Protonterapia
e tumori pediatrici

I.O.V.
ISTITUTO ONCOLOGICO VENETO I.R.C.C.S

Giovanni Scarzello
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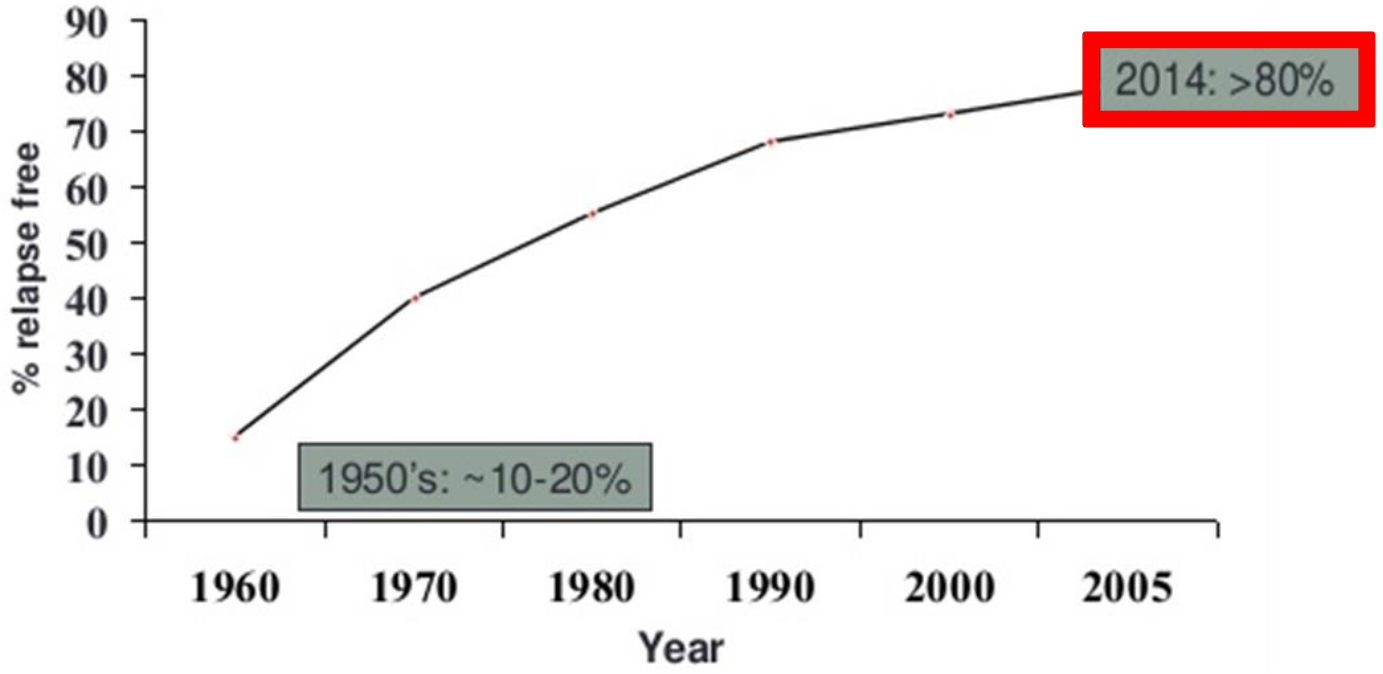
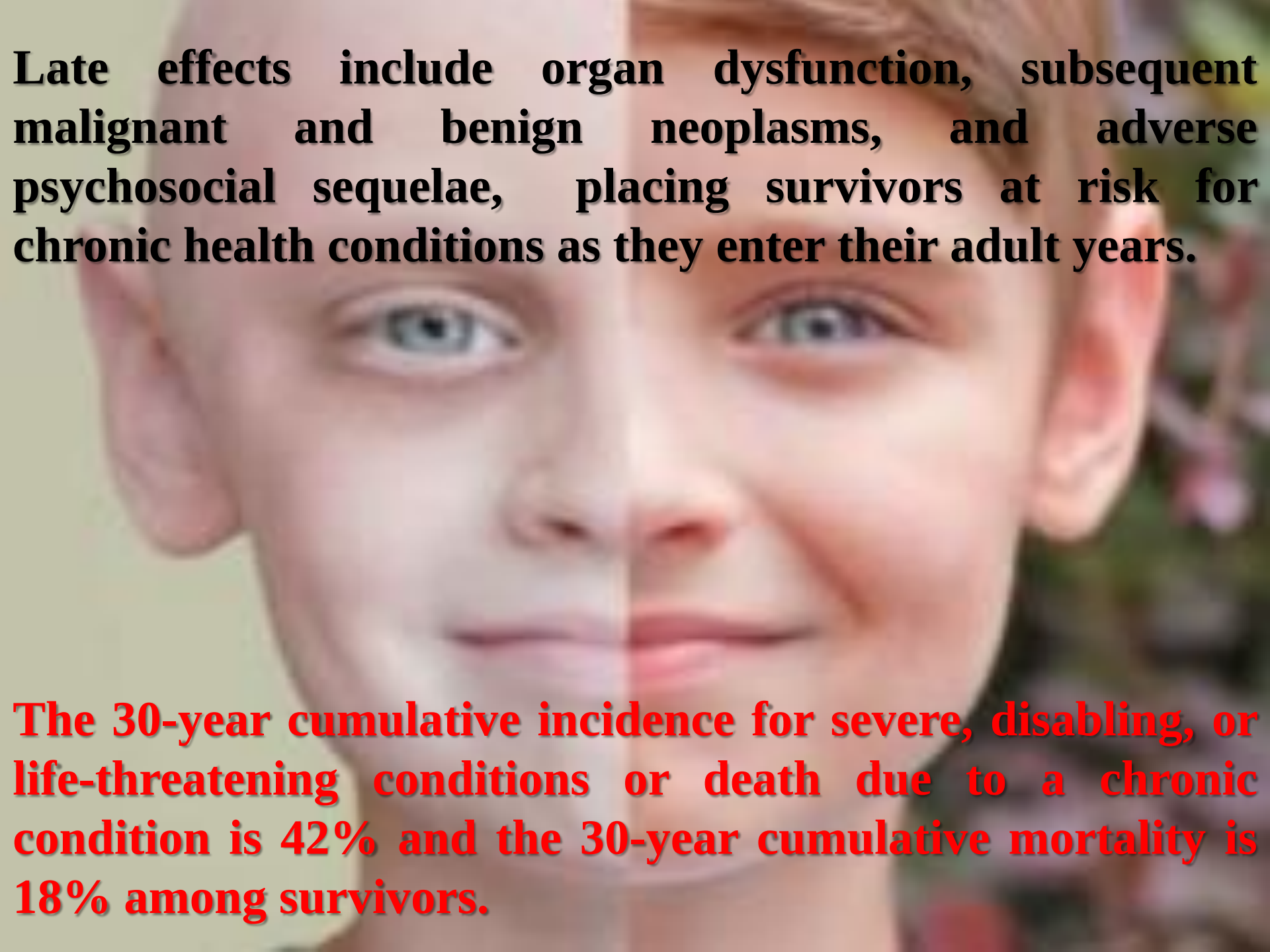
The outcome of children with tumors has improved dramatically over the past few decades with the use of multimodality therapy.





Late effects include organ dysfunction, subsequent malignant and benign neoplasms, and adverse psychosocial sequelae, placing survivors at risk for chronic health conditions as they enter their adult years.

The 30-year cumulative incidence for severe, disabling, or life-threatening conditions or death due to a chronic condition is 42% and the 30-year cumulative mortality is 18% among survivors.

“Cure is not enough”

G. J. D’Angio

Minimizing the RT morbidity

Avoiding RT

Postponing RT

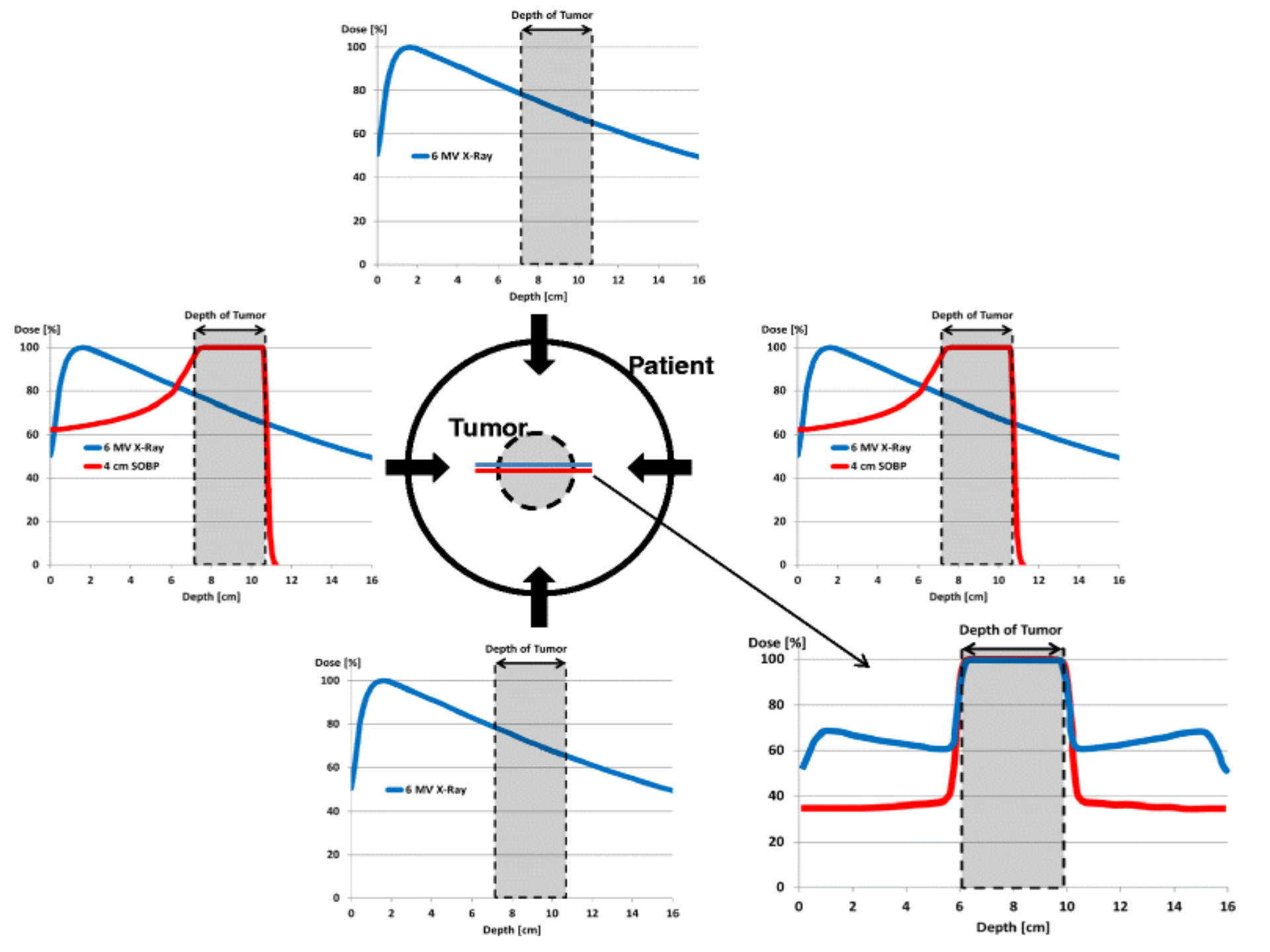
Reducing dose

Reducing target volume

Improving technique

Investigating novel fractionation


New radiation therapy modalities enable radiation oncologists to increase dose to tumor while avoiding surrounding normal structures.
3DCRT
IMRT
IORT
Brachy
Stereotaxis
Particle


Depth of Tumor
Dose [%]
100
80
60
40
20
0
6 MV X-Ray
0 2 4 6 8 10 12 14 16
Depth [cm]
Depth of Tumor
Dose [%]
6 MV X-Ray
4 cm SOBP
Depth [cm]
Patient
Tumor
Depth of Tumor
Dose [%]
6 MV X-Ray
4 cm SOBP
Depth [cm]
Depth of Tumor
Dose [%]
6 MV X-Ray
Depth [cm]
Depth of Tumor
Dose [%]
Depth [cm]

A "different" dose distribution is not the same as an improved clinical outcome.

We often hear a classic circular argument:

A different dose distribution = a different clinical outcome, because protons give a different dose distribution = a different clinical outcome,

then protons are better because they give a better dose distribution…and around and around.

J Med Ethics 35:684-7, 2009 B. Hoffmann

Disease	Number of cases in USA per year	% of cases irradiated	Number of cases irradiated
Acute Lymphocytic Leukemia	2400	10	240
Acute Non-Lymphocytic Leukemia	850	5	43
Lymphoma	1700	30	510
Medulloblastoma	460	90	400
Astrocytoma, including brainstem	1140	50	570
Ependymoma	200	60	120
Neuroblastoma	650	10	65
Wilms	500	10	50
Ewing	200	60	120
Rhabdomyosarcoma	350	60	210
NRSTS	550	50	275
	9000	29	2603

Cancer Incidence & Survival among Children and Adolescents JACR 1:488,2004

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Critical Review

Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers

Roos Leroy, PhD,* Nadia Benahmed, MSc,* Frank Hulstaert, MD,* Nancy Van Damme, PhD,† and Dirk De Ruysscher, PhD‡

*Belgian Healthcare Knowledge Centre (KCE), Brussels; †Belgian Cancer Registry, Brussels; and ‡Department of Radiation Oncology, University of Leuven, Leuven, Belgium

Received Apr 8, 2015, and in revised form Oct 5, 2015. Accepted for publication Oct 13, 2015.

Most suffered from serious methodologic limitations, yielding a very low level of clinical evidence for the outcomes in all indications.

investigation are lacking. High-quality clinical research in this area is needed.

Craniopharyngioma (3)

At present very low-level clinical evidence that PT compared with IMRT does not result in significant differences in 3-year OS, 3-year CFFS, 3-year NFFS, toxicity or cyst dynamics.

Retinoblastoma (2)

At present very low level clinical evidence that PT results in lower risk of developing RT induced in-field secondary malignancies.

Review Article

Treatment of common pediatric CNS malignancies with proton therapy

Arpit Chhabra[1], Anita Mahajan[2]

[1]Department of Radiation Oncology, The University of Maryland School of Medicine, Baltimore, Maryland, USA; [2]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Conclusions

… the ultimate hope is to complete a well controlled prospective trial comparing proton and photon radiation therapy. In the interim, PRT should be strongly considered when treating pediatric CNS tumors in an effort to allow children to live and mature with minimal treatment sequelae.

Review Article

A Systematic Review of the Cost and Cost-Effectiveness Studies of Proton Radiotherapy

Vivek Verma MD[1]; Mark V. Mishra MD[2]; and Minesh P. Mehta MBChB[2]

BACKGROUND: Economic analyses of new technologies, such as proton-beam radiotherapy (PBT), are a public health priority. To

Careful patient selection is absolutely critical to assess cost-effectiveness. Together with increasing PBT availability, clinical trial evidence, and ongoing major technological improvements, cost-effectiveness data and conclusions from this analysis could change rapidly.

has not been demonstrated that PBT is cost-effective for prostate cancer or early stage NSCLC. Careful patient selection is absolutely critical to assess cost-effectiveness. Together with increasing PBT availability, clinical trial evidence, and ongoing major technological improvements, cost-effectiveness data and conclusions from this analysis could change rapidly. ***Cancer*** **2016;122:1483-501.** © *2016 American Cancer Society.*

KEYWORDS: cost-effectiveness, health care economics, operational costs, proton radiation therapy.

Practical Radiation Oncology (2014) 4, 336-341

practical radiation oncology
pro
www.practicalradonc.org

Original Report

Practice patterns of photon and proton pediatric image guided radiation treatment: Results from an International Pediatric Research Consortium

Our results suggest that IGRT is commonly used for radiation delivery in the management of pediatric tumors but that there is notable variability in when and how it is employed among institutions for a given treatment site.

These data highlight the need for consensus recommendations to guide clinical decision making for IGRT in the treatment of children.

Acta Oncologica, 2014; 53: 126–133

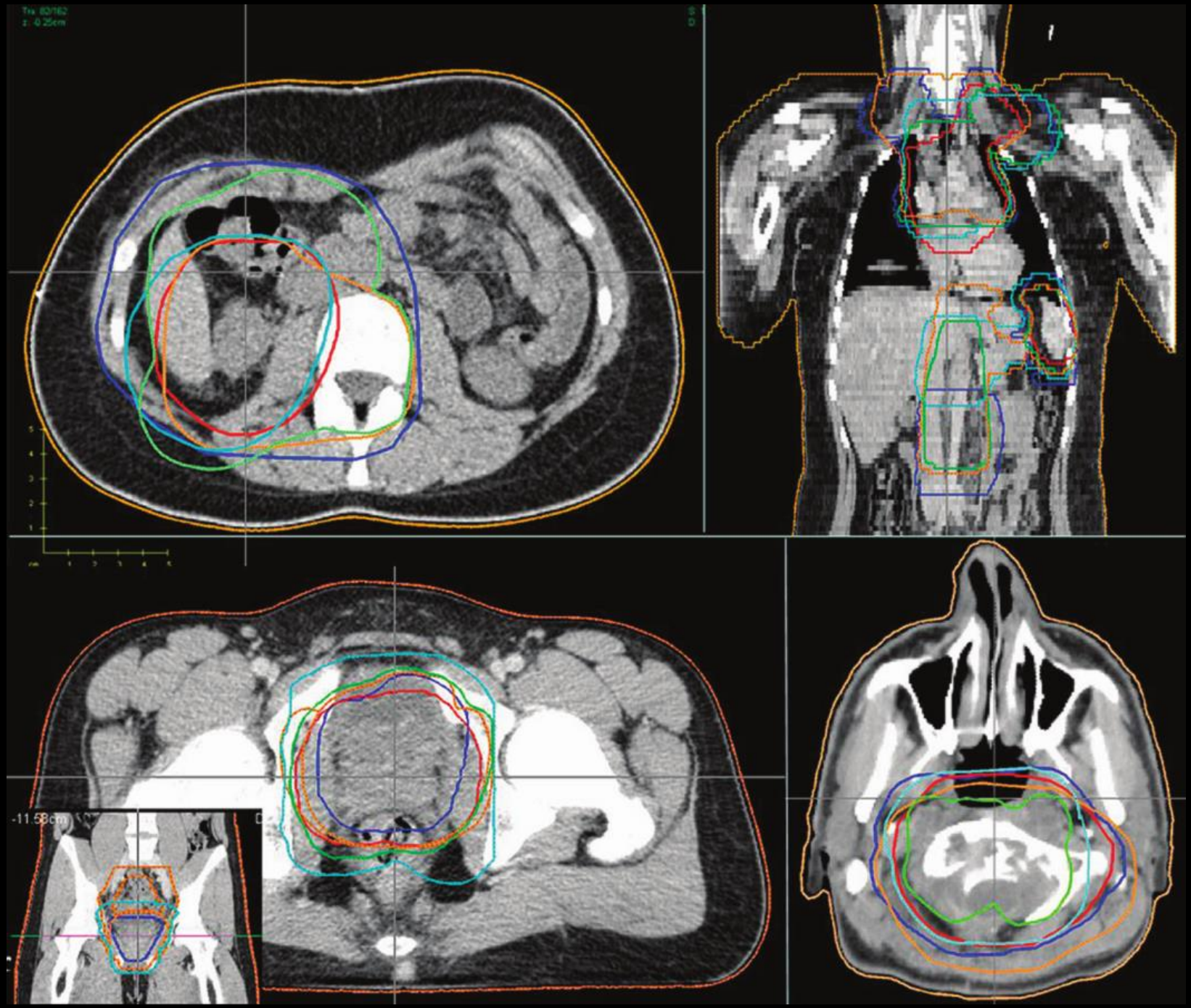
informa
healthcare

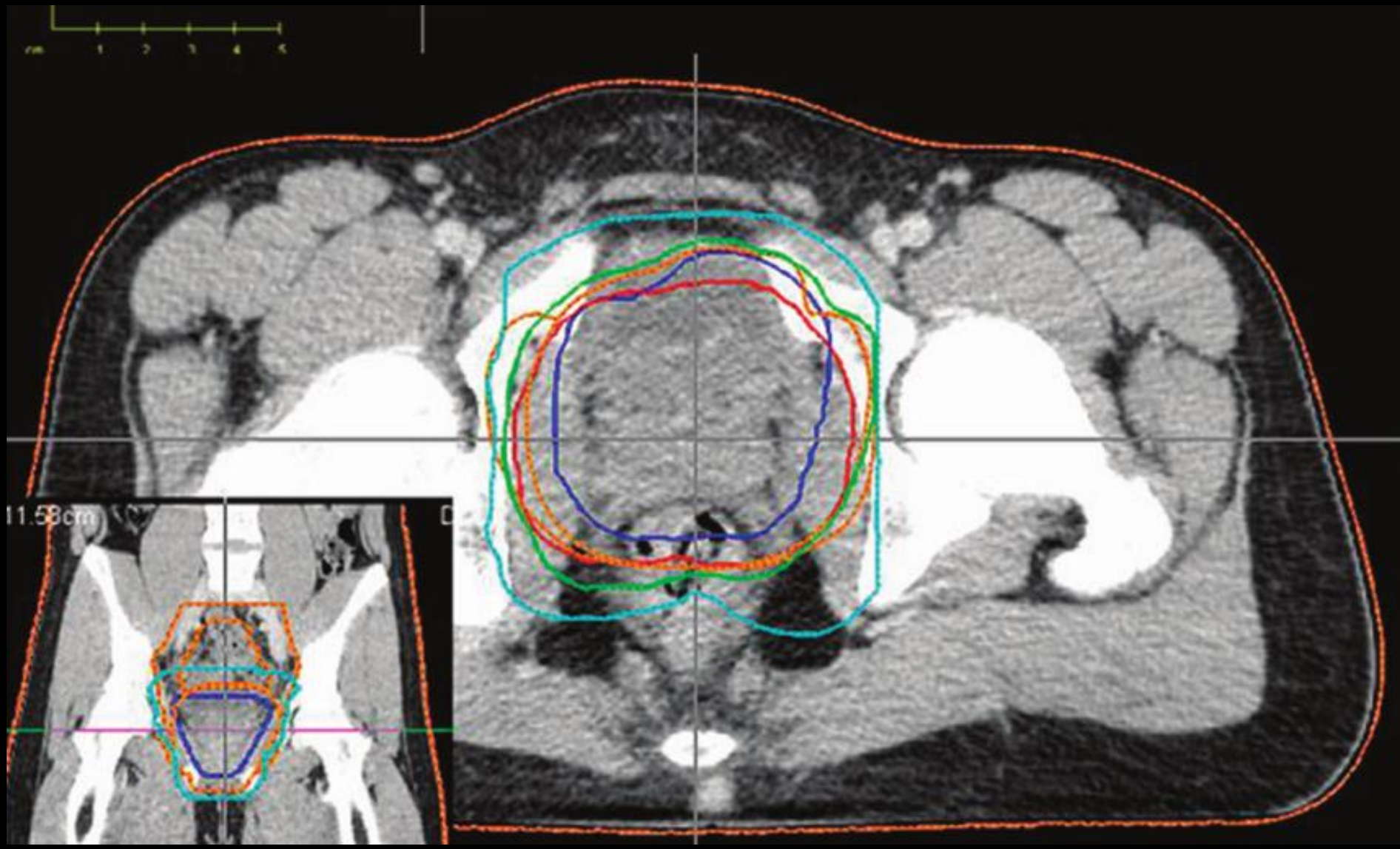
ORIGINAL ARTICLE

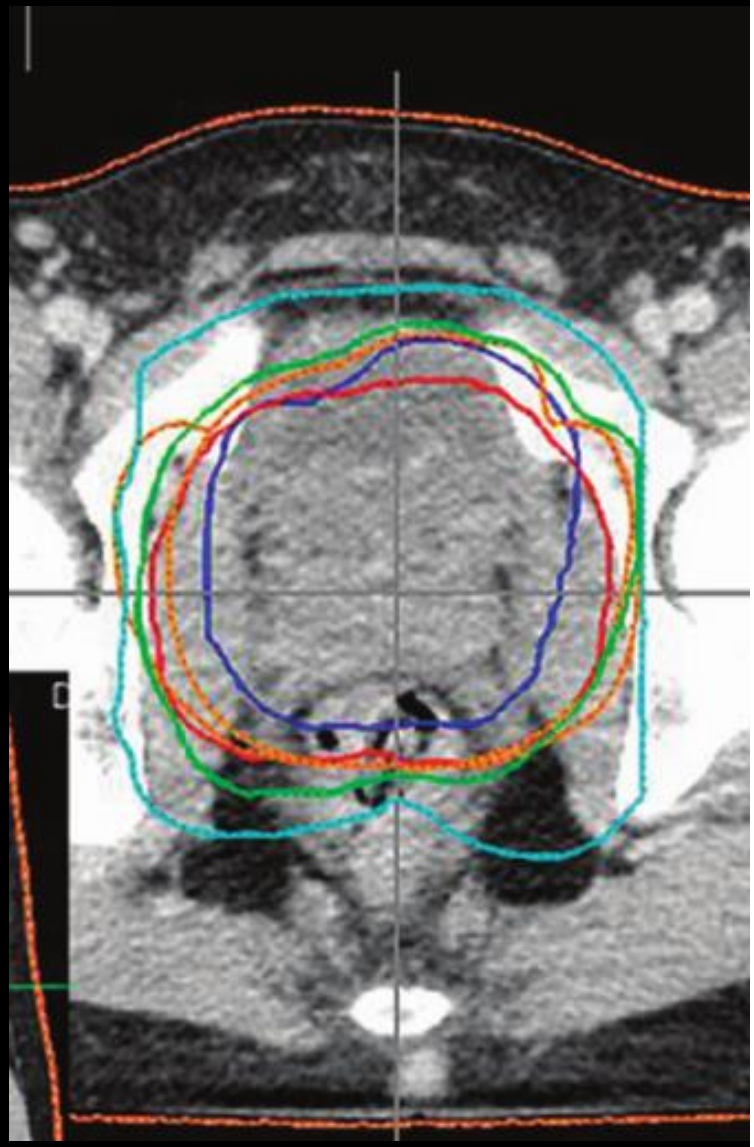
Assessment of volume segmentation in radiotherapy of adolescents; a treatment planning study by the Swedish Workgroup for Paediatric Radiotherapy

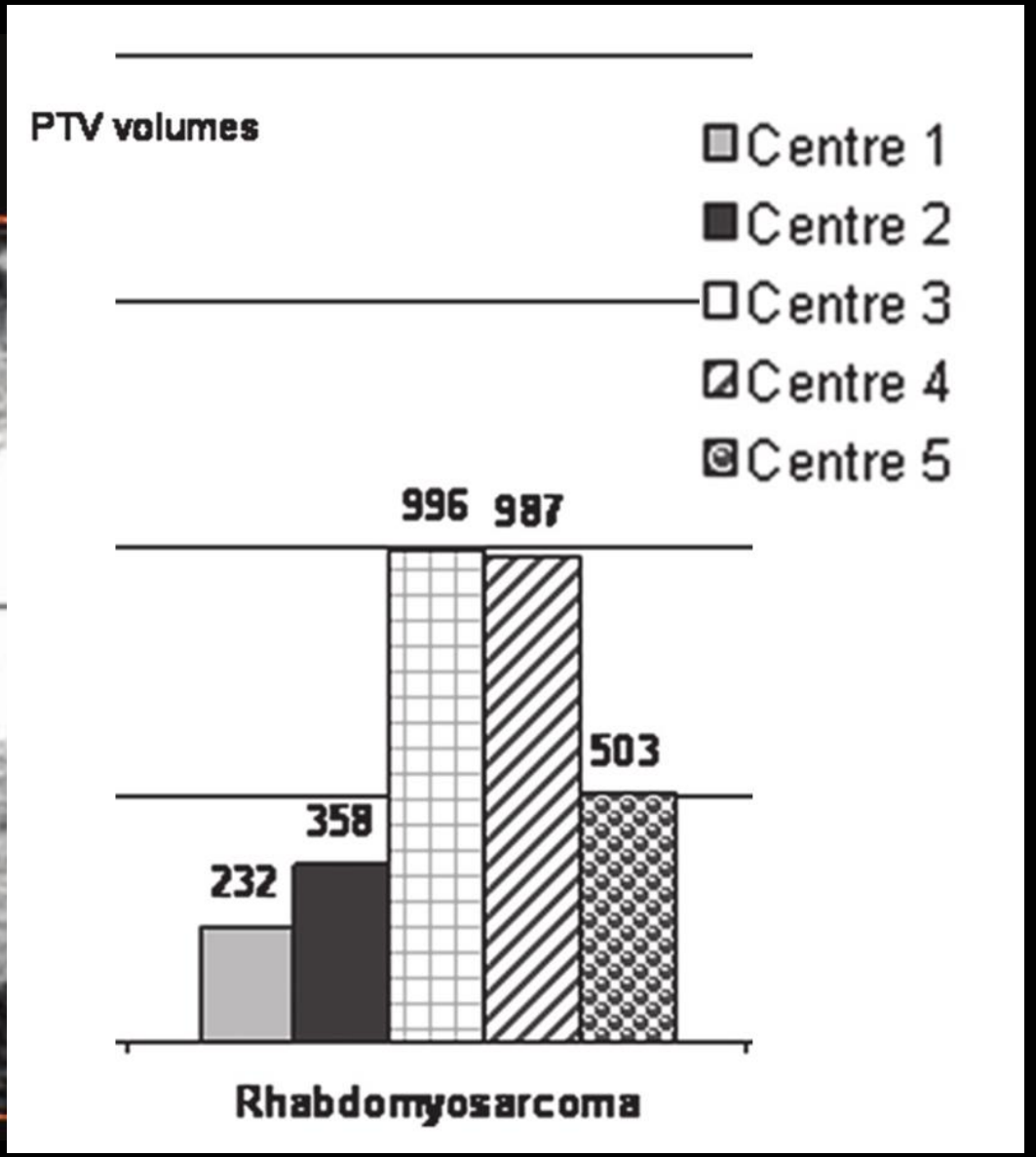
INGRID KRISTENSEN[1,2], MÅNS AGRUP[3], PER BERGSTRÖM[4], JACOB ENGELLAU[5], HEDDA HAUGEN[6], ULLA MARTINSSON[7], KRISTINA NILSSON[7], ZAHRA TAHERI-KADKHODA[6], JACK LINDH[4] & PER NILSSON[2,5]

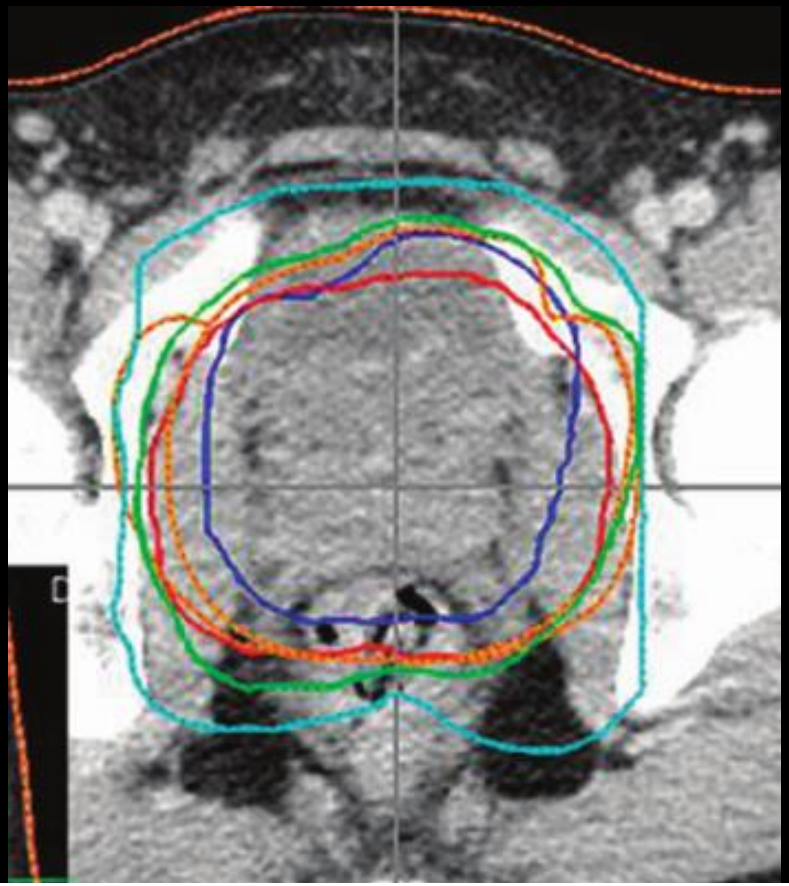
[1]*Department of Clinical Sciences, Oncology, Lund University, Lund, Sweden,* [2]*Department of Radiation Physics, Skåne University Hospital, Lund University, Lund, Sweden,* [3]*Department of Oncology, Linköping University Hospital, Linköping, Sweden,* [4]*Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden,* [5]*Department of Oncology, Skåne University Hospital, Lund University, Lund, Sweden,* [6]*Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden and* [7]*Department of Oncology, Uppsala University Hospital, Uppsala, Sweden*

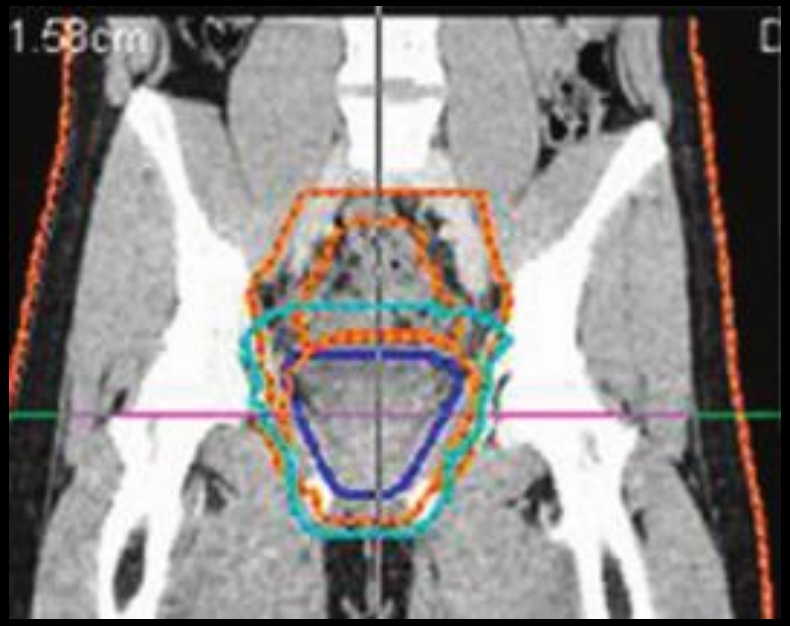







PTV volumes
Centre 1
Centre 2
Centre 3
Centre 4
Centre 5
232
358
996
987
503
Rhabdomyosarcoma





		Dose (Gy)	Dose constraints* (protocol)	Treated volume $V_{95\%}$ (litres)	Irradiated Volume $V_{50\%}$ (litres)
Case 3	*Bladder*	43.6 (37.2–51.7)	–		
	Rectum	33.2 (24.6–48.2)	–		
	Body			0.48 (0.20–1.11)	3.20 (1.43–5.96)

QUARTET
Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials
A SIOPE Project

SIOPE
SIOP Europe
the European Society for Paediatric Oncology

Fondatioun Kriibskrank Kanner
25 JOËR

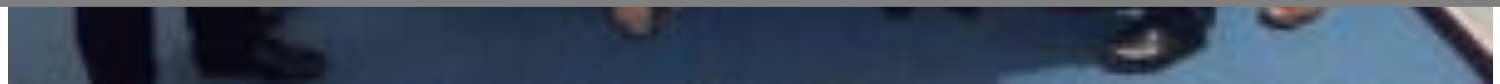
To provide high level reproducible RT for all children
prospective RTQA

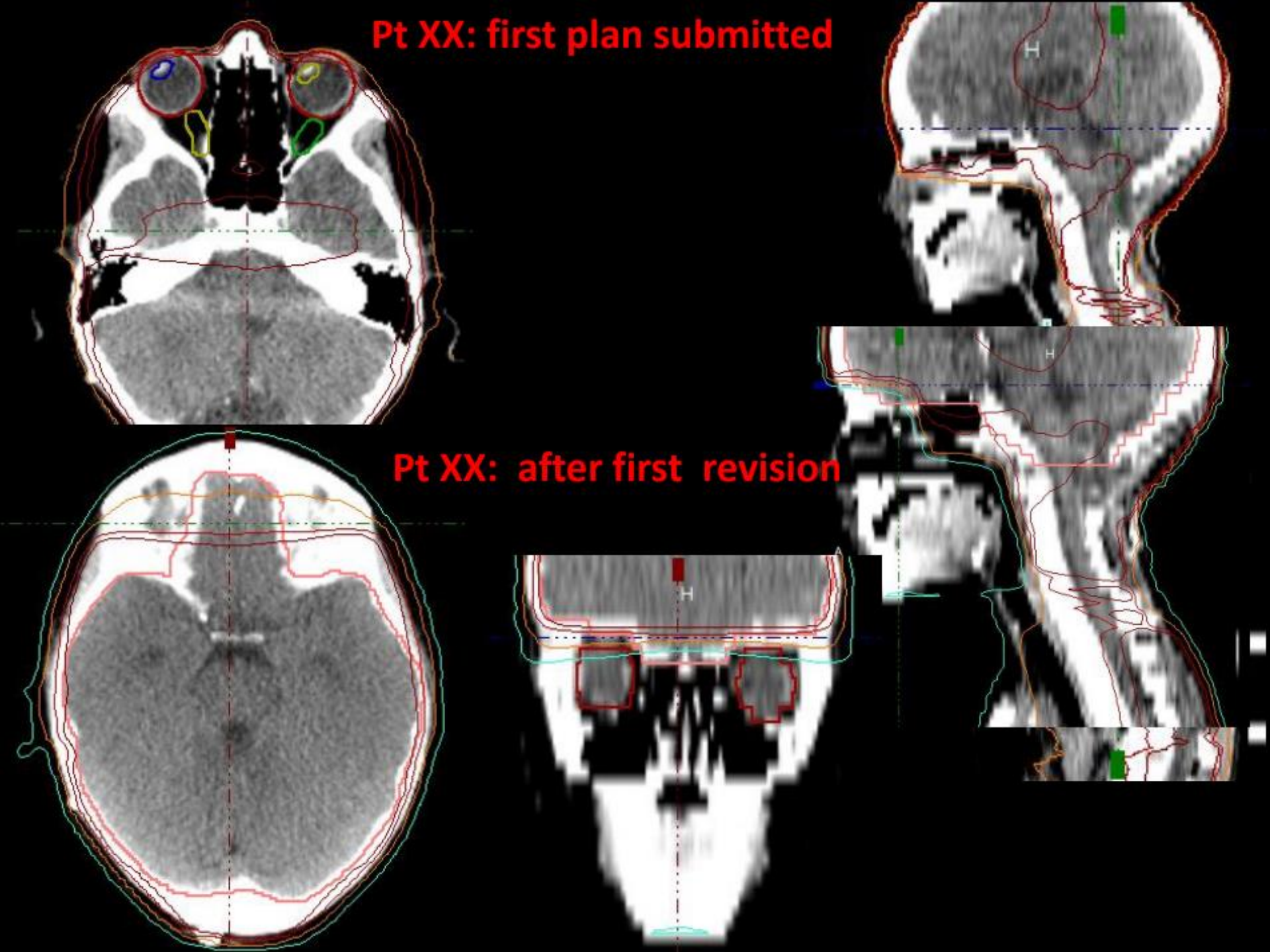
EpSSG
SIOPEN
SIOP Brain tumors
Hodgkin's lymphoma
Wilms' tumor

SIOP Brain tumors
PNET 5

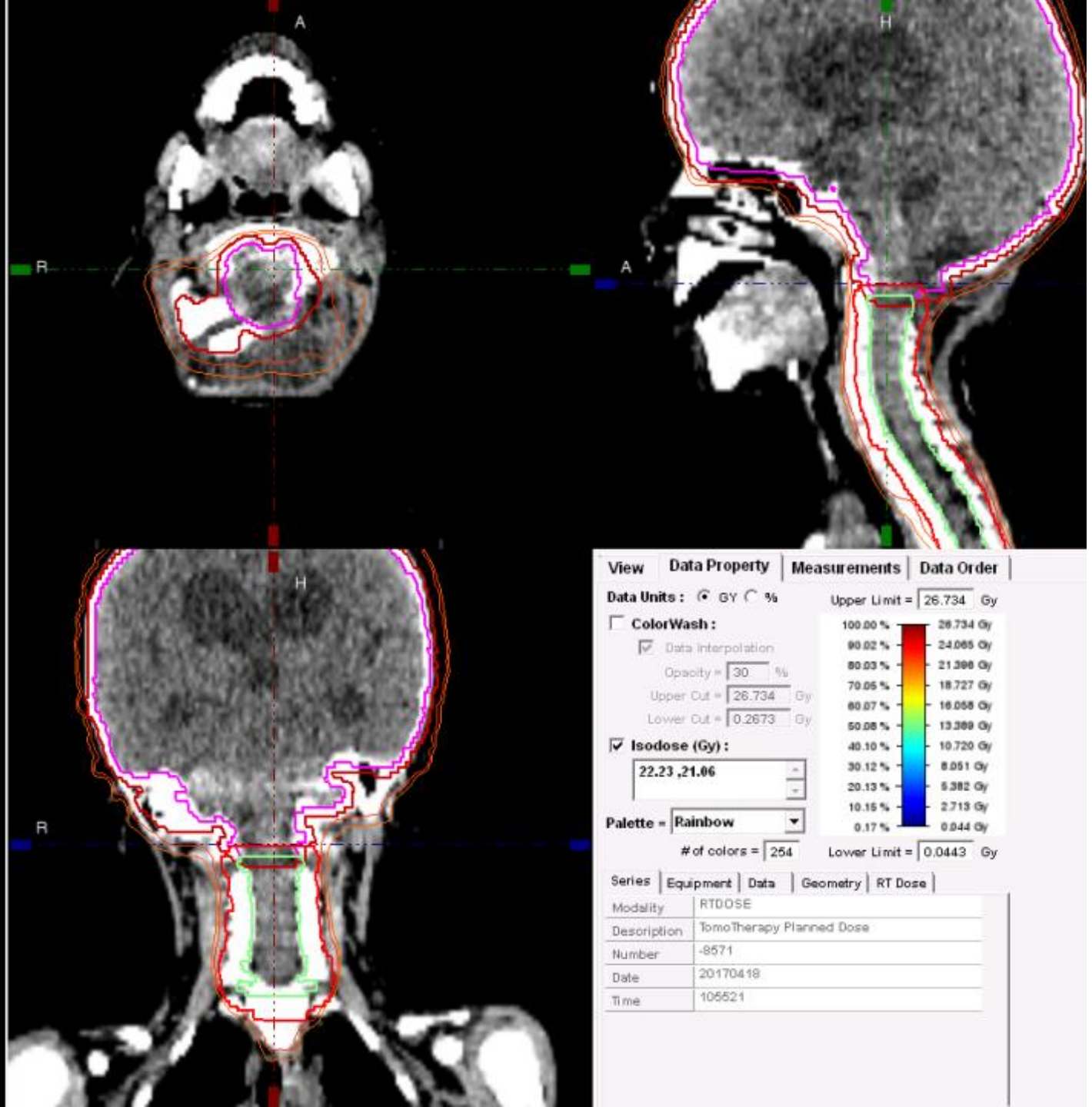
QA and its influence
long term toxicity

To establish funding for as many trials as possible

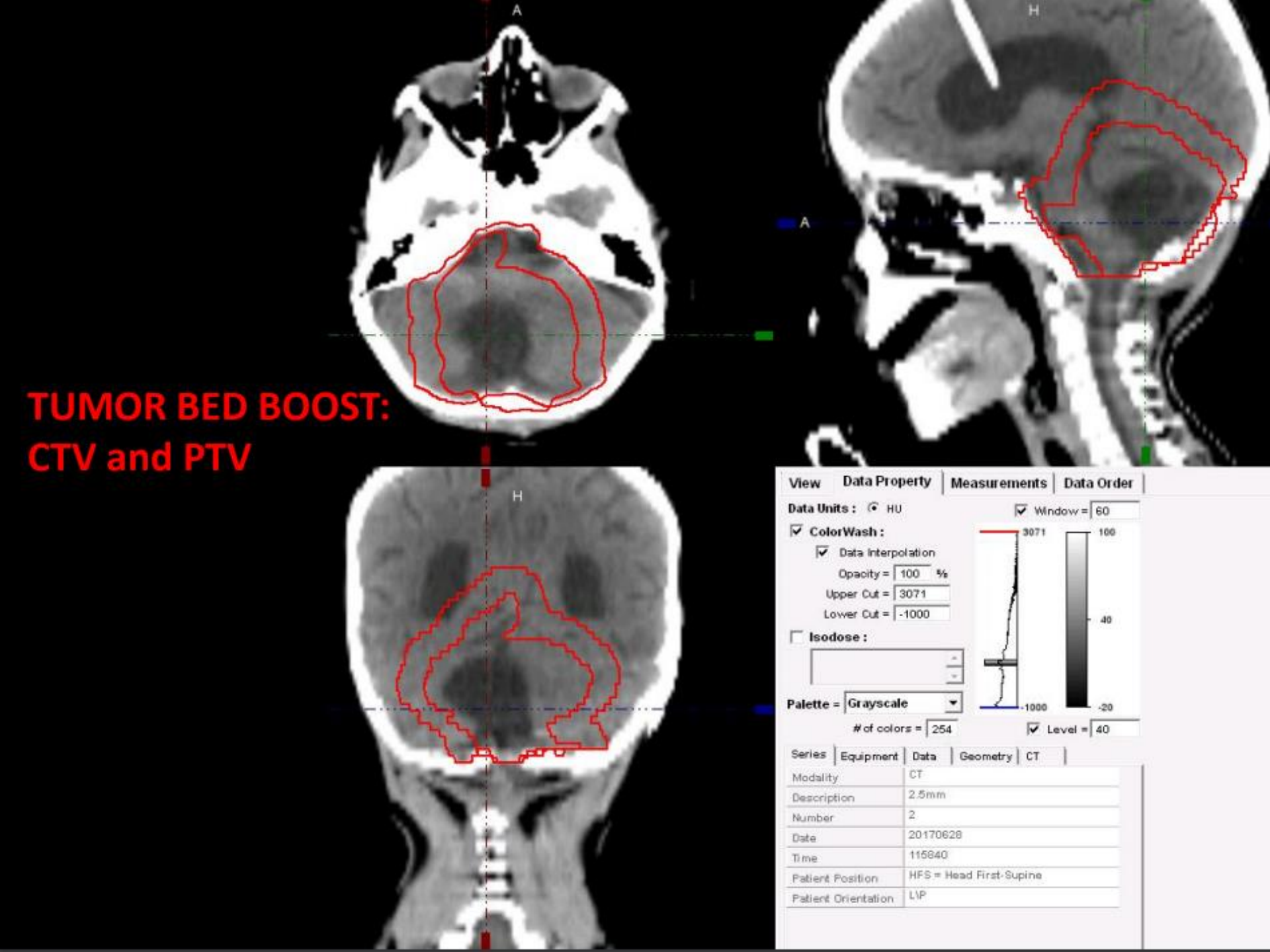



Pt XX: first plan submitted
Pt XX: after first revision

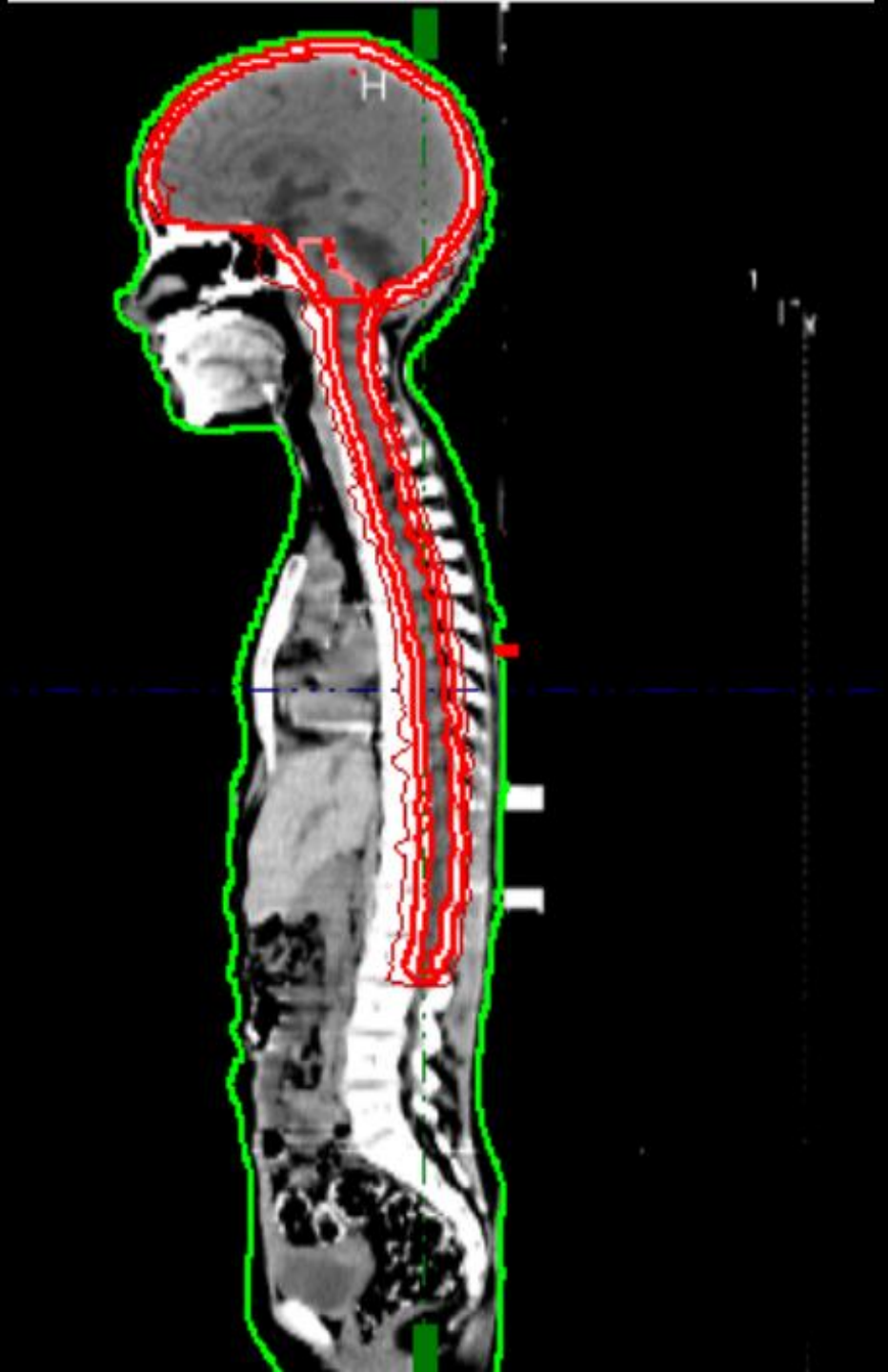
CTV→ PTV


A
R
H
A
H
R
View
Data Property
Measurements
Data Order
Data Units : GY %
Upper Limit = 26.734 Gy
ColorWash :
Data Interpolation
Opacity = 30 %
Upper Cut = 26.734 Gy
Lower Cut = 0.2673 Gy
Isodose (Gy) :
22.23 ,21.06
Palette = Rainbow
# of colors = 254
100.00 % 26.734 Gy
90.02 % 24.065 Gy
80.03 % 21.396 Gy
70.05 % 18.727 Gy
60.07 % 16.058 Gy
50.08 % 13.389 Gy
40.10 % 10.720 Gy
30.12 % 8.051 Gy
20.13 % 5.382 Gy
10.15 % 2.713 Gy
0.17 % 0.044 Gy
Lower Limit = 0.0443 Gy
Series
Equipment
Data
Geometry
RT Dose
Modality RTDOSE
Description TomoTherapy Planned Dose
Number -8571
Date 20170418
Time 105521

TUMOR BED BOOST:
CTV and PTV



UNESPECTED!!!



SIOP PNET 5 MB — **RADIOTHERAPY QUALITY CONTROL**
AIEOP PLAN REVISION FORM

Centre ID 132 **MARVIN ID** GPOH.07869

Dosimetric verifications **Dosimetric aims:** 90 % of prescribed dose to 100 % of PTV
95 % of prescribed dose to 95 % of PTV
107 % of prescribed dose to ≤5 % of PTV

Brain File DVH => ENCEFALO_EclipseDoses_DVH_CT_1_PTVBrain_20170330_144736.txt

95% isodose to **99.3** % of PTV
- (•) Correct
- ( ) Minor deviation (95% isodose between 90 and 95% of PTV)
- ( ) Major deviation (95% isodose to less than 90% of PTV)

Deviation site:
- ( ) Frontal lobe
- ( ) Cribriforme plate
- ( ) Temporal lobe
- ( ) Other:

107% isodose to **0.0** % of PTV
- (•) Correct
- ( ) Minor deviation (107% isodose between 5 and 10% of PTV)
- ( ) Major deviation (107% isodose to more than 10% of PTV)

Deviation site:
- ( ) Frontal lobe
- ( ) Cribriforme plate
- ( ) Temporal lobe
- ( ) Other:

Comments

SIOP PNET 5 MB — **RADIOTHERAPY QUALITY CONTROL**
AIEOP PLAN REVISION FORM

Centre ID 132 **MARVIN ID** GPOH.07869

Dosimetric verifications **Dosimetric aims:** 90 % of prescribed dose to 100 % of PTV
95 % of prescribed dose to 95 % of PTV
107 % of prescribed dose to ≤5 % of PTV

Spine File DVH => ENCEFALO_EclipseDoses_DVH_CT_1_PTVSpine_20170330_144736.txt

95% isodose to **97.1** % of PTV
- (•) Correct
- ( ) Minor deviation (95% isodose between 90 and 95% of PTV)
- ( ) Major deviation (95% isodose to less than 90% of PTV)

Deviation site:
- ( ) Cervical spine
- ( ) Thoracic spine
- ( ) Lumbar spine
- ( ) Other:

107% isodose to **0.0** % of PTV
- (•) Correct
- ( ) Minor deviation (107% isodose between 5 and 10% of PTV)
- ( ) Major deviation (107% isodose to more than 10% of PTV)

Deviation site:
- ( ) Cervical spine
- ( ) Thoracic spine
- ( ) Lumbar spine
- ( ) Other:

Comments

VOLUME 27 · NUMBER 4 FEBRUARY 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Hyperfractionated Accelerated Radiotherapy in the Milan Strategy for Metastatic Medulloblastoma

Lorenza Gandola, Maura Massimino, Graziella Cefalo, Carlo Solero, Filippo Spreafico, Emilia Pecori, Daria Riva, Paola Collini, Emanuele Pignoli, Felice Giangaspero, Roberto Luksch, Serena Berretta, Geraldina Poggi, Veronica Biassoni, Andrea Ferrari, Bianca Pollo, Claudio Favre, Iacopo Sardi, Monica Terenziani, and Franca Fossati-Bellani

Milan protocol

Metastatic medulloblastoma

(and LCA histology since 2/2009)

Surgery

↓

HD-MTX (8g/m²) —>HD-VP16 (2.4g/m²) —> HD-CYCLO (4g/m²) —> CBDCA (800mg/m²)

↓ ↓ ↓ ↓

0 1 4 7 weeks

↓ ↓

+ G-Csf for PBSC harvest

HART 3-4 wks after CBDCA

Arm A. 4 weeks after HART:
VCR (1.4 mg/ m²) any 3 sett x 18
CCNU (80 mg/m²) any 9 sett x 6

.... if CR pre HART

Arm B. 4 weeks after HART:
Thiotepa 900 mg/m² in 3 days for 2 courses (4-6 wks interval)

.... if ED pre HART

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Hyperfractionated Accelerated Radiotherapy (HART)

	Neuraxis	Posterior fossa
	39 Gy	60 Gy
3 - 10 yrs*	31.2 Gy	59.7 Gy
Fractionation	1.3 Gy x 2/day	1.5 Gy x 2/day

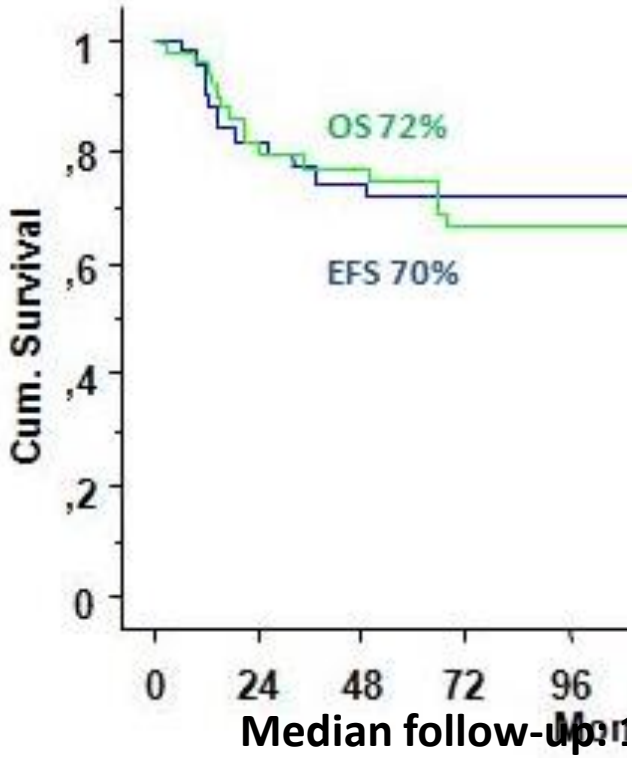
Total treatment days: 22

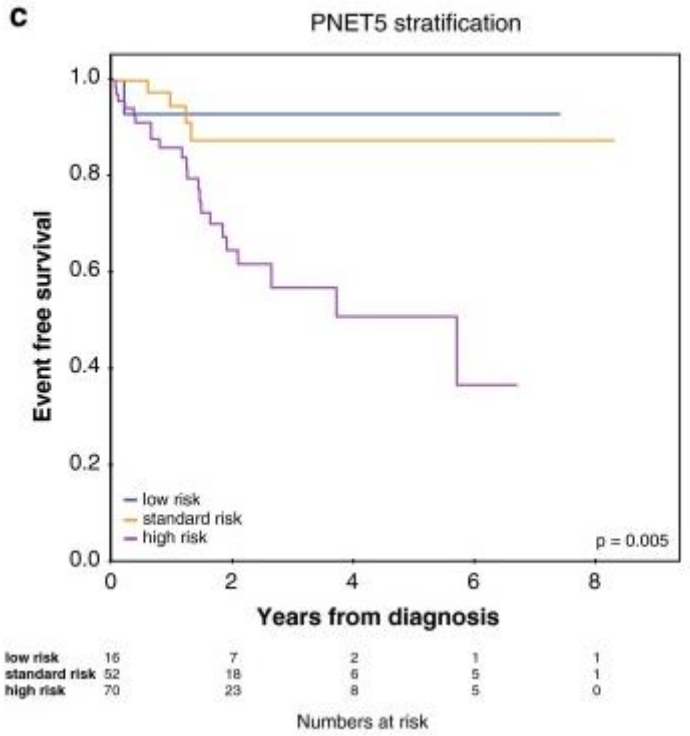
Boost to metastases: 9 Gy in 6 fractions of 1.5 Gy, 3 treatment days

**** If CR or PR before HART***

Milan series of 54 metastatic medulloblastoma patients

EFS and OS were 70%/67% and 72%/64% at 5/10 yrs, respectively





SIOP Brain Tumor Working Group

High Risk Medulloblastoma Study

- **October 2012: active discussion began**
- **“Milan strategy”: experimental arm of the randomized study**
- **April/May 2014: some European Centers reported cases of *unexpected* neurotoxicity and suspended the use of the HART protocol**
- **SIOP PNET WG Meeting in Singapore, July 2014:**

  Decisions:

  - **European survey on grade 3-4 neurotoxicity in all the recent/ongoing clinical trials for HR MBL**
  - **Estimate of total number of patients treated according to the Milan strategy and of number of severe neurotoxicities**
  - **2 days meeting in Milan: 1 day for Radiation Oncologists and Physicists only to collegially review the radiotherapy plans of children showing severe neurotoxicity after combined intensive treatments to highlight possible correlations with radiotherapy technique and dosimetry**

SIOP-Europe Brain Tumor Working Group - High Risk Medulloblastoma Meeting

Radiation Oncologists and Physicists Meeting, Milan 6 November 2014

- **Period of study: 2009-2014**
- **Estimated number of children treated according to the HART strategy: 240**
- **Reported grade 3-4 neurotoxicity : 27 cases**
  - **18 global neuro-functional impairments**
  - **4 myelitis**
  - **5 brainstem/cerebellum radionecrosis**
- **17/27 radiotherapy treatment plans were reviewed and discussed**

SIOP-Europe Brain Tumor Working Group - High Risk Medulloblastoma Meeting

Radiation Oncologists and Physicists Meeting, Milan 6 November 2014

- **Global neuro-functional impairment**
  - **Children younger than 10**
  - **High-dose Thiothepa administered after HART**
  - **No correlation with radiotherapy technique and dosimetry**

Milan series of 60 High Risk Medulloblastoma children:

- **5 severe global neurotoxicity**
- **all 5 children younger than 8 years, all received 2 cycles of HD Thiothepa**
- **3/5 poor neurological conditions after surgery, 2/5 progressive disease**
- **median time to worsening 6 months (6-36 months) after treatment end**
- **worsening reaches a clinical plateau with some improvement**
- **4/5 received CSI 39 Gy only without posterior fossa boost, 1/5 CSI 31,2 Gy with posterior fossa boost**

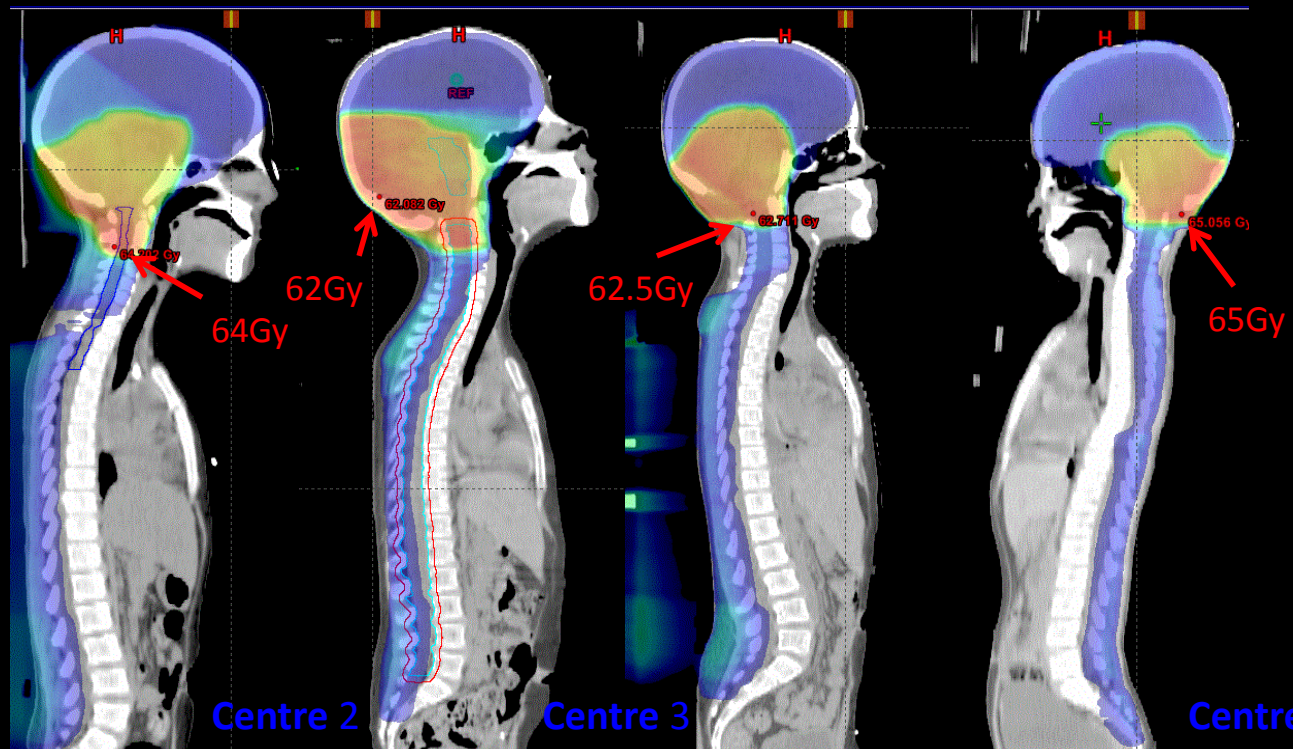
SIOP-Europe Brain Tumor Working Group - High Risk Medulloblastoma Meeting

Radiation Oncologists and Physicists Meeting, Milan 6 November 2014

❑ Myelitis

- **High-dose Thiothepa administered after HART in all cases**
- **Upper cervical cord included in the posterior fossa boost volume**

The summed doses all showed that the hot volumes were at the base of the brain within the head fields.



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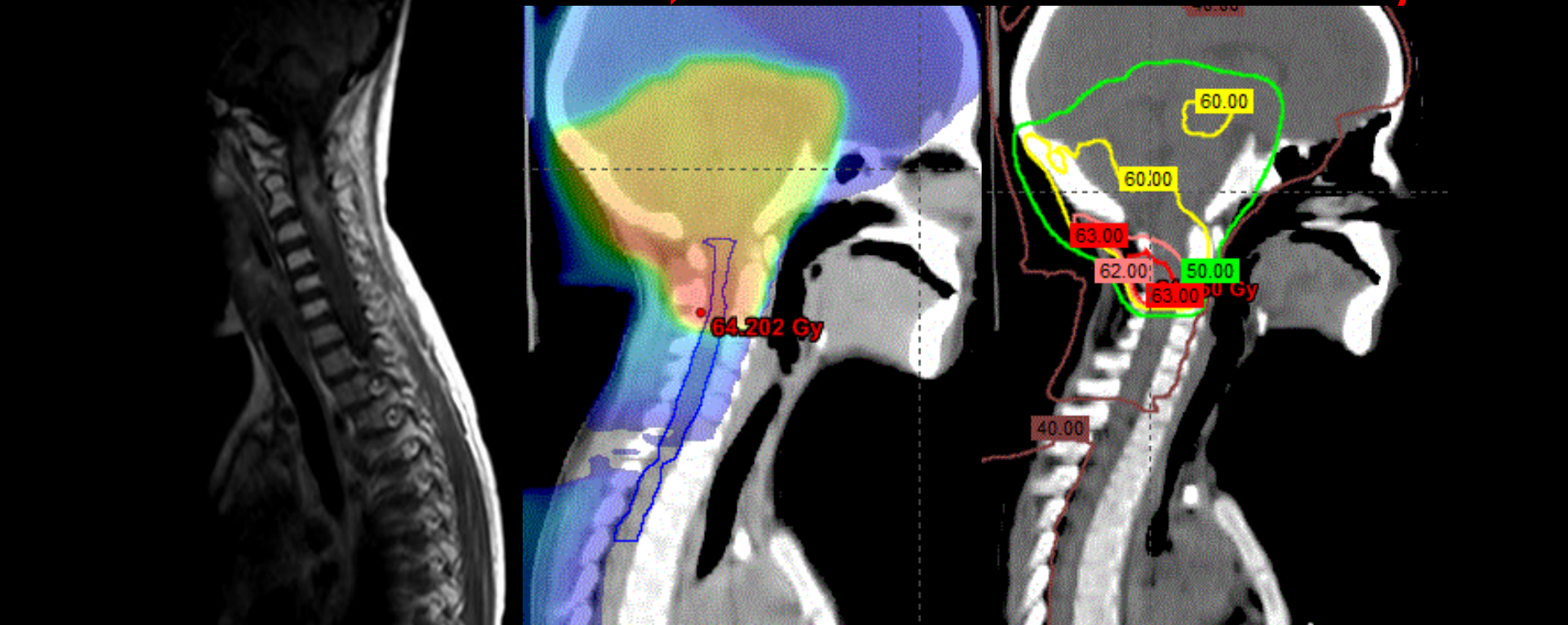
❑ Myelitis

- **High-dose Thiothepa administered after HART in all cases**
- **Upper cervical cord included in the posterior fossa boost volume**

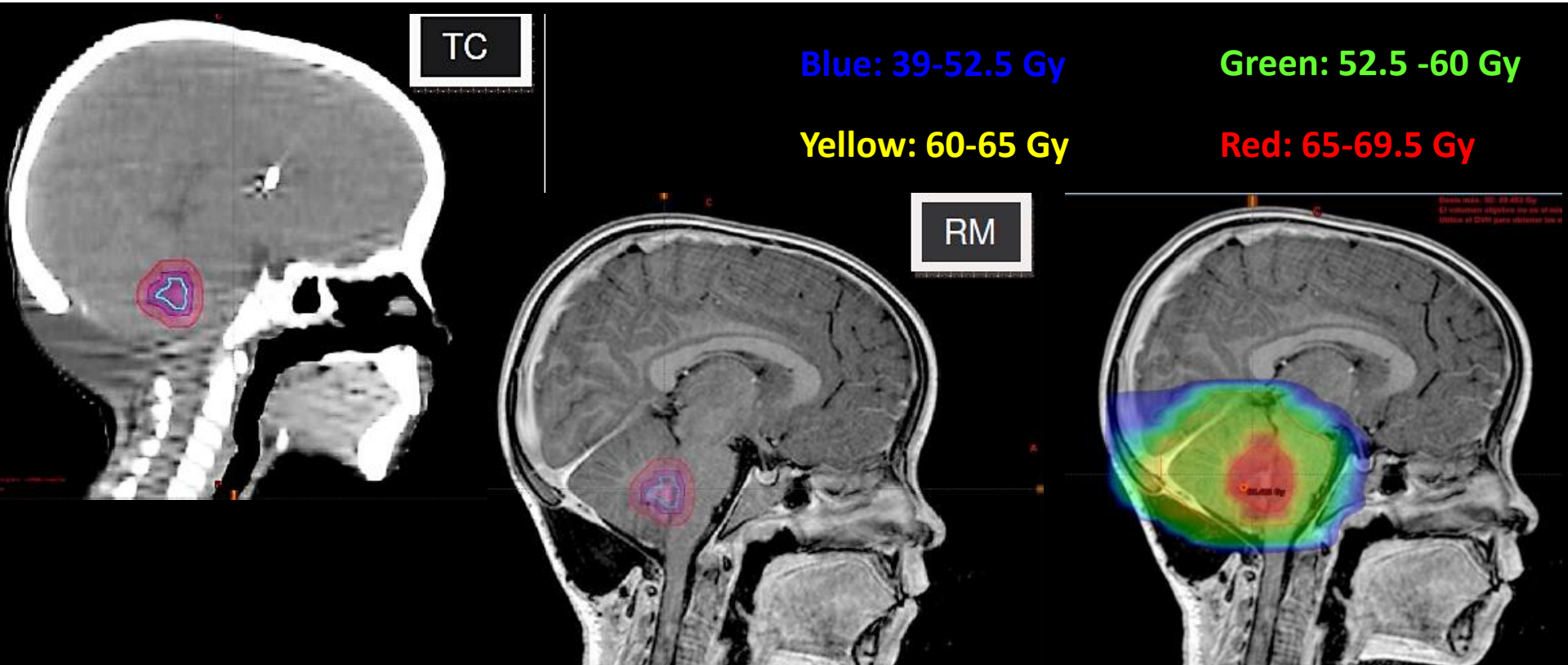
Sum of Phase 1 and Phase 2 ➡ Maximum dose to cord was 63 Gy



SIOP-Europe Brain Tumor Working Group - High Risk Medulloblastoma Meeting

Radiation Oncologists and Physicists Meeting, Milan 6 November 2014

- **Brainstem/cerebellum radionecrosis**
  - **Additional 9 Gy boost to posterior fossa residuum (not contemplated in the original HART approach)**



RIUNIONE PROTONTERAPIA

Torino, 07 giugno 2016

Partecipanti:

Presidente e vice presidente AIEOP	Franca Fagioli, Marco Zecca
Consiglieri CD AIEOP	Maura Massimino, Arcangelo Prete
Segretaria CD AIEOP	Paola Quarello
Componenti GdL AIEOP “Radioterapia”	Giovanni Scarzello, Salvina Barra, Lorenza Gandola, Maurizio Mascarin, Anna Mussano
Centro CNAO Pavia	Francesca Valvo, Alberto Iannalfi
Centro protoni Trento	Maurizio Amichetti, Barbara Rombi, Sabina Vennarini
Presidente AIRO	Elvio Russi

Tutti i presenti concordano che solo stabilendo delle modalità comuni di gestione del paziente, in centri di consolidata alta specializzazione e competenza, sia possibile proporre il trattamento radiante più idoneo, contenendo campagne mediatiche che possano influenzare negativamente l'iter terapeutico.

Il 70-80% dei pazienti è arruolato in protocolli diagnostico-terapeutici nazionali o internazionali che prevedono direttive radioterapiche precise per dose, frazionamento e timing, presupponendo una strettissima collaborazione del team multidisciplinare che ha in carico il paziente.

Sono stati identificati i Centri autorizzati al trattamento mediante questionari di valutazione e visite ispettive sulla base dei criteri di Good Clinical Practice (GCP) e secondo la normativa Europea.

Sono stati anche identificati i professionisti esperti che possono essere coinvolti nel percorso di cura del paziente.

Attualmente nessun protocollo pediatrico è aperto nei due Centri di Protonterapia Italiani, ne consegue che il trattamento con particelle implica l'esclusione del paziente dal protocollo in cui è stato precedentemente arruolato.

In Europa esistono centri in cui il radioterapista pediatrico della struttura di oncoematologia pediatrica, segue il paziente nel centro di protonterapia garantendo la continuità di cura.

ELSEVIER MASSON

ScienceDirect
www.sciencedirect.com

EM|consulte
www.em-consulte.com

Review article

Paediatric brain tumours: A review of radiotherapy, state of the art and challenges for the future regarding protontherapy and carbontherapy

Tumeurs cérébrales pédiatriques : revue de la littérature en radiothérapie, état de l'art et défis pour l'avenir en ce qui concerne la protonthérapie et la carbonethérapie

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Proposta di istituzione di una figura di radioterapista pediatrico esperto che possa svolgere attività di consulenza presso il centro di protonterapia.

Tutelare la prosecuzione del percorso diagnostico-terapeutico all'interno del protocollo.

Promuovere la crescita specifica in ambito pediatrico dei due centri italiani di protonterapia mediante la stipula di una consulenza a costo zero (eventuale copertura delle spese di trasferta da parte di AIEOP) tra il centro di protonterapia ed un radioterapista pediatrico esperto e certificato.