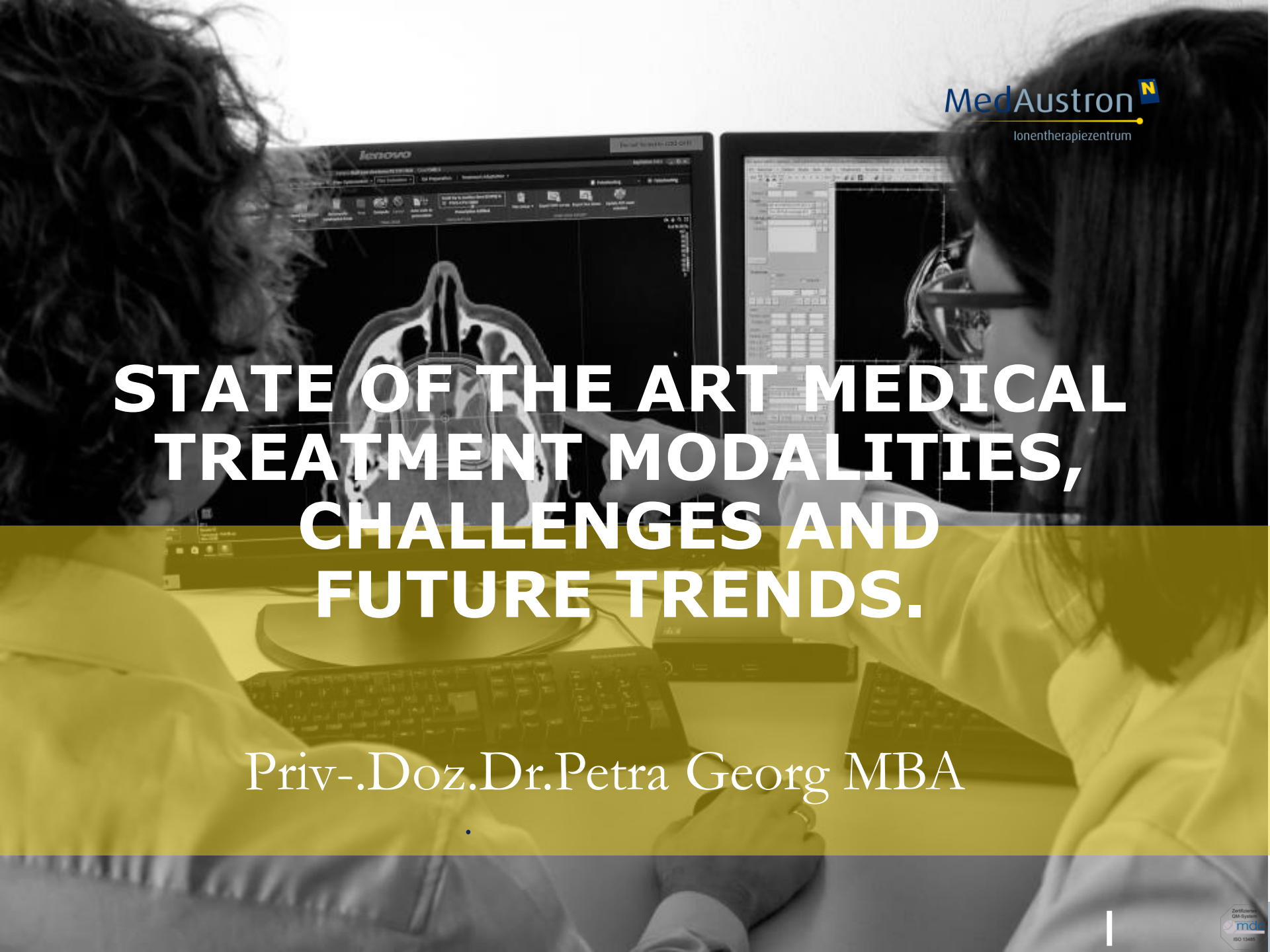


MedAustron
Ionentherapiezentrum

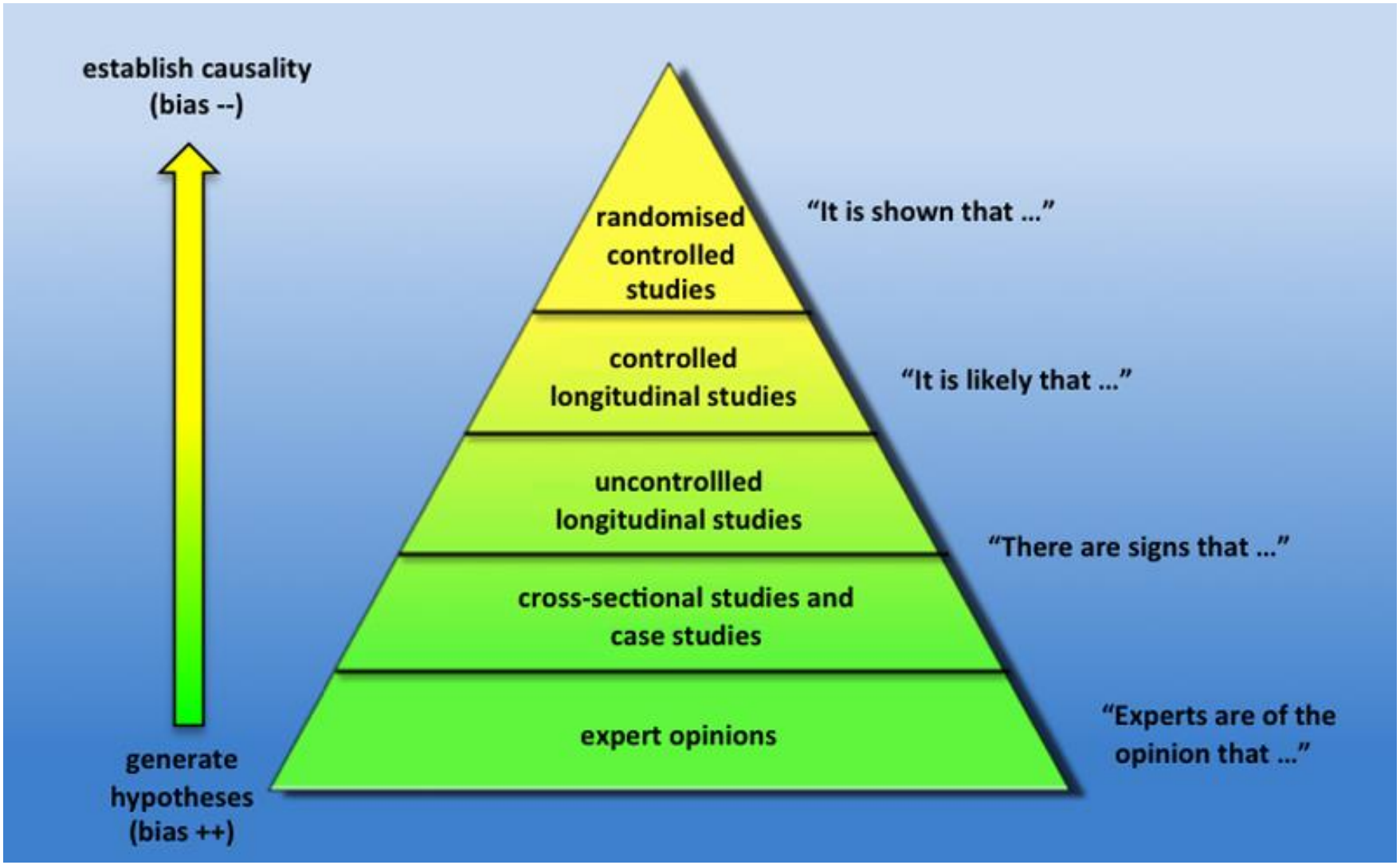
STATE OF THE ART MEDICAL TREATMENT MODALITIES, CHALLENGES AND FUTURE TRENDS.

Priv-.Doz.Dr.Petra Georg MBA

WHAT IS „STATE OF THE ART“

Refers to the **highest level**
of general development,
as of device, technique, or **scientific field**

HIGHEST LEVEL OF EVIDENCE



STATE OF THE ART

Radiation Oncology

SERVICES

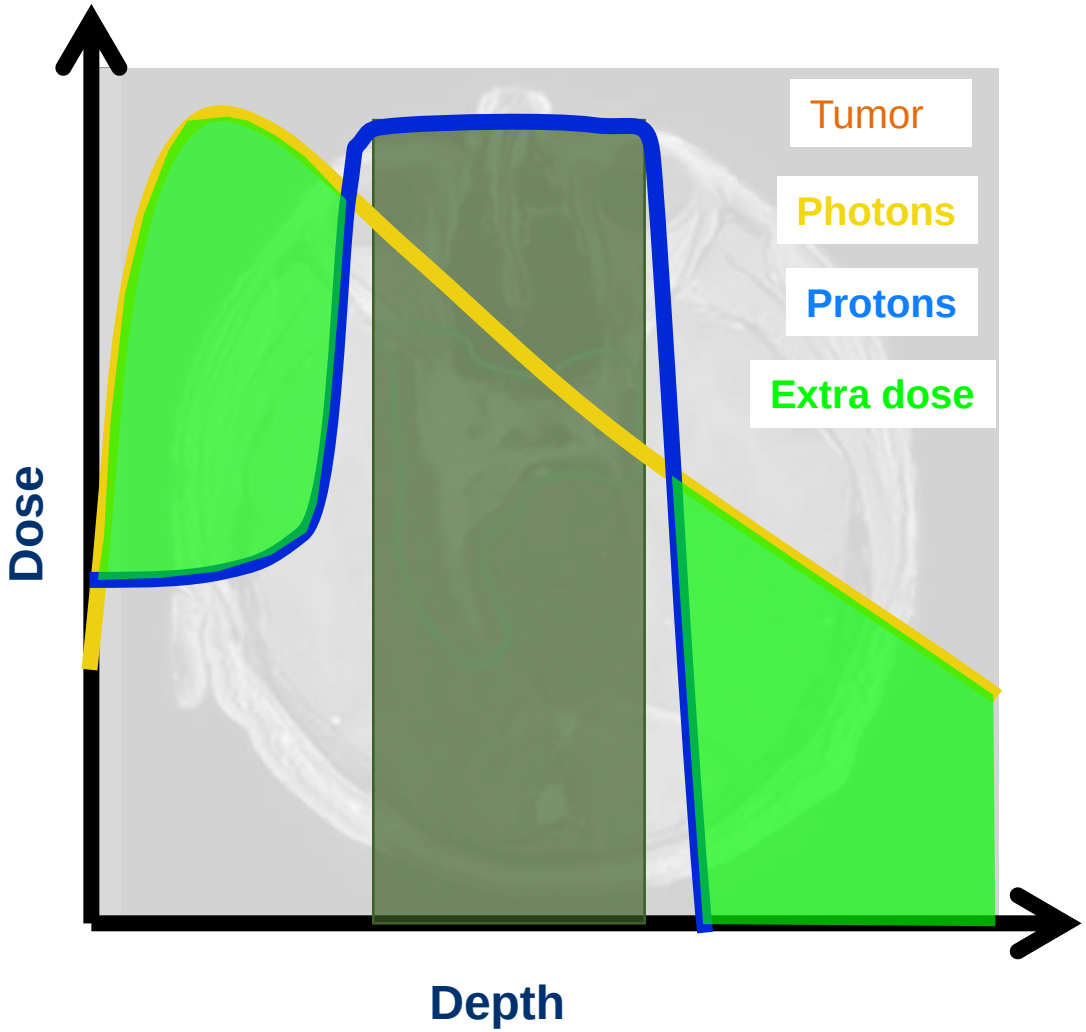
Genetic Counseling
Imaging
Instructions for your PET Scan
Medical Oncology
Radiation Oncology
Chemotherapy
Radiation Oncology
Surgical Oncology
Interventional Radiology

PATIENT PORTAL

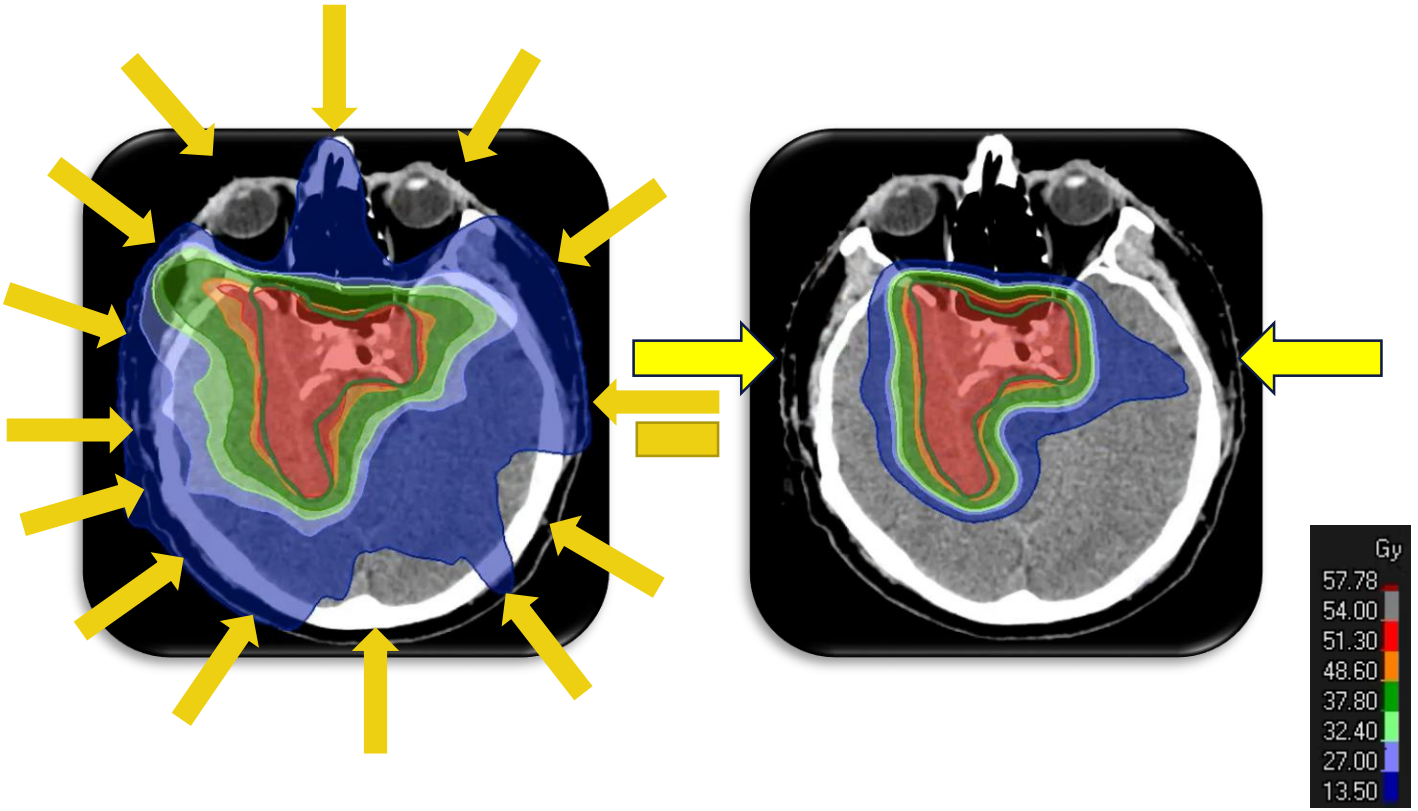
Our Radiation Oncologists treat all types of cancers, offering state-of-the-art treatment modalities, as listed below.

- Intensity Modulated Radiation Therapy (IMRT)
- Image Guided Radiation Therapy (IGRT)
- Short Course Stereotactic Radiation Therapy (SBRT)
- Single Session Stereotactic Radiosurgery (SRS)
- Brachytherapy, Low Dose Rate (LDR) and High Dose Rate (HDR)
- Prostate Seed implants
- Hypofractionated (short course) Treatment Options for Breast, Lung, Palliative Bone Metastasis, Heterotopic, and Keloid Patients

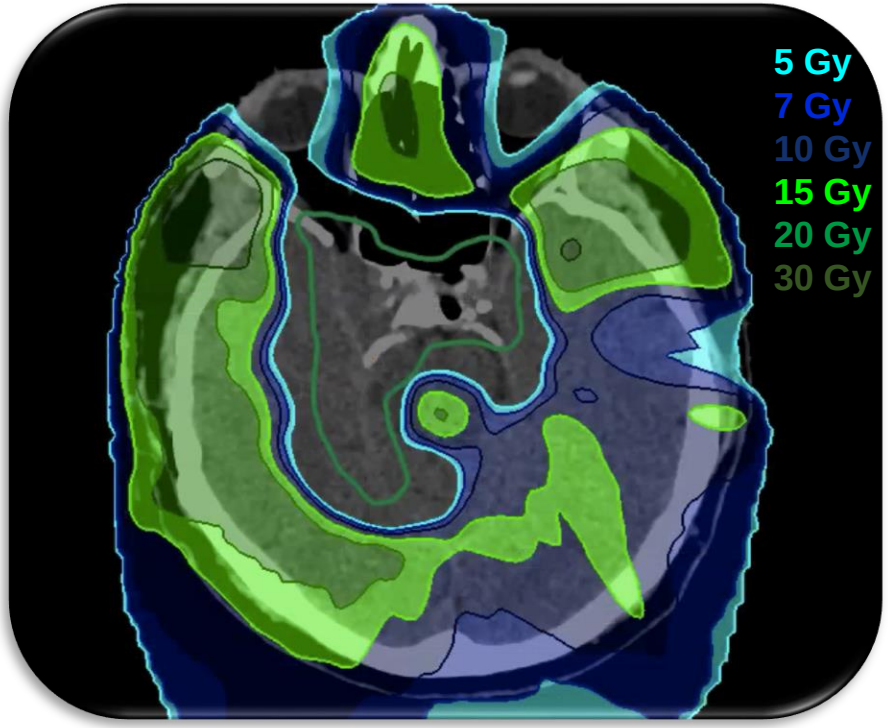
WHAT DO WE EXPECT FROM PARTICLE TREATMENT?


Tumor
Photons
Protons
Extra dose
Dose
Depth

PHOTONS VS PROTONS



DOSE DIFFERENCE = UNNECESSARY DOSE DEPOSITION



Photons minus Protons

CONSEQENCES OF BRAIN TISSUE SPARING

- Dosimetric difference suggests better clinical outcome

BUT

- How to messure the clinical outcome?
- How to messure brain function?

- Example: neurocognitive testing
  - Memory
  - Executive functions
  - Processing speed
  - Attention
  - …..

NEUROPROTECTIVE POTENTIAL OF PROTON

- Many papers describe the ***potential*** neuroprotective benefits of proton beam RT
  - Based on the physics of protons
  - Models with hypothetical data suggest benefit for medulloblastoma and craniopharyngioma
- Few studies with ***actual*** neurocognitive outcomes for patients treated with PRT vs. other published so far

Merchant et al. PBC, 2008
Miralbell et al. IJROBP, 1997

NEUROCOGNITIVE EFFECTS

- **Cognition**
  - 20 long term survivor treated <3 y.o. with RT
    - 85% impaired cognition
    - 55% special education
    - Worse with cranial dose 30-35 Gy

- **Must obtain baseline function**
  - POG I Baseline testing
    - 45% 15 pt lower than norm
    - 29% 30 pt lower than norm

Duffner et al Pediatr Neurol, 7 237-242

CRANIAL RADIATION THERAPY (RT)- SUMMARY

- **Risk of neurocognitive late effects**
  - Declines of 2-4 IQ points per year
  - Risks associated with:
    - Younger age
    - Higher RT doses
    - Larger irradiated brain volumes

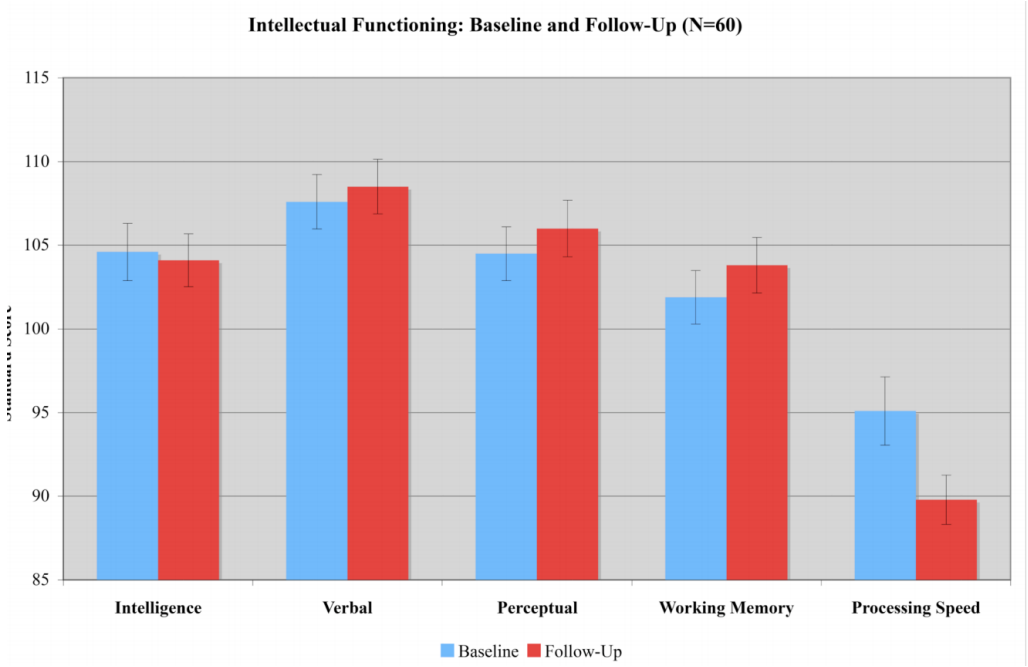
Ris et al. JCO 2001
Palmer et al. JCO 2001
Silber et al. JCO 1992
Roman et al. IJROBP1995
Merchant et al. JCO 2009
Mulhern et al. Lancet Onc 2004

WHAT MATTERS?

- **Dose relationship**
  - With increasing the dose the cognitive function ist worsening
- **Volume relationship**
  - With increasing the volume of healthy brain tissue irradiated the cognitive function ist worsening

EARLY COGNITIVE OUTCOMES AFTER PROTON RT FOR CHILDREN WITH CNS TUMORS

- 60 pt ≥ 6y for MB, LGG, ependymoma, CP, other
  - Baseline FSIQ, verbal, perceptual and WMI compared to f/u testing
  - Mean f/u 2.5y
- Processing speed declined significantly (mean 5.2)
- FSIQ, verbal, perceptual, WMI all stable
- Cognitive outcomes not related to gender, RT vol, dose, tumor location, histology, SES, chemo or surgery



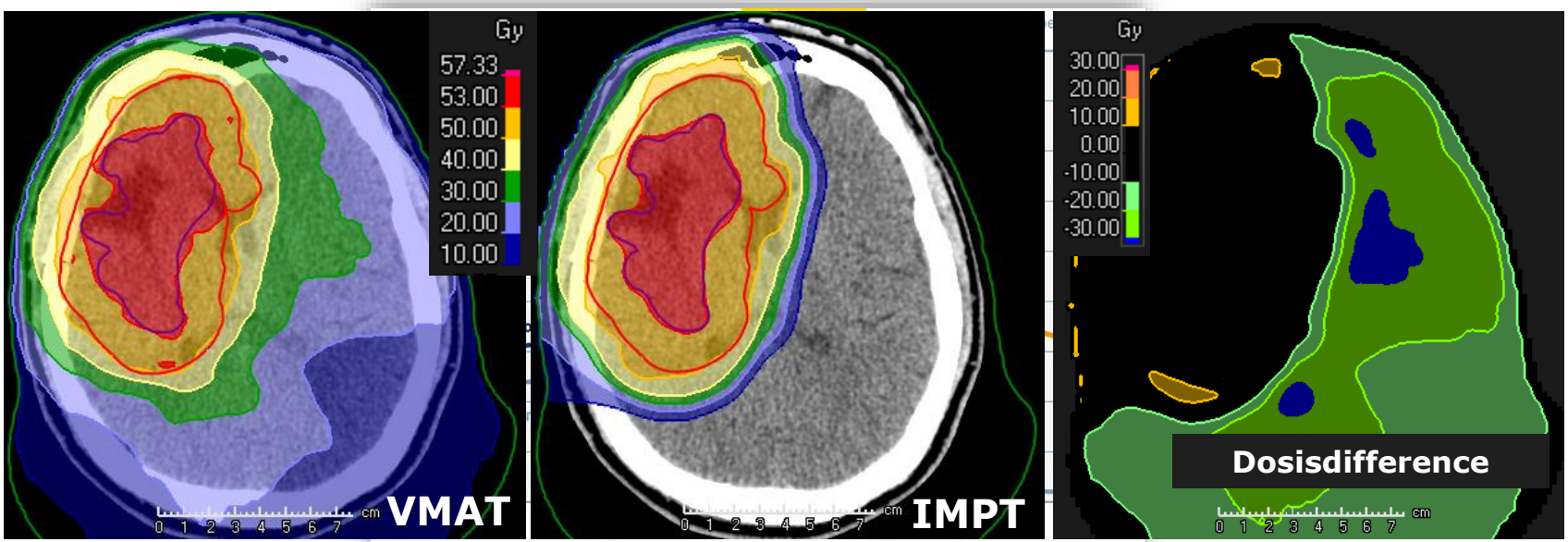
Pulsifer et al, IJROBP 93(2) 400-7, 2015

AIM

- **Brain tissue sparing**

- **Who does benefit?**
  - Children
  - Young adults
  - Long surviving patients

ADULT PATIENTS WITH LOW GRADE GLIOMAS



Planning comparison
Photons (VMAT) vs. Protons (IMPT)

MOTIVATION
BRAIN TISSUE SPARING

- **Neurocognition**
- **Secondary malignacies**
- **Anatomical Changes**
  - Cortical Thinning

Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2016 February 1; 94(2): 297–304. doi:10.1016/j.ijrobp.2015.10.026.

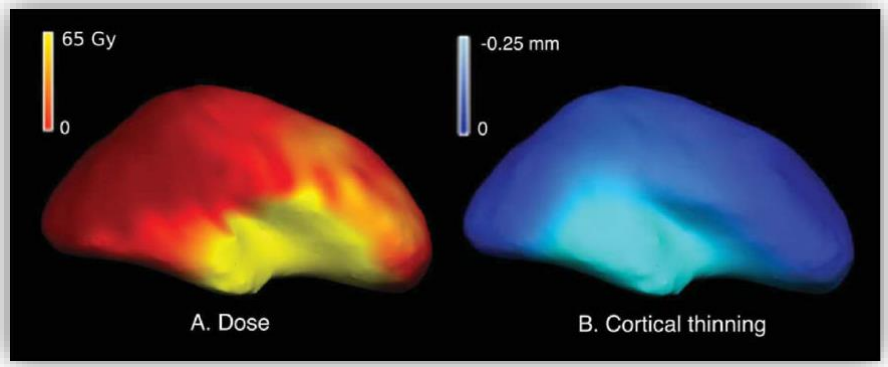
Dose-dependent Cortical Thinning After Partial Brain Radiation in High-grade Glioma

Roshan Karunamuni, PhD[1], Hauke Bartsch, PhD[2], Nate S. White, PhD[2], Vitali Moiseenko, PhD[1], Ruben Carmona, MD, MAS[1], Deborah Marshall, BA[1], Tyler M. Seibert, PhD, MD[1], Carrie R. McDonald, PhD[3], Nikdokht Farid, MD[2], Anithapriya Krishnan, PhD[2], Joshua Kuperman, PhD[2], Loren Mell, MD[1], James B. Brewer, PhD, MD[2], Anders M. Dale, PhD[2], and Jona A. Hattangadi-Gluth, MD[1]

[1]Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, California

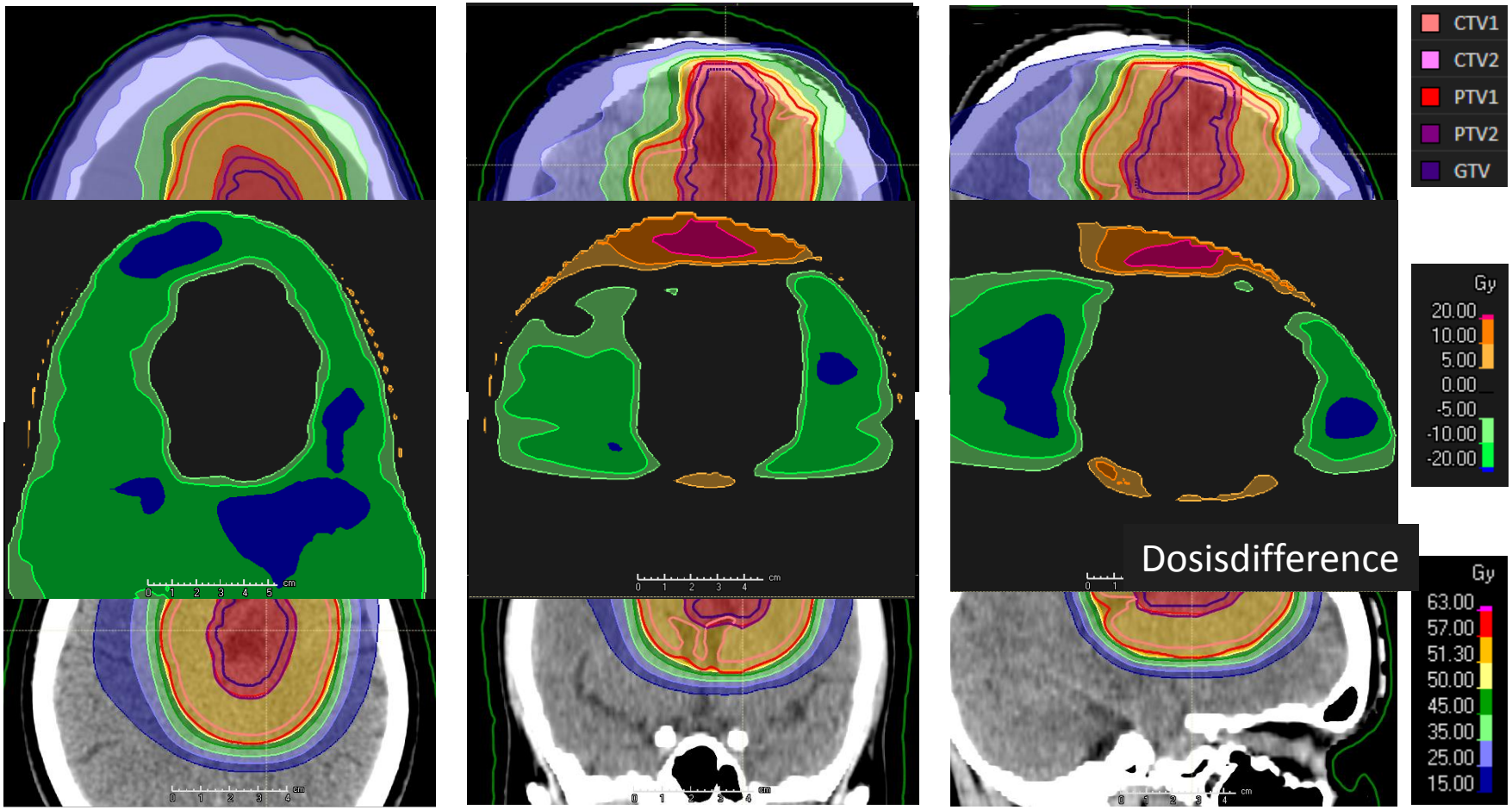
[2]Department of Radiology, University of California San Diego, La Jolla, California

[3]Department of Psychiatry, University of California San Diego, La Jolla, California



"Dose-dependent thinning of cerebral cortex was observed after fractionated partial brain radiotherapy in high-grade glioma patients. Magnitude of the thinning paralles one-year atrophy rates seen in neurodegenerative diseases like Alzheimer's, and may contribute in part to cognitive decline following brain RT."

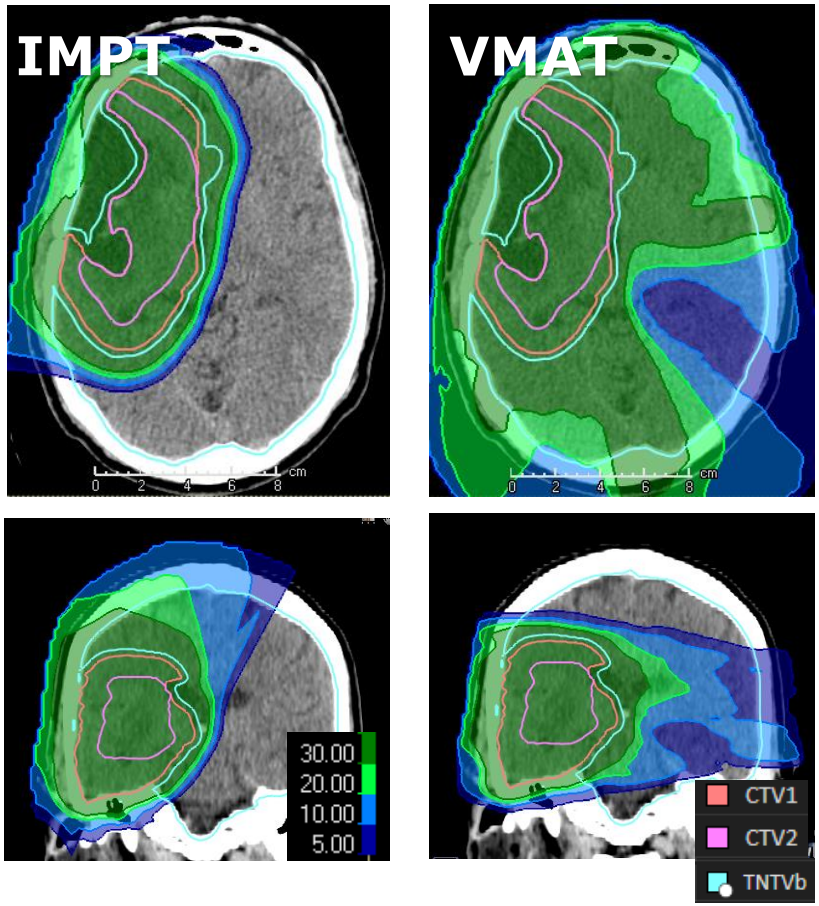
RESULTS


VMAT
IMPT
CTV1
CTV2
PTV1
PTV2
GTV
Gy
20.00
10.00
5.00
0.00
-5.00
-10.00
-20.00
Dosisdifference
Gy
63.00
57.00
51.30
50.00
45.00
35.00
25.00
15.00

RESULTS

TOTAL NORMAL TISSUE VOLUME BRAIN ($TNTV_B$)

N = 7 pts		VMAT	IMPT	Av. Diff%
$V_{TNTb,5Gy}$ [%]	Median (Range)	83% (62-94)	41% (27-57)	-43%
$V_{TNTb,10Gy}$ [%]	Median (Range)	76% (57-89)	33% (23-49)	-42%
$V_{TNTb,20Gy}$ [%]	Median (Range)	50% (42-65)	24% (17-34)	-25%
$V_{TNTb,30Gy}$ [%]	Median (Range)	27% (18-40)	17% (12-29)	-10%
		Median V_{TNTb} = 1126 ccm (887 - 1369 ccm)		
$D_{TNTb,50\%}$ [Gy]	Median (Range)	19,7 Gy (16,7-26,0)	1,5 Gy (0,1-9,5)	-18,2 Gy



EVIDENCE FOR ADULTS

N=20 pts

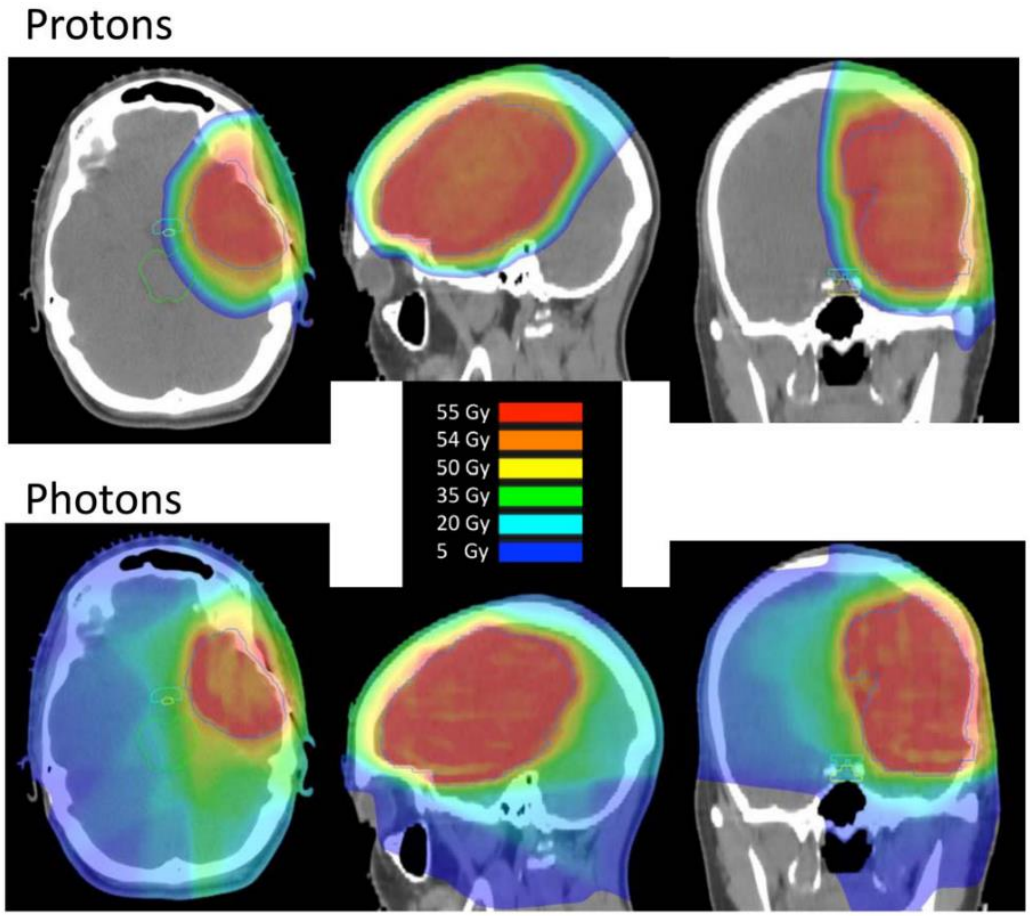


Figure 1. Dosimetric plans of proton therapy versus photon therapy for a low-grade glioma of the left temporal lobe are shown. Equivalent tumor target dose coverage is achieved but markedly less radiation is delivered to nontarget tissues with proton therapy.

Shih HA et al. Cancer 2015; 121:171-9

TABLE 2. Neurocognitive and Quality-of-Life Outcomes

Domain	Tests	Baseline Score: Mean ± SD (Range)	Average Score Change per Year: Average ± SE	*P*
Intellectual	WAIS-III Full Scale IQ	0.47 ± 0.56 (−0.47, −1.40)	0.07 ± 0.04	.1400
Visuospatial	WAIS-III Perceptual Organization Index	0.54 ± 0.69 (−0.60, −2.33)	0.13 ± 0.05	.0187
Language	WAIS-III Verbal Comprehension Index, Boston Naming Test, Auditory Naming Test	−0.50 ± 2.19 (−5.72, −1.00)	0.07 ± 0.09	.4462
Attention and working memory	WAIS-III Working Memory Index and Spatial Span; Continuous Performance Test: Inattention Score and Vigilance Score	0.24 ± 0.49 (−0.37, −1.58)	0.04 ± 0.04	.3292
Processing speed	WAIS-III Processing Speed Index; Trail Making Test A	0.06 ± 0.83 (−1.86, −1.33)	0.10 ± 0.07	.1679
Executive function	Trail Making Test B; Controlled Oral Word Association Test F-A-S; Wisconsin Card Sorting Test; Continuous Performance Test Impulsivity Score	−0.18 ± 0.62 (−1.18, −0.77)	0.12 ± 0.06	.0501
Verbal memory	HVLT-R: Total Recall, Delayed Recall, and Retention	−0.72 ± 1.19 (−2.67, −0.93)	0.04 ± 0.07	.5316
Visual memory	BVMT-R: Total Recall and Delayed Recall	−0.81 ± 1.41 (−3.00, −1.05)	−0.003 ± 0.06	.9644
Clinical trials battery	HVLT-R Total Recall; WMS-III Trails A and Trails B; Controlled Oral Word Association Test F-A-S	−0.35 ± 0.78 (−1.57, −1.13)	0.11 ± 0.06	.0742
Emotional[a]	Beck Anxiety Inventory	8.9 ± 8.0 (0–25)	−0.50 ± 0.36	.1870
	Beck Depression Inventory	12.71 ± 9.85 (0–31)	−0.05 ± 0.54	.9212
Quality of life	FACT-G Total Score	77.0 ± 18.4 (39–102)	0.41 ± 0.58	.4919
	FACT-Fatigue Score	32.7 ± 14.8 (8–52)	1.05 ± 0.44	.0265
	FACT-Br Total Score	131.0 ± 28.5 (84-174)	1.47 ± 0.89	.1154

Abbreviations: BVMT-R, Brief Visual Memory Test-R; FACT, Functional Assessment of Cancer Therapy; FACT-Br, Functional Assessment of Cancer Therapy-Brain; FACT-G, Functional Assessment of Cancer Therapy-General; HVLT-R, Hopkins Verbal Learning Test-R; SD, standard deviation; SE, standard error; WAIS-III, Weschler Adult Intelligence Scale, third edition; WMS, Weschler Memory Scale.

[a] Three patients were not assessed by Beck Inventories at baseline.

Shih HA et al. Cancer 2015; 121:171-9

CONCLUSION PART 1

- **Who does benefit from proton treatment?**
  - Children, young patients, adults, long survivors with brain tumors

- **Why?**
  - Because we are able to spare normal tissue

WHAT ELSE CAN WE REACH?

HEAD AND NECK

- Hoppe et al., IJROBP, 2008
  - Inoperable sinonasal cancers
  - 5-y local control 21%, overall survival 15%
  - The only factor improving survival was the dose ≥ 65 Gy.

METAANALYSIS

Patel et al., Lancet Oncol, 2014

- **Primary and recurrent sinonasal cancers**
- 43 cohorts and 41 non-comparing studies
- Median follow up
  - Photons 40 months
  - Particles 38 months

PROTONS VS IMRT(PHOTONS)

	Cohorts (n)	Patients (n)	Event rate (95% CI)	I^2	Relative risk (95% CI)	p
Overall survival*						
PBT	8	191	0·63 (0·53–0·76)	59·3%	1·02 (0·77–1·35)	0·89
IMRT	8	348	0·62 (0·50–0·77)	86·9%	..	..
5-year overall survival						
PBT	5	124	0·66 (0·52–0·85)	69·7%	1·39 (0·99–1·94)	0·057
IMRT	4	212	0·48 (0·38–0·60)	45·1%	..	..
Disease-free survival*						
PBT	2	56	0·49 (0·21–1·16)	83·6%	0·98 (0·40–2·42)	0·97
IMRT	3	187	0·50 (0·38–0·67)	69·3%	..	..
5-year disease-free survival						
PBT	1	36	0·72 (0·59–0·89)	..	1·44 (1·01–2·05)	0·045
IMRT	3	187	0·50 (0·38–0·67)	69·3%	..	..
Locoregional control*						
PBT	7	147	0·81 (0·71–0·92)	55·2%	1·26 (1·05–1·51)	0·011
IMRT	4	258	0·64 (0·57–0·72)	33·7%	..	..
5-year locoregional control						
PBT	2	36	0·43 (0·09–2·10)	89·5%	0·73 (0·15–3·58)	0·70
IMRT	2	166	0·59 (0·52–0·67)	0·0%	..	..

I^2 ≥50% suggests high heterogeneity across studies. IMRT=intensity-modulated radiation therapy. PBT=proton beam therapy. *At longest duration of complete follow-up.

Table 4: Comparison of primary outcomes for proton beam therapy cohorts and intensity-modulated radiation therapy cohorts

PARTICLE VS PHOTONS

	Cohorts (n)	Patients (n)	Event rate (95% CI)	I^2	Relative risk (95% CI)	p	NNT* (95% CI)
Overall survival†							
CPT	10	242	0·66 (0·56–0·79)	77·5%	1·27 (1·01–1·59)	0·037	7·09 (3·57–480·55)
Photon therapy	26	1120	0·52 (0·46–0·60)	86·0%	..	..	..
5-year overall survival							
CPT	6	146	0·72 (0·58–0·90)	80·1%	1·51 (1·14–1·99)	0·0038	4·12 (2·37–15·60)
Photon therapy	15	779	0·48 (0·40–0·57)	84·1%	..	..	..
Disease-free survival†							
CPT	3	78	0·67 (0·48–0·95)	79·4%	1·51 (1·00–2·30)	0·052	..
Photon therapy	8	411	0·44 (0·35–0·56)	76·5%	..	..	..
5-year disease-free survival							
CPT	2	58	0·80 (0·67–0·95)	41·6%	1·93 (1·36–2·75)	0·0003	2·60 (1·74–5·15)
Photon therapy	6	341	0·41 (0·30–0·56)	80·9%	..	..	..
Locoregional control†							
CPT	10	208	0·76 (0·68–0·86)	54·0%	1·18 (1·01–1·37)	0·031	8·55 (4·40–143·44)
Photon therapy	14	736	0·65 (0·59–0·71)	60·3%	..	..	..
5-year locoregional control							
CPT	3	58	0·66 (0·43–1·02)	81·2%	1·06 (0·68–1·67)	0·79	..
Photon therapy	8	546	0·62 (0·55–0·71)	73·0%	..	..	..

I^2≥50% suggests high heterogeneity across studies. CPT=charged particle therapy. NNT=number needed to treat. *Calculated when the difference between CPT and photon therapy was significant. †At longest duration of complete follow-up.

Table 3: Comparison of primary outcomes for charged particle therapy cohorts and photon therapy cohorts

METAANALYSIS

Comparing clinical outcomes recorded in charged particle therapy studies with those reported in photon therapy studies suggests that charged particle therapy might be associated with better outcomes for malignant diseases of the nasal cavity and paranasal sinuses. The growing number of institutions providing charged particle therapy are encouraged to collaborate and report their outcomes.

Pattel et al. Lancet Oncology 2014

Head and Neck Cancers

Long-Term Outcomes After Proton Beam Therapy for Sinonasal Squamous Cell Carcinoma

Andrea L. Russo, MD,* Judith A. Adams, CMD,* Elizabeth A. Weyman, BA,* Paul M. Busse, MD,* Saveli I. Goldberg, PhD,* Mark Varvares, MD,† Daniel D. Deschler, MD,† Derrick T. Lin, MD,† Thomas F. Delaney, MD,* and Annie W. Chan, MD*

**Radiation Oncology, Massachusetts General Hospital, and †Head and Neck Surgical Oncology, Massachusetts Eye and Ear Infirmary; Harvard Medical School, Boston, Massachusetts*

- 54 pts
- Stage III und IV
- Median Doses **72.8** Gy RBE
- 69% had previous resection
- 74% had also neck irradiation

All patients were treated with curative intent. The total median dose delivered to the gross tumor volume (GTV) was 72.8 Gy (relative biological effectiveness, RBE). An RBE value of 1.1 was used. For patients who underwent a GTR or partial resection, the median dose was 70.0 Gy(RBE) (range, 59.4-79.4). For biopsy-only patients, the median total dose was 76 Gy(RBE) (range, 70.0-78.1). Patients were treated

Russo et al. IJROBP 2016

RESULTS

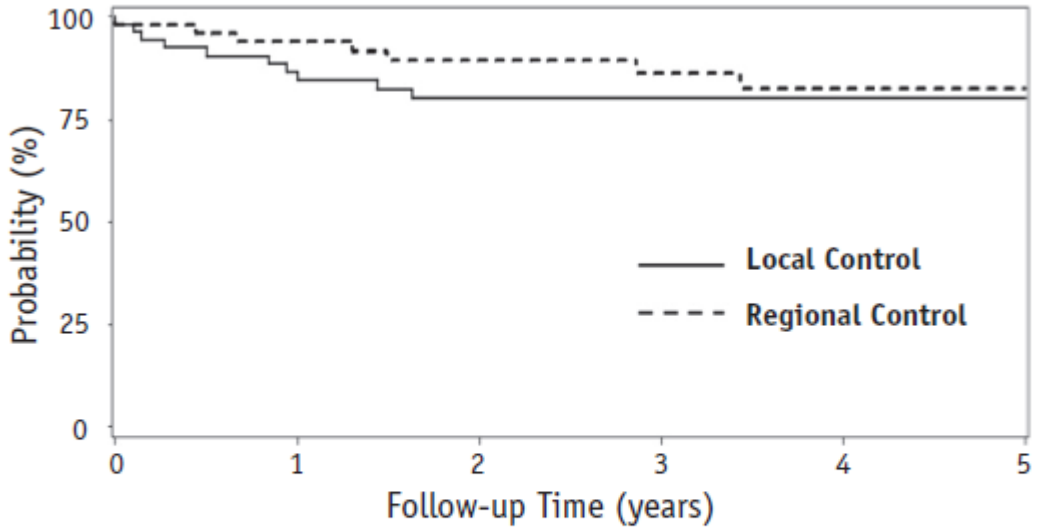


Fig. 1. Kaplan-Meier curve showing local and regional control with 5-year estimates of 80% and 83%, respectively.

Russo et al. IJROBP 2016

Outcomes of Sinonasal Cancer Treated With Proton Therapy

Roi Dagan, MD, MS,*,† Curtis Bryant, MD,*,† Zuofeng Li, DSc,*,†
Daniel Yeung, PhD,*,† Jeb Justice, MD,‡ Peter Dzieglewiski, MD,‡
John Werning, MD,‡ Rui Fernandes, MD, DMD,§
Phil Pirgousis, MD, DDS,§ Donald C. Lanza, MD,‖
Christopher G. Morris, MS,*,† and William M. Mendenhall, MD*,†

*Departments of *Radiation Oncology and ‡Otolaryngology, University of Florida, Gainesville, Florida; and Departments of †Radiation Oncology and §Oral and Maxillofacial Surgery, University of Florida, Jacksonville, Florida; and ‖Sinus & Nasal Institute of Florida, St. Petersburg, Florida*

- 84 pts
- Median Dose **73.8 Gy** RBE
- Histologies: SCC,ACC,olfact. Neuroblastomas

Fractionation	
1.2 Gy (RBE) twice daily	83 (99%)
2 Gy (RBE) once daily	1 (1%)
Total dose, Gy (RBE)	73.8 (62.4-74.4); 85% received ≥70
Total fractions	61 (33-62)
Neck RT	
Elective	66 (78%)
RT for positive neck	4 (5%)
Adjuvant (after positive neck dissection)	4 (5%)
No	10 (12%)

Dagan et al. IJROBP 2016

RESULTS

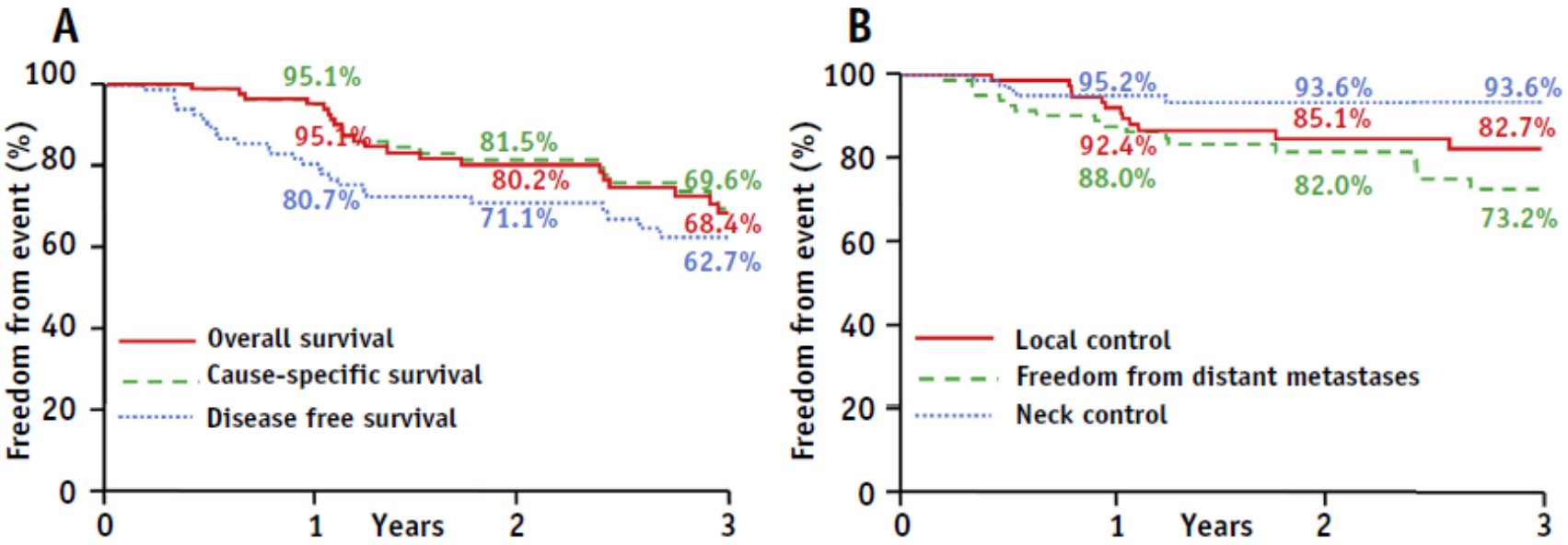


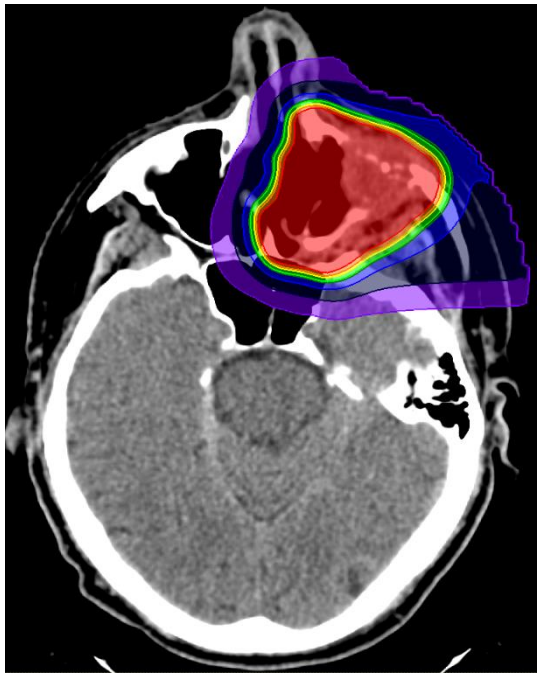
Fig. 1. (A) Survival and (B) disease control outcomes.

Dagan et al. IJROBP 2016

CONCLUSION PART II

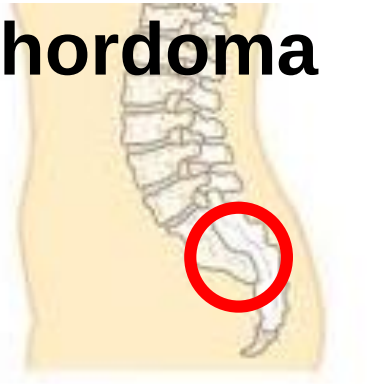
Why are oucome data so encouraging?

- **Dose escalation**
- **Better target coverage**

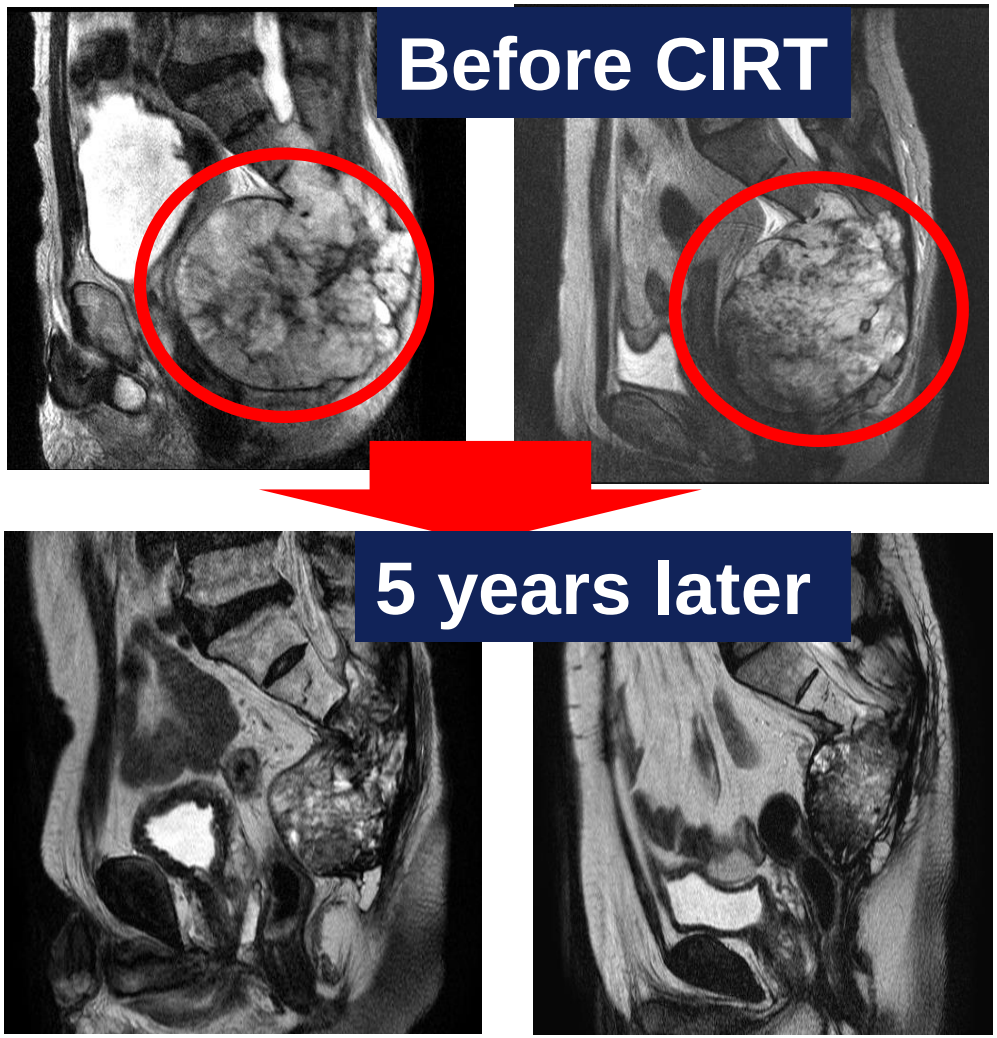


CARBON IONS

Sacral chordoma

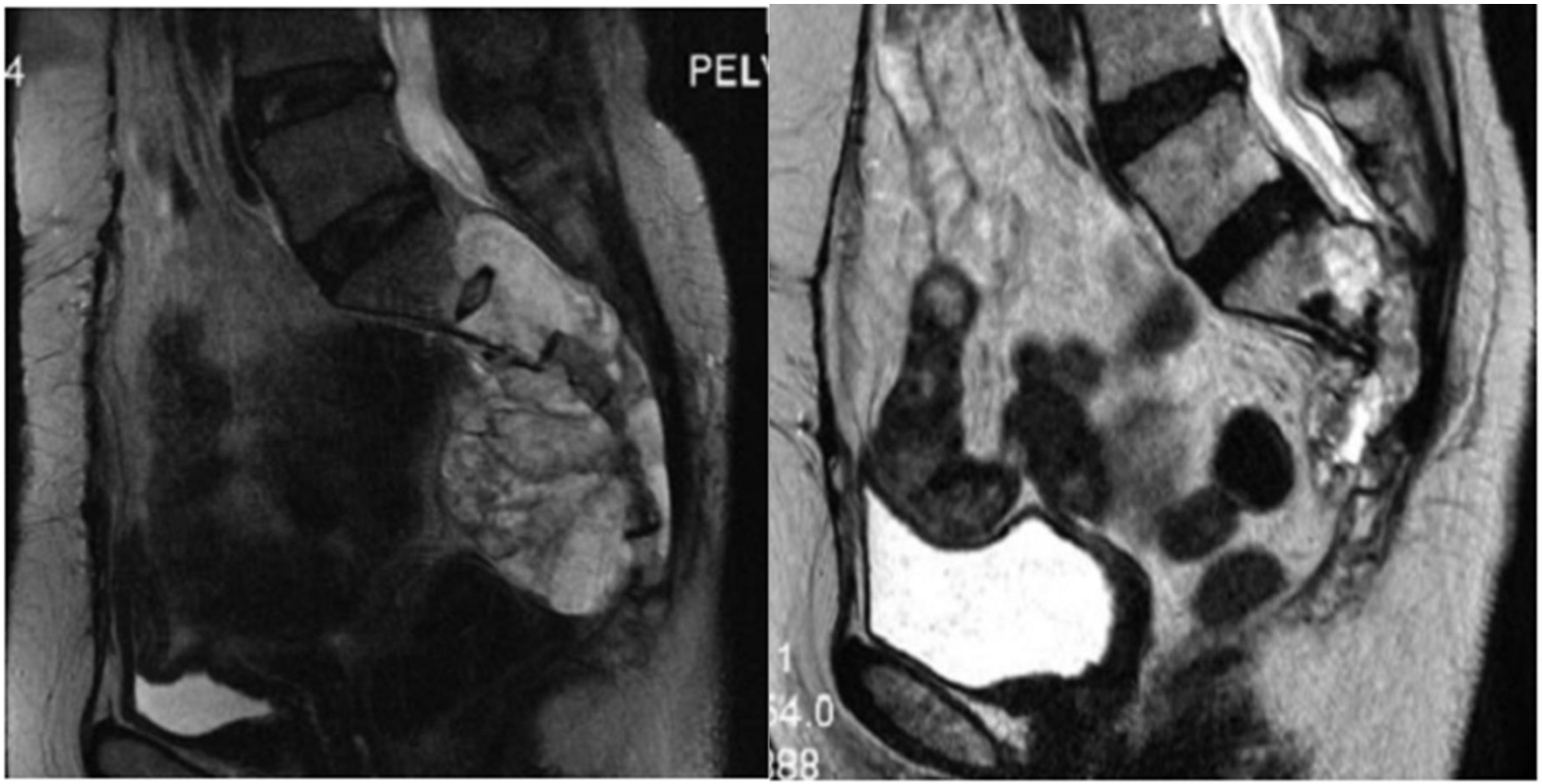


- Rare malignant tumor
- 20-30 pts/ year in Japan.
- Chemotherapy and x-ray RT are not effective.
- Resection sacrifices sacral nerves.



Courtesy: H. Tsujii

EVIDENCE-SACRAL CHORDOMA

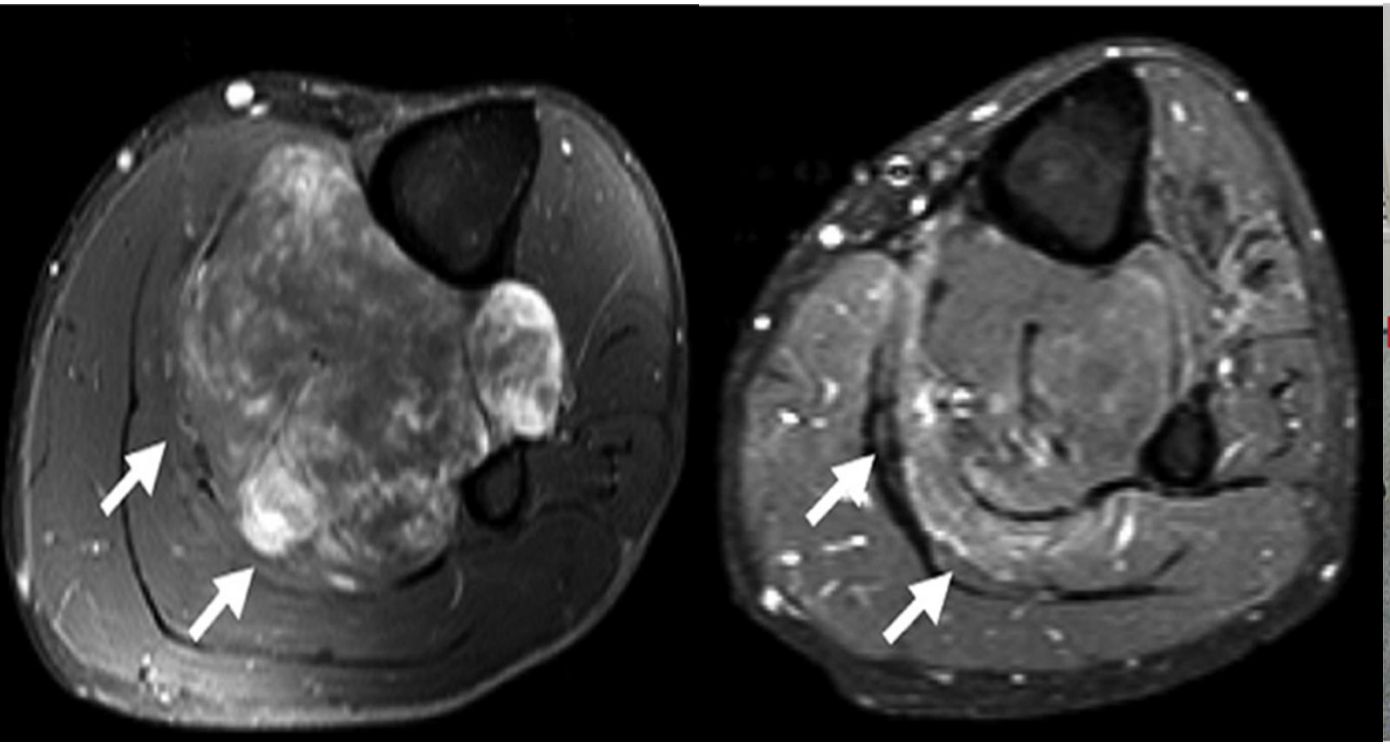


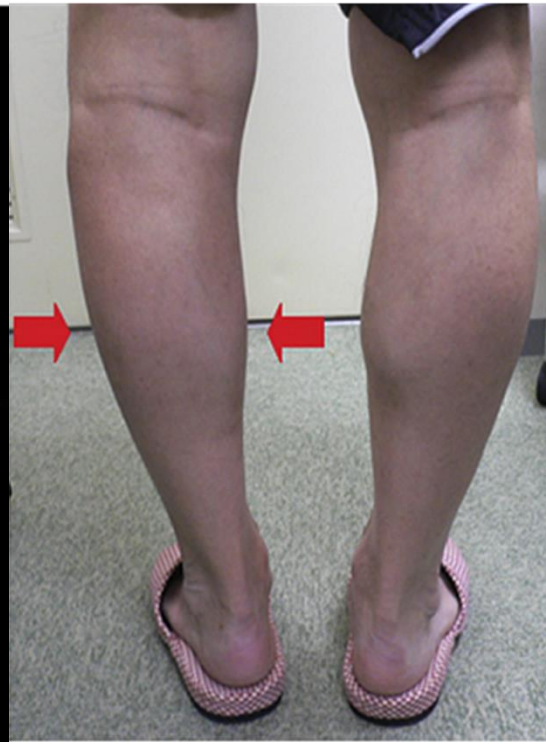
Before CIRT

4years after CIRT

Imai et al. IJROBP 2010, Imai et al. BJR 2011

EXTREMITY SOFT TISSUE SARCOMA





Before RT

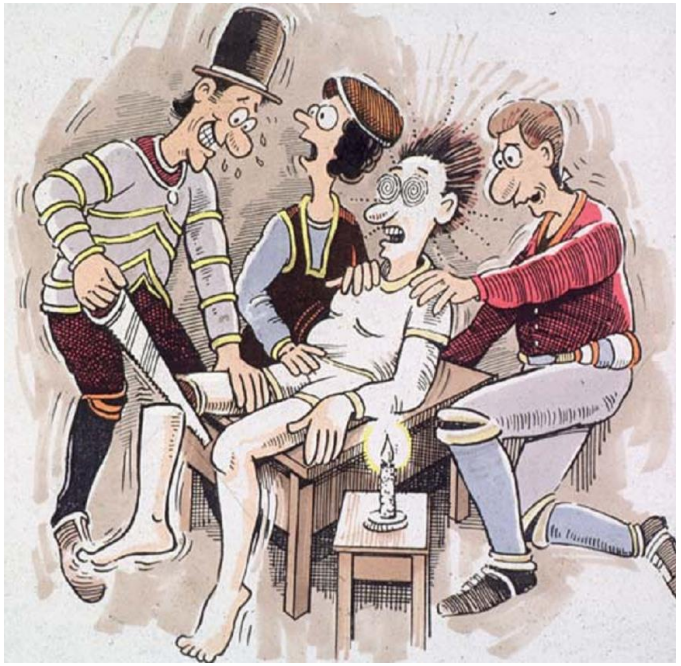
66 months after RT

Sugahara et al. R&O 2012

CONCLUSION PART III

What else can we achieve?

- **We can avoid mutilating surgeries**



OTHER MEDICAL INDICATIONS

LITERATURE OVERVIEW

PANCREAS CARCINOMA-PREOPERATIVE

Author	Patients (n)	Therapy	Overall Survival (%) @ 5Y	Late Toxicity ≥ G3 (%)
Ishikawa 1994	17	**Photons +** OP	28	
Stessin 2008	190	**Photons +** OP	21	
Satoi 2012	27	**Photons +** OP	30	
Hong 2014	48	**Protons-CHT** + OP	42 (2y)	4.1
Shinoto 2013	21	**Carbon Ions+** OP	52	5

Ishikawa et al. Arch Surg 1994; 129(10):1075-80
Stessin et al. IJROBP 2008; 72(4):1128-33
Satoi et al. Pancreas 2012; 41:333-5

Hong et al. IJROBP 2014; 89(4):830-38
Shinoto et al. Cancer 2013; 119:45-51

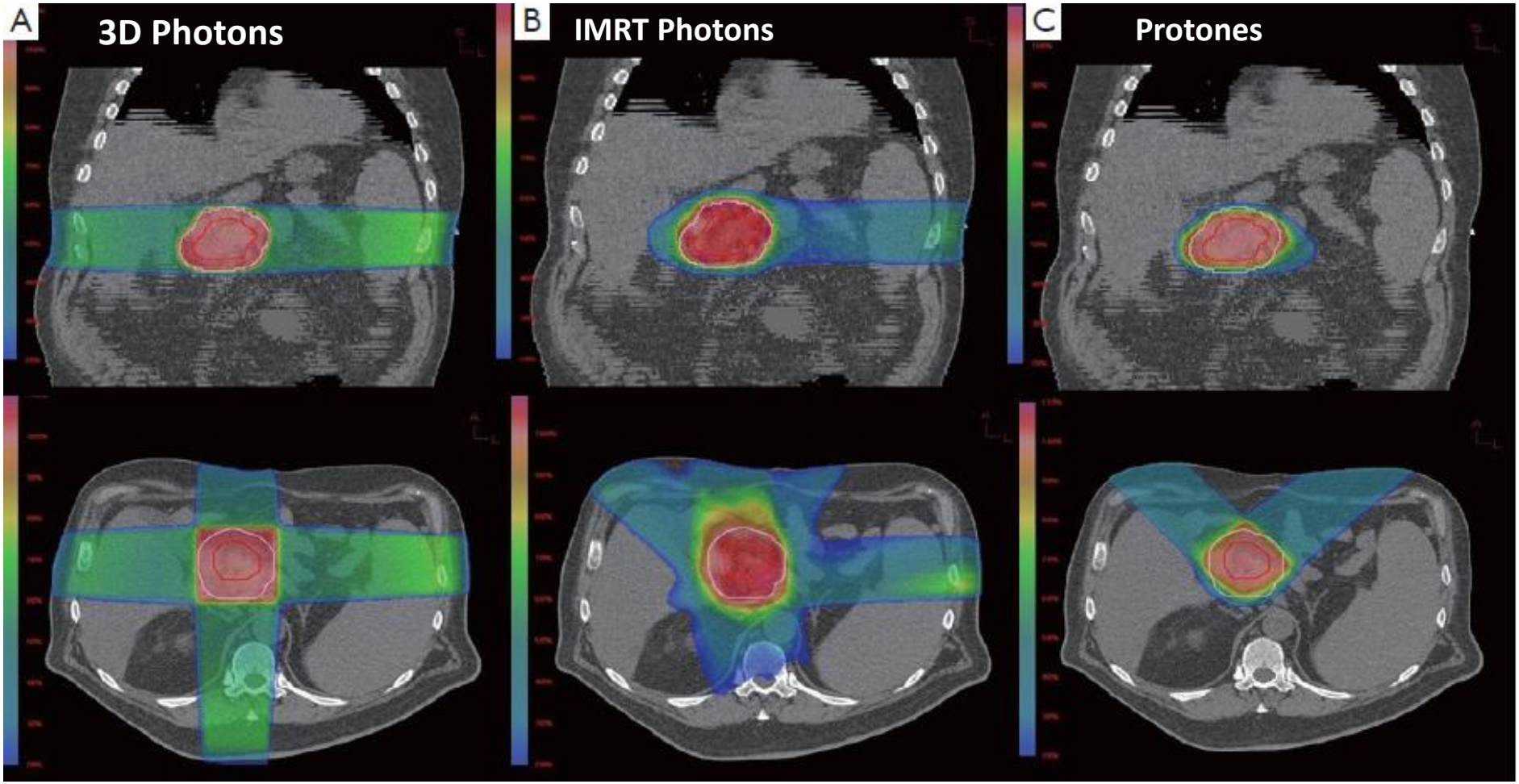
PANCREAS CANCER-INOPERABLE

Author	Patients (n)	Treatment	Overall survival (%) @ 2Y	Toxicity ≥ G3 (%)
Chauffert 2008	49	CHT+**Photon** Adj. CHT	16	32-36
Loehrer 2011	34	CHT+**Photon**	12	80
Sudo 2011	34	CHT+**Photon**	25	42
Mukherjee 2013	74	CHT+**Photon**	7	
Wang 2015	27	CHT+**Photon (IMRT)**	41	15
Terashima 2012	50	CHT+**Proton**	51	10
Kamada 2015	47	CHT+**Carbon Ion**	54	2

Chauffert et al. 2008, Ann of Oncol 19:1592-99
Loehrer et al. 2011, JCO 29(31):4105-4112
Sudo et al. 2011, IJROBP 80(1):119-125

Mukherjee et al. 2013, Lancet Oncology 14:317-326
Wang et al. 2015, Radiation Oncology 10:14
Terashima et al. 2012, Radiother Oncol 103:25-31
Kamada et al. 2015, Lancet Oncology 16:93-100

DOSE DISTRIBUTION



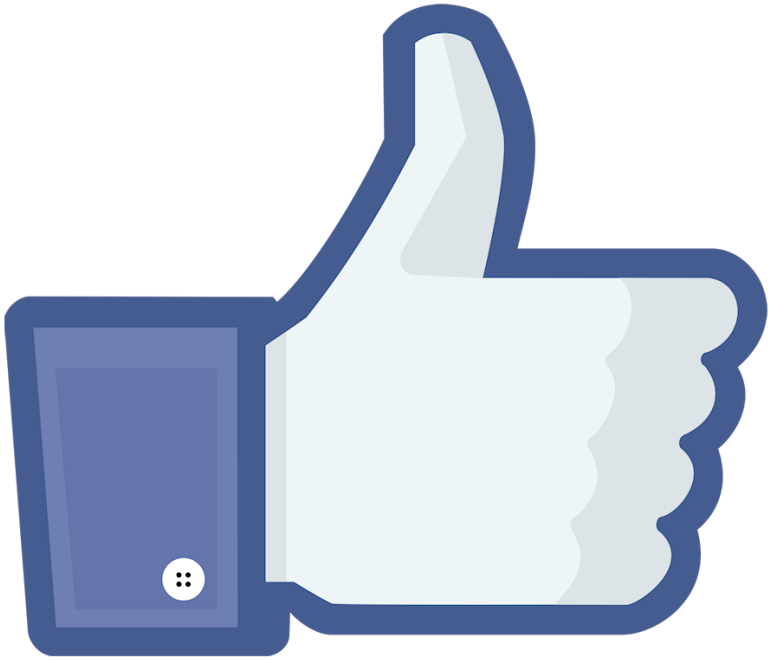
Ling et al. J Gastrointest Oncol 2015; 6(2): 108-114

CONCLUSION PART IV

- **We can improve the survival data**

EVERYTHING SEEMS TO BE PERFEKT

- **Treatment with particles**



JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non–Small-Cell Lung Cancer

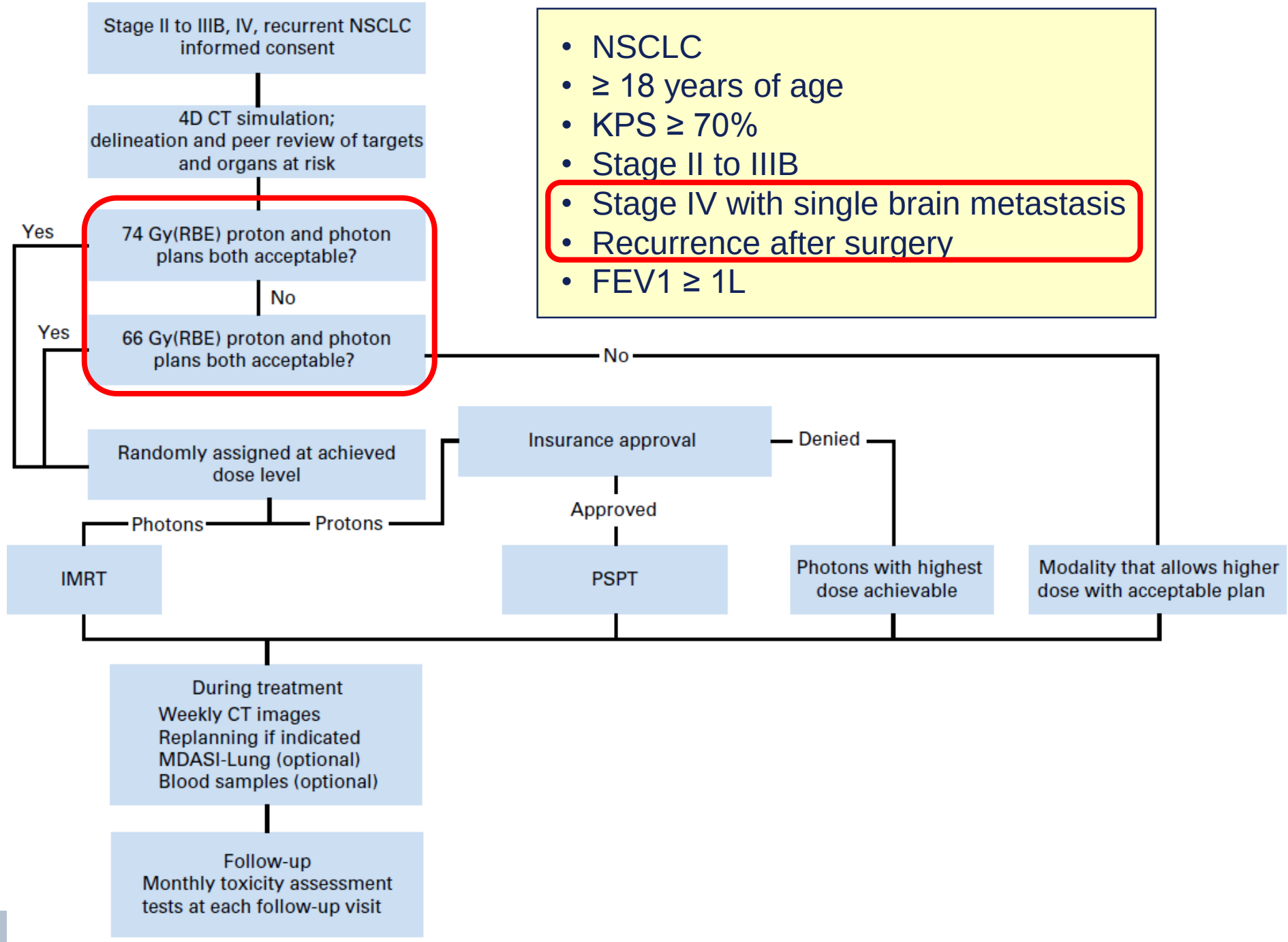
Zhongxing Liao, J. Jack Lee, Ritsuko Komaki, Daniel R. Gomez, Michael S. O'Reilly, Frank V. Fossella, George R. Blumenschein Jr, John V. Heymach, Ara A. Vaporciyan, Stephen G. Swisher, Pamela K. Allen, Noah Chan Choi, Thomas F. DeLaney, Stephen M. Hahn, James D. Cox, Charles S. Lu, and Radhe Mohan

Hypothesis

… **proton therapy** exposes significantly
less lung tissue to radiation than photon therapy,
which thus **reduces toxicity**
without compromising tumor control.

Study Design

Bayesian adaptive randomization
PSPT superior to IMXT
Concomitant Radiotherapy / Chemotherapy


Stage II to IIIB, IV, recurrent NSCLC informed consent
4D CT simulation; delineation and peer review of targets and organs at risk
74 Gy(RBE) proton and photon plans both acceptable?
Yes
No
66 Gy(RBE) proton and photon plans both acceptable?
Yes
No
Randomly assigned at achieved dose level
Photons
Protons
Insurance approval
Denied
Approved
IMRT
PSPT
Photons with highest dose achievable
Modality that allows higher dose with acceptable plan
During treatment
Weekly CT images
Replanning if indicated
MDASI-Lung (optional)
Blood samples (optional)
Follow-up
Monthly toxicity assessment
tests at each follow-up visit
• NSCLC
• ≥ 18 years of age
• KPS ≥ 70%
• Stage II to IIIB
• Stage IV with single brain metastasis
• Recurrence after surgery
• FEV1 ≥ 1L

	IMXT (n=92)	PSPT (n=57)
Lung Dose		
MLD	16.6 ≈	≈ 16.1
$V_{5\text{-}10}$	higher	lower
$V_{20\text{-}80}$	lower	higher
Lung Toxicity	(15 %)	(5 %)
≥ G3 Radiation Pneumonitis @ 12 m	6.5%	10.5%
Local Failure	(25 %)	
PTV + ≤ 1 cm @ 12 m	10.9%	10.5%
Combined LF + RP	17.4%	21.1%

Discussion

⇒ **Initial estimations on historical data?**

⇒ **Saftey margins?**

⇒ *Beam directions?*

⇒ *Passive scattering?*

Conclusions

Primary goal missed

⇒ Heart sparing

⇒ Improvement over time

CONCLUSION PART V

- **There is enough evidence to handle particle therapy as „state of the art" treatment for some indications**

BUT

- **It is still important to perform clinical studies**
- **Study protocols need to be well designed**

THANK YOU FOR YOUR ATTENTION