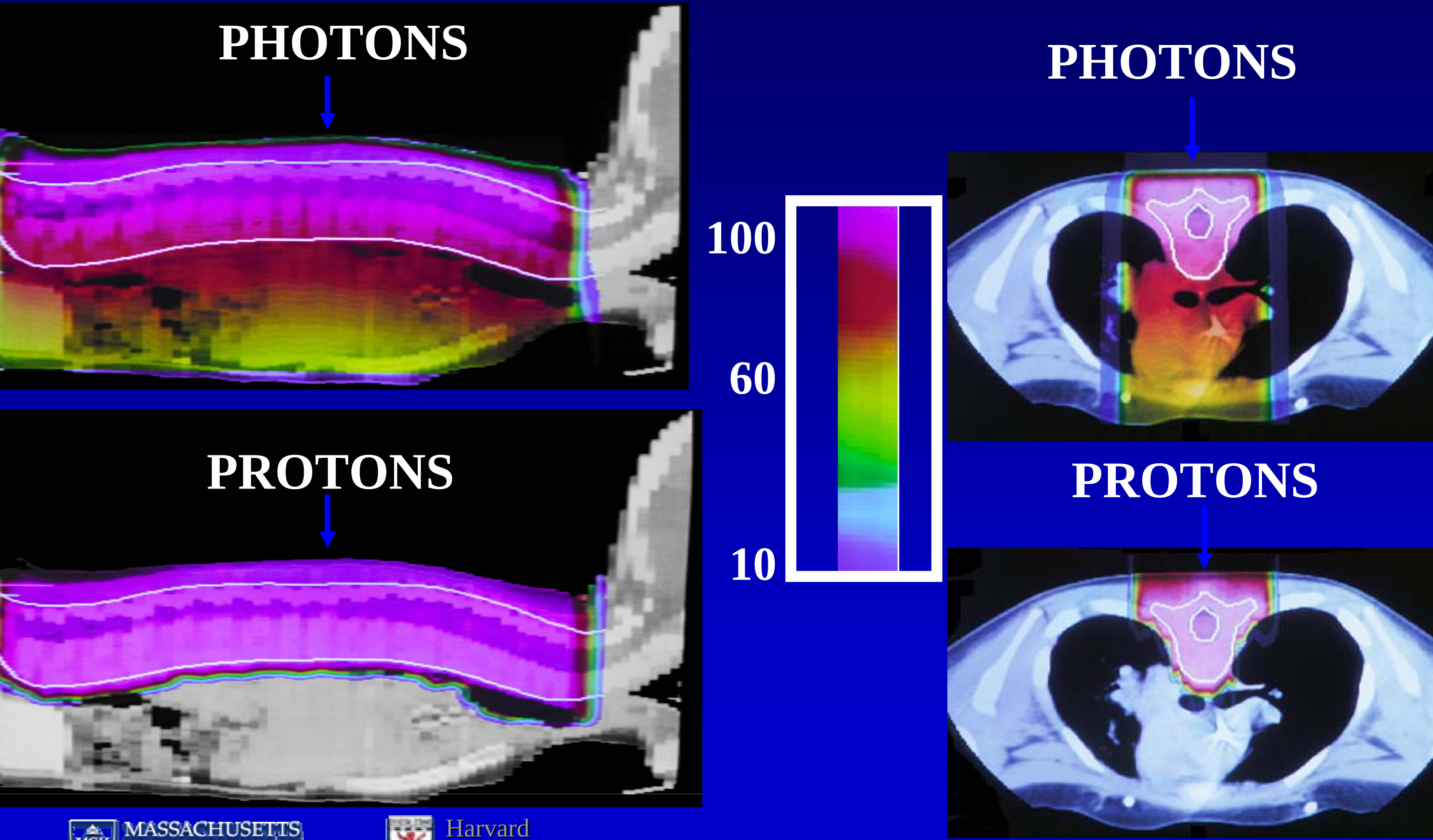


3D Protons

Proton Clinical Research

- **Morbidity Reduction Project**
  - Medulloblastoma – Phase II
  - Retinoblastoma – Phase II
  - Rhabdomyosarcoma – Phase II
  - Partial Breast Irradiation-Phase I
  - Prostate IMRT vs Protons-Phase III (proposed)
  - Low Grade Gliomas : IMRT vs. Protons (proposed)
  - Pelvic Sarcomas- Phase II (proposed)
  - Left Chest Wall Irradiation- Phase II (proposed)

MEDULLOBLASTOMA



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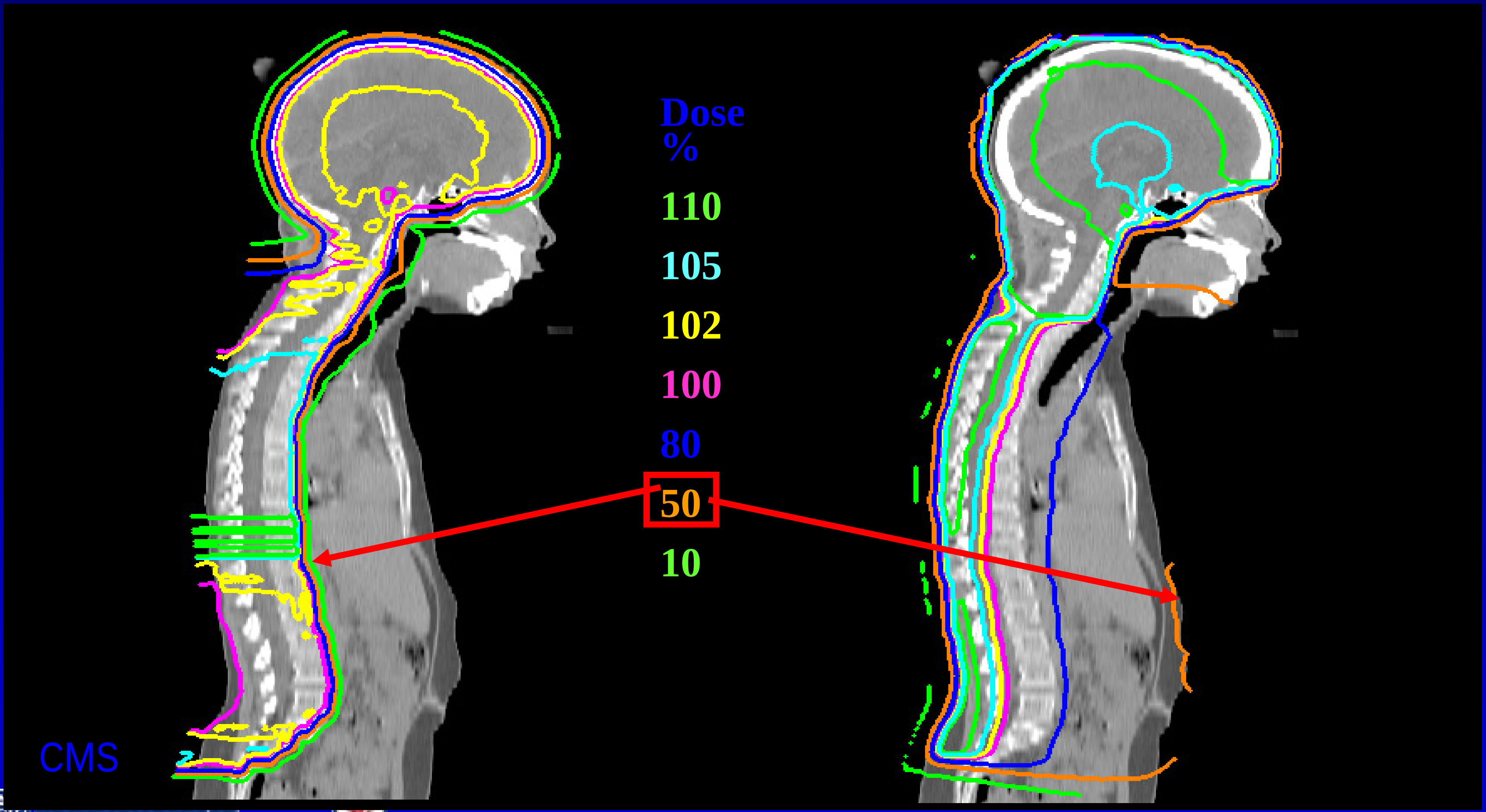
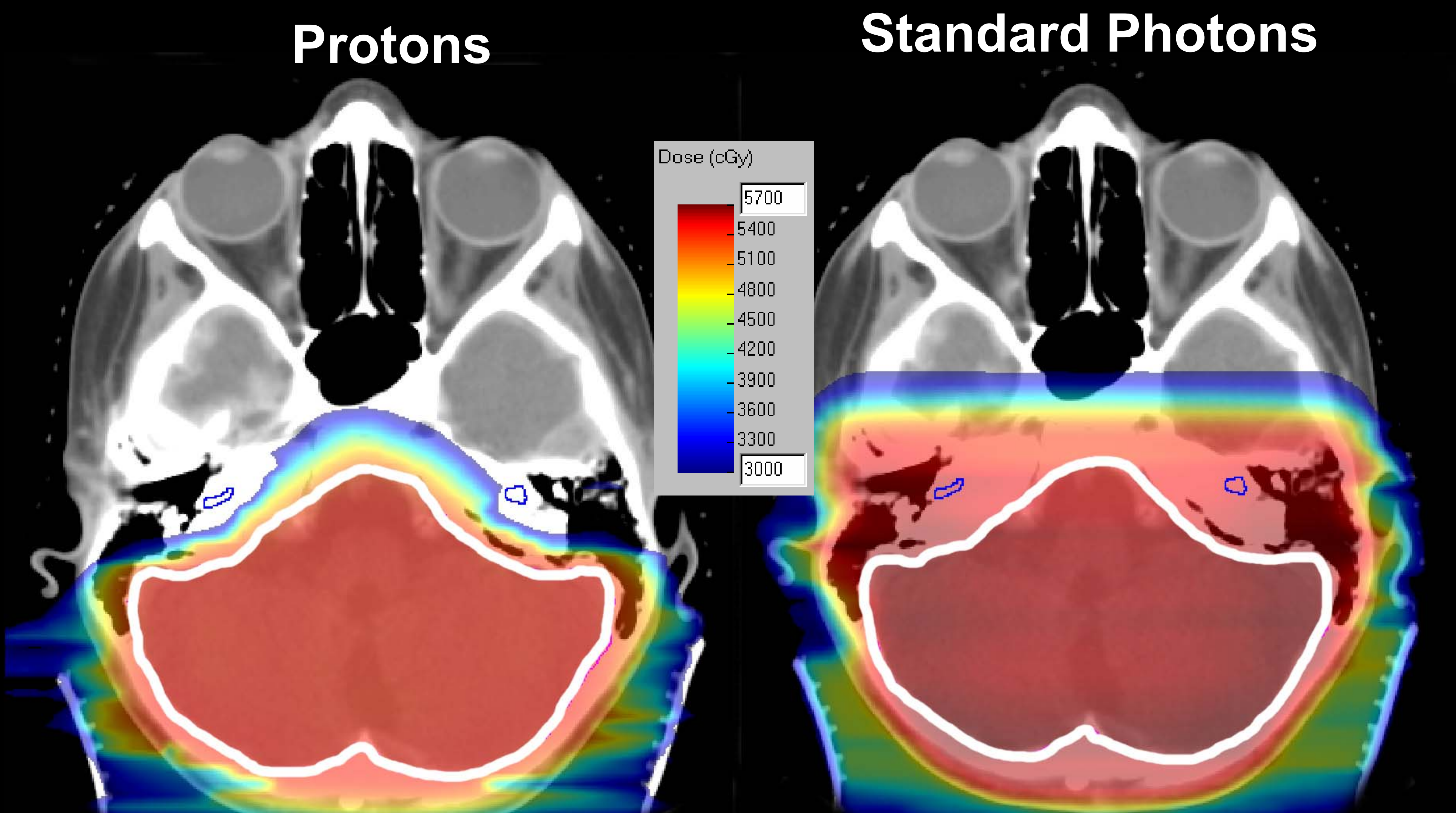
Proton vs. X-Ray Craniospinal Dose Distribution



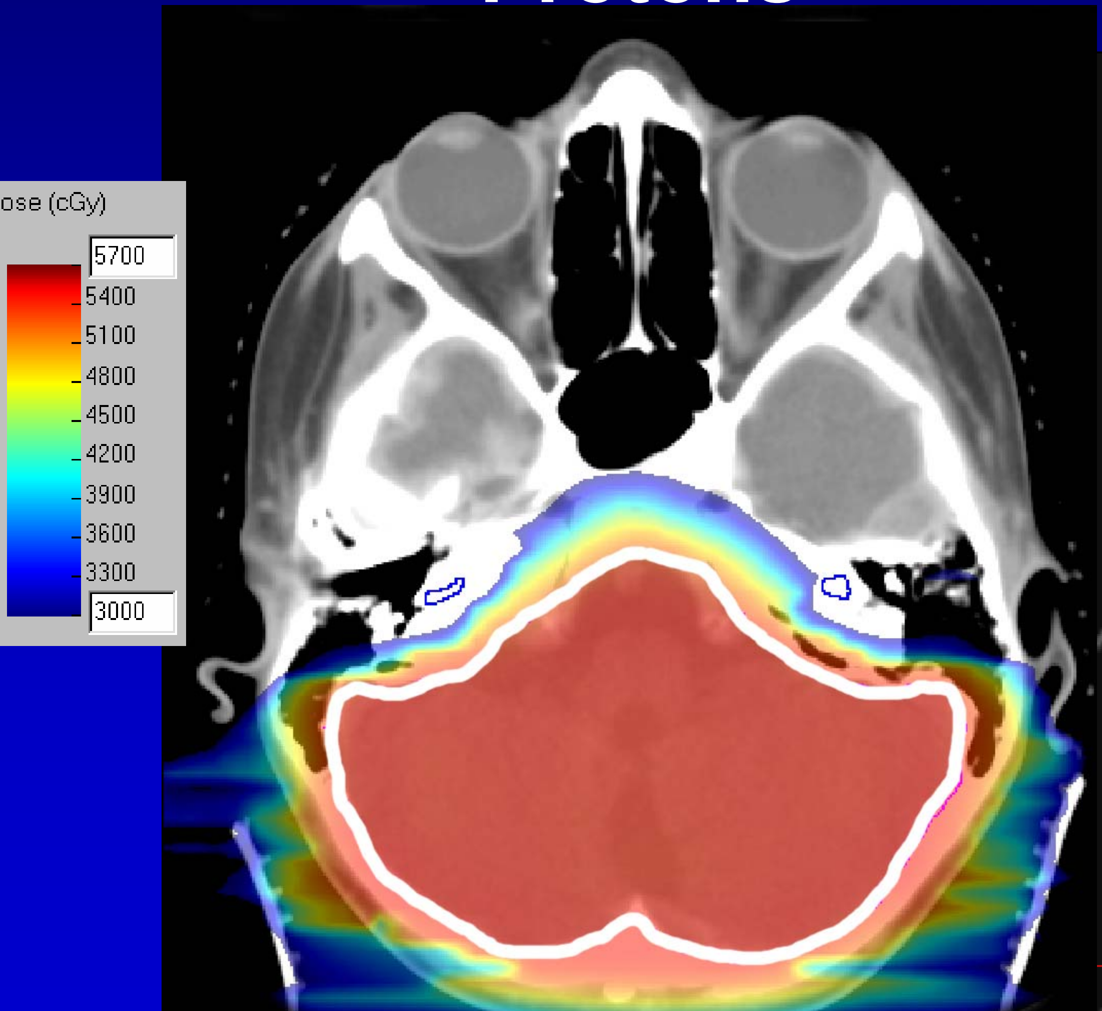
Medulloblastoma

Whole Brain + Posterior Fossa Boost

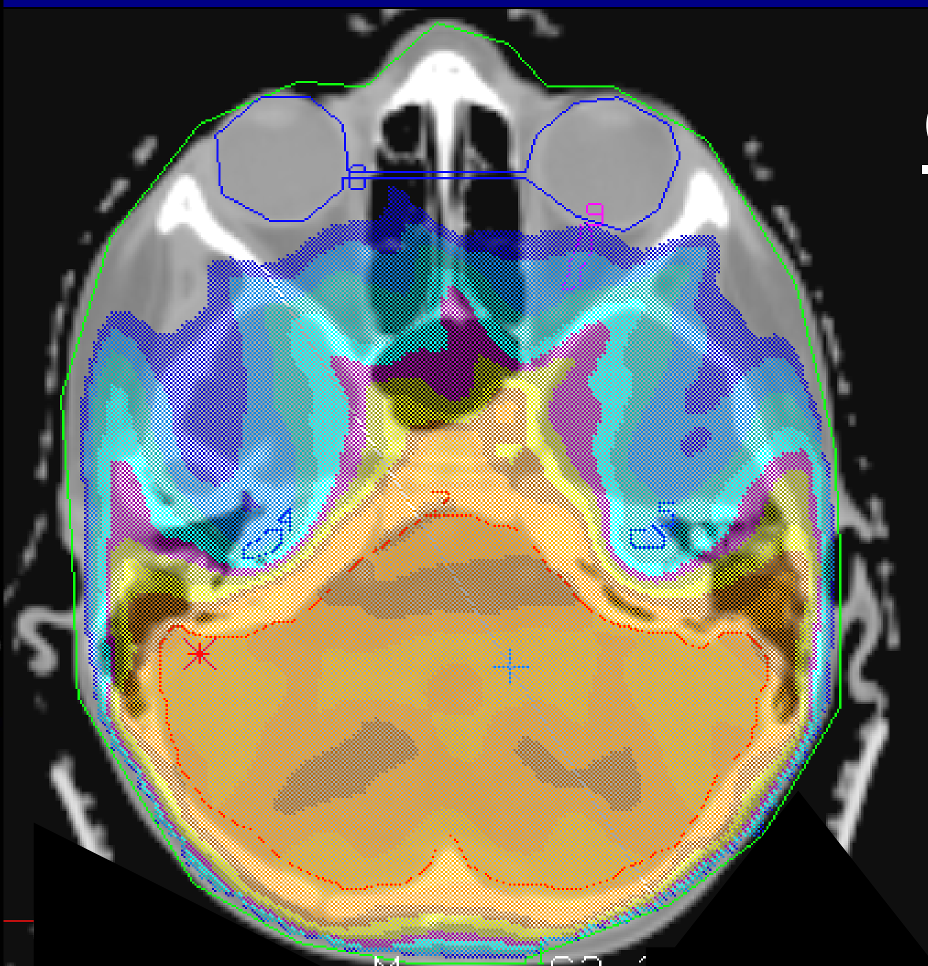


Medulloblastoma
Posterior Fossa Boost

Protons



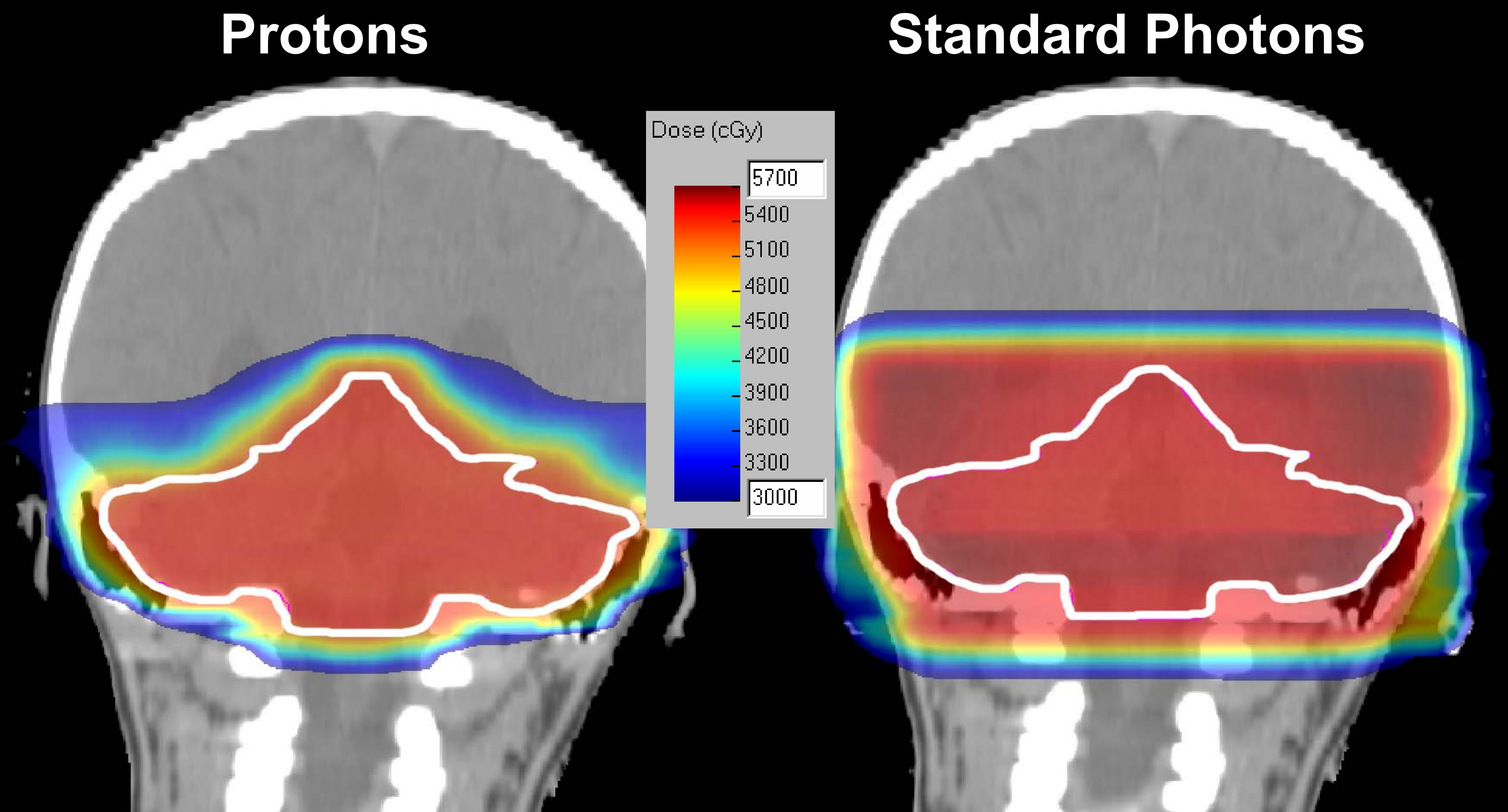
IMRT



Gy

57
54
45
42
39
36
30

Medulloblastoma
Whole Brain + Posterior Fossa Boost



Research Report: Proton Radiotherapy for Parameningeal Rhabdomyosarcoma

Stephanie Krejcarek, B.Sc.

Nancy J. Tarbell, M.D.

Alison Friedmann, M.D.

Beow Yeap, Sc.D.

Torunn I. Yock, M.D.

Francis H. Burr Proton Therapy Center

Massachusetts General Hospital

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Boston, MA

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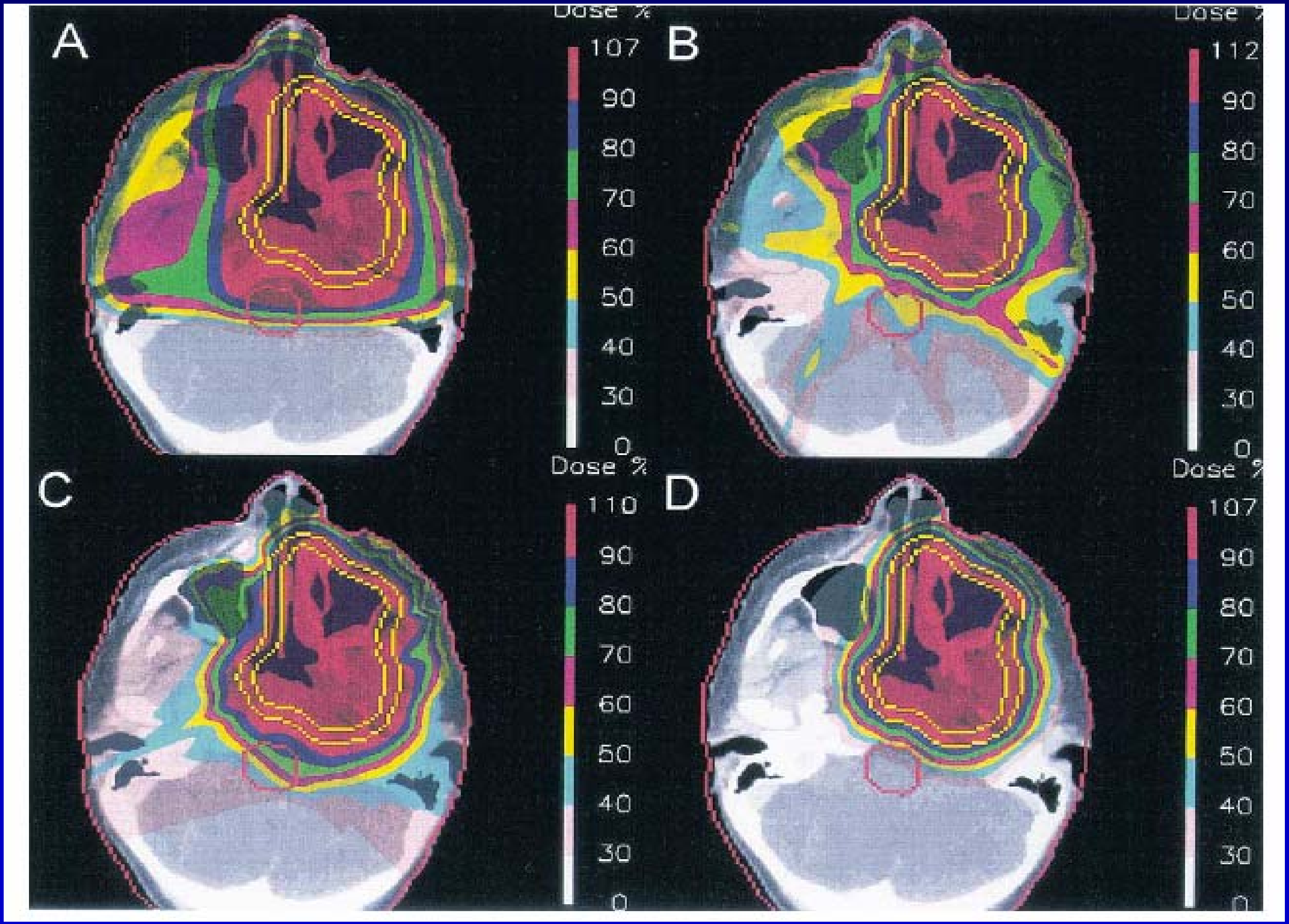
MassGeneral Hospital for Children

Dose Comparisons

Miralbell et al. (2002)
IJROBP 54(3): 824–829



A) Conventional X-rays B) IMRT

C) Spot-scanned Protons D) IMPT

Protons: Late Effects

- 10 patients in original cohort without recurrence
- Median follow-up: 40 months (range 12-112)
- Chart Review
  - Clinic Visits: 6 weeks after RT, every 6 months for first two years, yearly thereafter
  - Referring Physician Form—specifically asked about the late toxicities of interest

- Compare to 213 pts. in IRS II-III

Raney et al. Med Pediatr Oncol 33:362-371 (1999)

IRS Late Effects

- 213 pts. in IRS II & III (1978-1991) with localized, nonorbital H&N RMS
  - 68% parameningeal sites (148 pts.)
    22% nonparameningeal, 10% neck
- Median age at Dx: 5 yrs.
- Median length of follow-up: 7 yrs.
- Late effects data collected from flow-sheets at chemo visits & follow-up visits
  - Submitted from over 100 institutions
  - No formal system for capturing late effects!
  - Tx differences to our cohort: WBRT & IT methotrexate

Statural Growth

- Age < 15, capable of further growth
- Heights plotted on National Center for Health Statistics Growth Curves & ranked into height categories
  - **(>95th percentile, 75-95th, 50-74th, 25-49th, 5-24th, <5th)**
- Decreases in 2 or more height categories considered decreased growth velocity
  - Protons: 2/10 (20%)
  - IRS: 92/190 (48%)

Growth Hormone Replacement

- Protons: 2/10 (20%)
  - 1 pt. only had decrease in 1 height category, who also required cortisol and T4 replacement
- IRS: 36/190 (19%)
  - 35/36 parameningeal sites
  - Median dose to pituitary: 45 Gy (30-57.6)
    - No dose-response relationship
  - 1 pt. also required cortisol for partial ACTH deficiency

Other Endocrinopathies

- Thyroid Hormone
  - – Protons: 1 pt. (10%) required T4 in addition to cortisol & GH replacement
  - – IRS: 17/213 (3%) pts. required T4
    - 4 pts. required GH in addition to T4
    - 13/17 (76%) received direct irradiation to thyroid (45Gy)

Facial Hypoplasia

- Protons: 6/10 (60%) noted to have “mild/minimal” asymmetry when specifically asked
- IRS: Flow-sheets from 76/213 (36%) commented on facial symmetry → 74/76 (97%) noted hypoplasia
  - 13/213 (6%) underwent one or more surgical reconstructive procedures

Dentition

- Protons:
  - Multiple caries – 3/10
  - Missing molars – 2/10

- IRS: 61 reported (% of reported)
  - Multiple caries – 27 (44%)
  - Malformed teeth – 20 (32%)
  - “Poor dentition” – 11 (18%)
  - Missing teeth – 3 (5%)
  - Surgical procedure – 11 (18%)

Visual Deficits

- Protons: 0
  - All visual deficits occurred *prior to RT*
    - Ipsilateral blindness from tumor (1)
    - Recurrent corneal erosion (2) (facial paralysis, enopthalmus)
- IRS:
  - 32 pts. (15%) developed visual deficits
    - Bilateral optic atrophy leading to blindness (1)
    - Unilateral (19) & bilateral (2) cataracts
    - Chronic Conjunctivitis (7)
    - Enucleation due to perforated cornea (2) or keratitis (1)
    - Retinopathy (1), retinal hemorrhage (1)
  - Only 4 pts. had optic atrophy attributed to the tumor

Auditory Complications

- Protons: 0
  - Ipsilateral hearing loss *prior* to RT (4 pts.)
    - 2 pts. had *improved* audition after RT
    - 2 pts. require ipsilateral hearing aids
- IRS:
  - 36/213 (17%) impaired hearing
    - 17 pts. received cisplatin
    - 9 required hearing aids, 5 bilaterally

Cognitive/CNS

- Protons:
  - Reading difficulties (1), unclear association w/ tx as pt. was not reading prior to RT
  - Speech delay *prior* to RT related to hearing loss (1)
- IRS:
  - 35/213 (16%) w/ learning disabilities—reading, math, speech, memory
  - 8/213 (4%) w/ CNS dysfunction
    - Mental retardation/borderline intelligence (2)
    - Seizures (3)
    - Poor coordination (2)
  - *Note: 22 of these pts. received WBRT (median dose 30 Gy, range 6-33), 16 received triple IT medications*

Secondary Malignancies

- Protons: none
  - median f/u only 40 mo. and only 10 pts.
- IRS II-III: 4/213 (1.9%)
  - 9 mo. - 7 years after therapy
  - 1 AML, 3 solid tumors
- IMRT: Wolden et al. (2005) IJROBP 61(5):1432-1438
  - 2/28 developed AML (median f/u: 2 yrs)
- Protons reduce risk of secondary malignancy: by a factor of >2
  - **Model based on Publication No. 60 of the International Commission on Radiologic Protection**
    - **Miralbell et al. (2002) IJROBP 54(3): 824-829**

Comparison of Late Effects

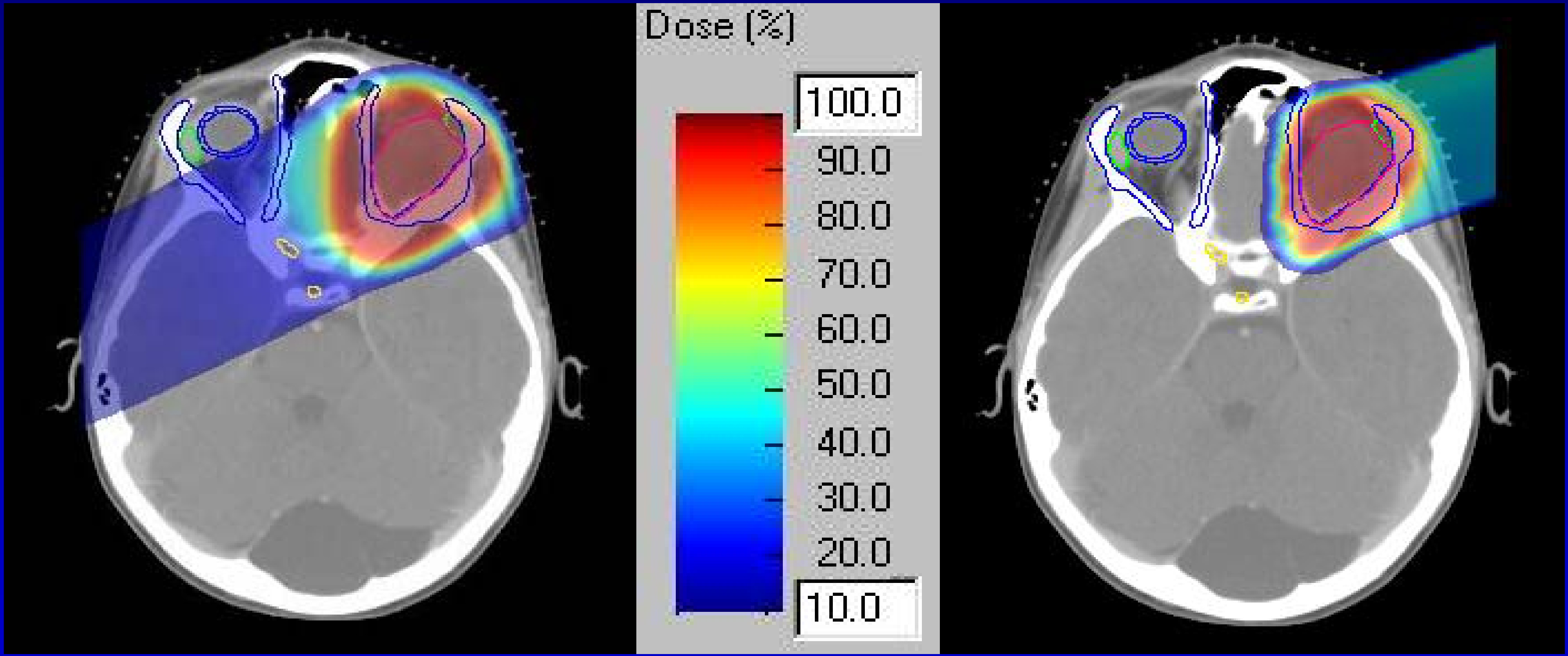
Toxicity	Protons	IRS	IMRT	U. Iowa
Decreased growth velocity	2/10 (20%)	92/190 (48%)	NR	9/15 (60%)
Growth hormone replacement	2/10 (20%)	36/190 (19%)	1/22 (5%)	6/15(40%)
Other Endocrinopathies	1/10 (10%)	17/213 (8%)	NR	1/15 (7%)
Facial hypoplasia	6/10 (60%)	74/76 (97%)	1/22 (5%)	11/15 (73%)
Visual complications	0	45/213 (21%)	2/22 (9%)	9/11 (82%)
Auditory complications	0	36/213 (17%)	NR	6/8 (75%)
Dentition	3/10 (30%)	61/213 (29%)	NR	7/7 (100%
Chronic nasal and sinus congestion	0	NR	4/22 (18%)	NR
Cognitive deficits	1/10 (10%)	35/71 (49%)	1/22 (5%)	3/15 (20%)
Secondary malignancies	0	4/213 (2%)	2/22 (9%)	1/17 (6%)

Summary

- Proton radiotherapy appears to reduce late toxicity due to the decreased dose to normal structures
  - Growth velocity
  - Visual Complications
  - Auditory Complications

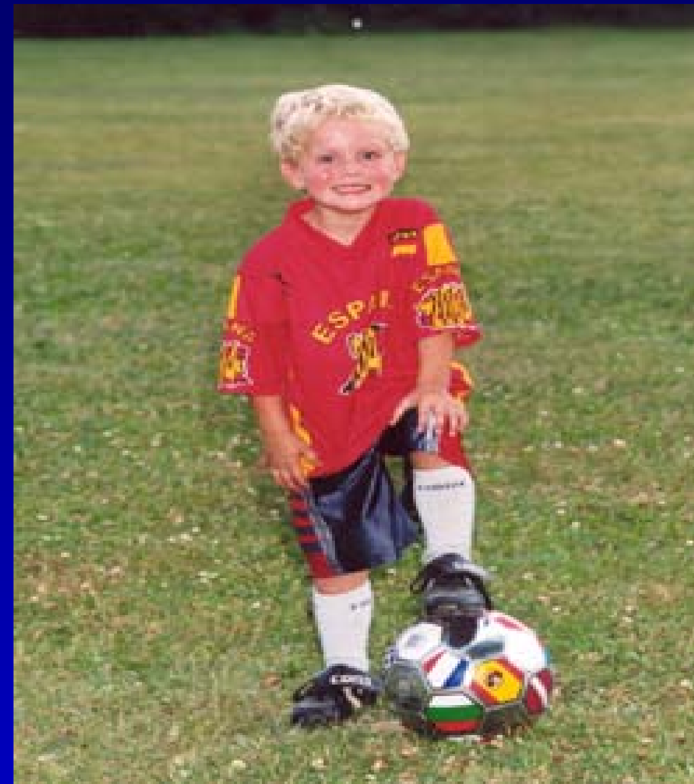
- Caveats:
  - More patients will be more informative
  - More years of follow-up may reveal more or other late sequelae

X-Rays   Protons



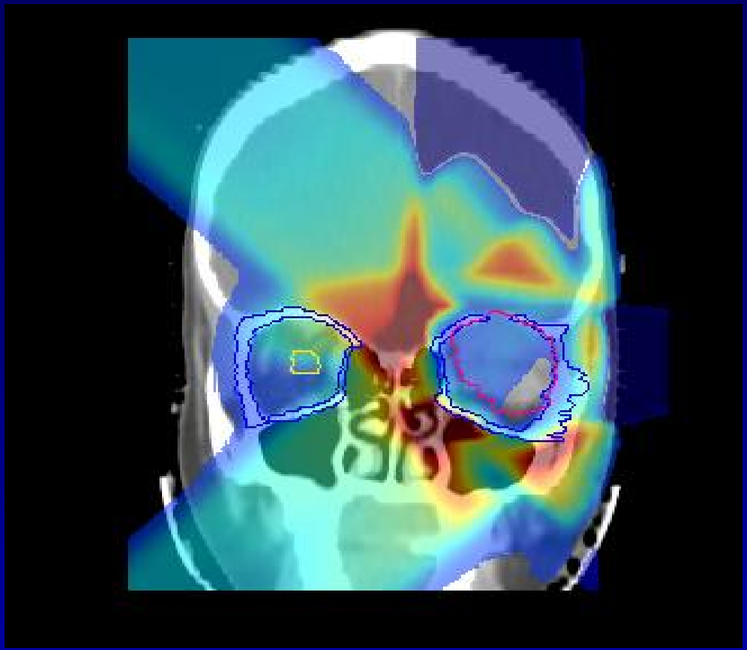
Prior to Proton RT

Last day of
Proton RT



3 years later

Results: Photon - Proton Plans, Dose Difference in 3 views



Note: Areas in red denote at least a 35% dose savings by using protons over 3-D conformal conventional radiation.