

# Role of Radiation Therapy in Paediatric, Chordoma, Chondrosarcoma and Osteosarcoma



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# Outline

- Childhood cancer – Epidemiology
- Chordoma, Chondrosarcoma
  - Epidemiology, Clinical features
  - Management
  - Radiation therapy –
    - Proton beam therapy evidence
  - Summary
- Osteosarcoma
  - Epidemiology, Clinical features
  - Management
  - Radiation therapy

# Incidence – Pediatric cancers

- Cancer in children occurs with an annual frequency of 13-14 in 1 lakh children upto 15 years
- In India, out of 8 lakh cancers diagnosed annually, about 50,000 are childhood cancers\*

J Indian Aca Oral Med Radiol 2013; 25(2): 126-30

<http://timesofindia.indiatimes.com/city/kolkata/Childhood-cancers-double-in-a-decade/articleshow/18411692.cms> February 2013

# Increasing incidence in India

- Childhood cancers double in a decade
  - According to the Indian Council for Medical Research (ICMR),
    - Decade back, childhood cancers were 2.5% of the total number of cancer cases
    - Today, they add up to 5.5%.

<http://timesofindia.indiatimes.com/city/kolkata/Childhood-cancers-double-in-a-decade/articleshow/18411692.cms>

February 2013

## Significance of childhood cancer

- In India cancer is the 9th common cause for the deaths among children between 5 to 14 years of age
- Of all cancers in India – 1.6% to 4.8% cancers occur in children less than 15 years
- Age standardized incidence rate for India – 38 to 124 per million children per year
- Annual incidence India – 55,000 children diagnosed with cancers

## Common pediatric cancers in India

**TABLE II CHILDHOOD CANCER INCIDENCE IN BROAD CANCER TYPES FOR SIX MAJOR REGISTRIES**

<i>Tumor type in Childhood (0-14 years)</i>	<i>AAR per million</i>	
	<i>Boys</i>	<i>Girls</i>
Leukemia	35.7-61.3	22.3-40.2
Lymphoma	9.9-25.6	2.9-10.1
Central-nervous-system tumor	6.6-19.8	3.0-16.0
SNS tumor	1.5-12.6	1.8-5.3
Retinoblastoma	1.9-12.3	1.3-6.7
Renal tumor	3.1-9.5	1.8-7.0
Hepatic tumor	0.5-2.0	1.0-1.8
Bone tumor	2.8-9.0	2.3-6.2
Soft tissue Sarcoma	2.8-7.2	1.6-7.6
Germ cell tumor	1.3-12.9	0.2-1.3

*AAR : Age-adjusted rates; Source: NCRP report 2009–2011 [4].*

## INCIDENCE CHILDHOOD CANCER

Incidence per million children (under 15 years old) in selected countries categorized by mean per capita gross national income

Country	Cancer incidence	Leukemia incidence	Nonleukemia incidence	Gross National income	Country	Cancer incidence	Leukemia incidence	Nonleukemia incidence	Gross National income
<b>Low-income countries (n = 9)</b>	102	16	85	491	<b>High-income countries (n=9)</b>	130	41	89	32872
Malawi	100.0	1.1	98.9	160	Finland	148.6	47.3	101.3	37460
Uganda	183.5	10.3	178.2	280	United Kingdom	118.2	38.6	79.6	37600
Zimbabwe	111.2	22.8	88.4	340	Japan	107.6	35.5	72.1	38980
Mali	77.4	4.0	73.4	380	Sweden	149.4	45.6	103.8	41060
Nigeria	71.2	8.6	62.6	560	USA	137.9	43.1	94.8	43740
Vietnam	108.4	33.4	75.0	620	Iceland	109.0	37.2	71.8	46320
Papua New Guinea	100.0	8.1	91.9	660	Denmark	149.3	47.2	102.1	47390
Pakistan	100.0	40.5	59.5	690	Switzerland	139.5	43.8	95.7	54930
India	64.4	19.2	45.2	730	Norway	143.2	44.0	99.2	59590

Incidence data are from the International Agency for Research on Cancer.

Low-income country (LIC): the mean per capita annual income in 2005 is less than US \$825;

high-income country (HIC): the mean per capita annual income is more than \$10,065.

Annual per capita figures in US dollars. Gross national incomes were taken from the world development indicators database of the World Bank for 2005.

Kaposi sarcoma accounted for 68.5 nonleukemia cancers per million per year in Uganda and 10.7 in Zimbabwe.

# Chordoma and chondrosarcoma in children

- Chordomas and Chondrosarcomas are uncommon tumours, diagnosed rarely in children
- Chordomas are slow-growing tumours that can metastasize, but more frequently pose a significant challenge to local control (LC) because of their location.



# Chordomas

- Chordomas (CHs) - rare, primary bone tumours that originate from remnants of the notochord
- During the embryologic period, the notochord is replaced by the bony and cartilaginous structures of the axial skeleton
- However, remnants can be entrapped by bone, particularly in the clivus, spine, and sacrum
- Account for 1% to 4% of all bone malignancies

# Chordomas - Incidence

- The Surveillance, Epidemiology, and End Results (SEER) data from a population-based study suggest
- Incidence - 0.08/100 000, with a predominance in men and a peak incidence at the age of 50 to 60 years
- Rarely affect children with <5% of all CHs arising in patients younger < 40 years
- Represent only 0.1% to 0.2% of all cranial malignancies in childhood

# Chordomas

- The tumour sites seem to be almost equally distributed between the base of the skull and the mobile spine
- Even though they generally arise in the midline, more-lateral CHs may develop, especially in the parasellar region or petrous bone

# Chordomas

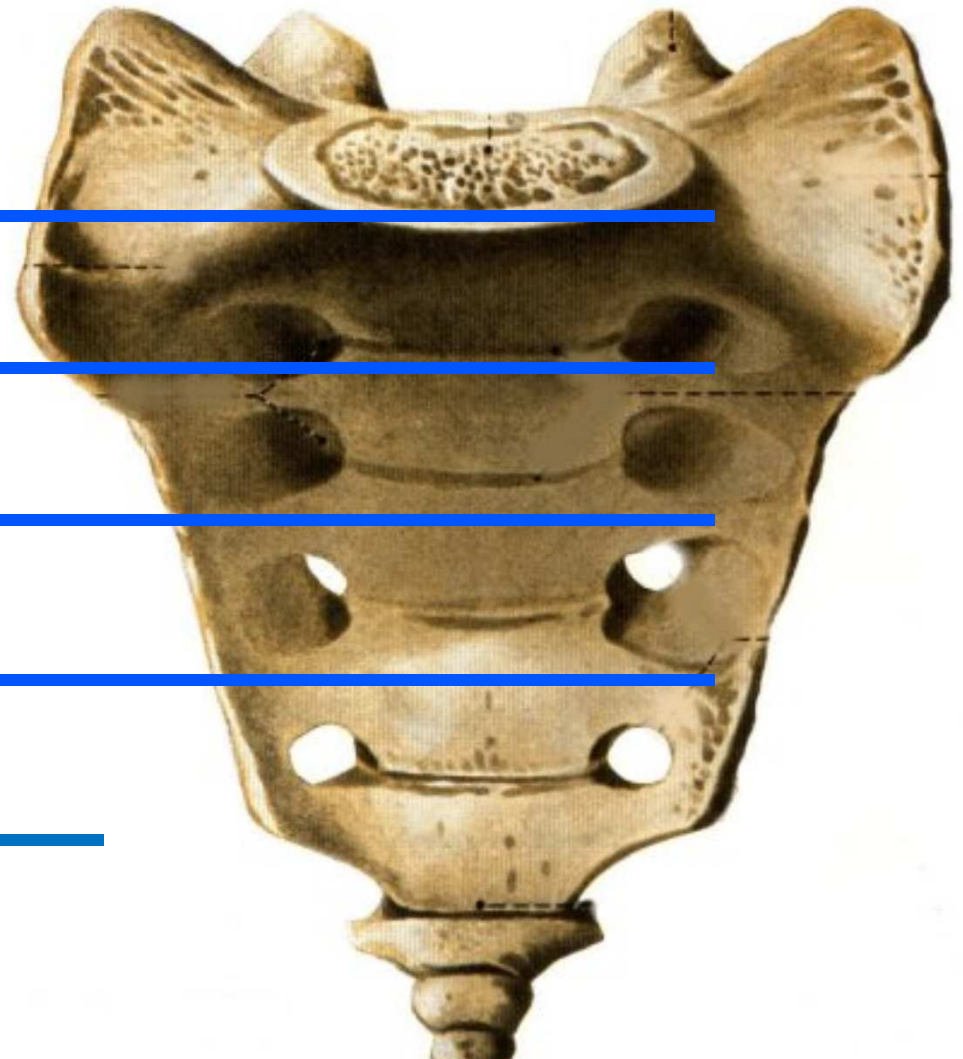
- Because CHs are locally aggressive and often invasive lesions, patients usually present with symptoms originating from local pressure being site specific rather than tumour specific
- Typical tumour sites are the clivus, vertebra, and the sacrococcygeal bone
- In most children, the tumour arises in the skull base
- Cranial CHs often arise from the clival body. The patient may present with headaches and diplopia because of unilateral or bilateral abducens nerve palsy

# Chordomas - Symptoms

- A CH of the clivus may extend into the nasopharynx, resulting in nasal obstruction, epistaxis, or dysphagia
- In clival tumors with superior extension, endocrinopathies or compression of the chiasm and visual impairment may be observed
- Inferior clival tumours may compress the brainstem or involve the foramen magnum, which can induce caudal cranial nerve dysfunctions or life-threatening emergencies
- CHs of the spine and sacrum can present with pain or radiculopathy related to the respective level at which they occur
- Bladder and bowel dysfunction can happen

## Sacral Chordoma : Level of Invasion

L5	10
S1	29
S2	29
S3	9
S4~	7
Post op rec	11



More than 70 % were S2 or higher level lesions

# Chondroma

- Maximal surgical resection is the mainstay of therapy, but complete resections are difficult to achieve
- For patients with chordoma, adjuvant RT is generally advocated because of the poor prognosis in those who recur.
- There is no effective role of chemotherapy in chordoma.

# Chondrosarcoma

- Chondrosarcoma (CS), although less aggressive, is also challenging to manage in the pediatric population
- Behave quite similar to the CHs
- Sometimes, distinguishing CSs from CHs is challenging when looking at clinical, radiologic, and histopathology features only
- CSs are malignant tumours that characteristically produce cartilage with ossification in a myxoid matrix



# Chondrosarcoma

- A CS shows local aggressiveness and has a high risk for recurrence
- Treatment concept is similar to that for CHs, requiring challenging surgical procedures and high-dose radiation therapy
- Many of the available studies investigated both CHs and CSs
- The CSs may have a slightly more-favorable outcome than CHs do

# Chondrosarcoma

- Maximum safe tumour resection is considered the treatment of choice followed by high dose radiotherapy
- Adjuvant RT is commonly employed, although it has been difficult to administer adequately high doses of radiation with older techniques
- Protons has repeatedly demonstrated its ability to control this disease safely and more effectively than photon techniques at doses of 70-76 Gy (RBE)

# Osteosarcoma:Epidemiology

- Osteosarcomas are primary malignant tumours of bone that are characterized by the production of osteoid or immature bone by the malignant cells
- Osteosarcomas account for approx. 3 % of childhood cancers overall
- Most common primary bone tumour affecting children and young adults
- Osteosarcomas comprise 56 % of all bone cancers in individuals < 20 year age, while Ewing sarcoma accounts for 34 to 36 %, and chondrosarcomas are responsible for less than 10 %

# Osteosarcoma: Epidemiology children

- In children, the peak incidence is between 13 and 16 years of age- rapid skeletal growth
- more common in boys than in girls, and in blacks compared to Caucasians
- Most common sites of osteosarcoma in children are the metaphyses of long bones, especially the distal femur (~60-75 %), proximal tibia, and proximal humerus

# Osteosarcoma: Clinical features

- The majority of patients with osteosarcoma present with localized pain, typically of several months' duration
- The most important finding on physical examination is a soft tissue mass, which is frequently large and tender to palpation
- 10 and 20 % have demonstrable metastatic disease at presentation, most often involving the lung.

# Osteosarcoma: Role of radiotherapy

- conventionally osteosarcoma is believed to be relatively resistant to radiation therapy.
- Also concerns of long term effects and development of secondary malignancies.
- Radiation is indicated in unresectable or incompletely resected osteosarcoma.

# Indications for radiation

- To improve local control in the era of limb sparing surgery- close or positive margins.
- Difficult sites: Skull, spine and pelvis- radical resection is not possible.
- Local control rates vary between **20-70%** in various series.
- Emerging role for extra-corporeal radiation in limb salvage.
- Current strategy- **high dose (66-70Gy)** and **high LET** radiation- PROTON BEAM THERAPY.

# Indications for radiation

- Prophylactic whole lung radiation has been used in an attempt to improve outcomes following surgery for non-metastatic localized disease; however, it is not effective in the absence of systemic chemotherapy
- Furthermore, in patients treated with effective surgery and chemotherapy, adjuvant radiation does not improve survival and increases the risk for secondary tumours; it should be considered only in the setting of an unresectable or incompletely resected primary tumour



# Radiotherapy in childhood tumor

- Tremendous progress in the field of pediatric oncology has been made over the past 2 decades, and currently over 70% of children diagnosed with cancer will be cured of their disease
- Radiotherapy is an integral component in the curative treatment of many childhood tumours

# Radiotherapy in childhood tumor

- Unfortunately, radiation exposure is a major contributor to treatment related late morbidity for long-term survivors
- Children are particularly susceptible to the late effects of radiation, even at low doses, as demonstrated in epidemiologic studies of exposed populations

# Radiotherapy in childhood tumour

- Reasons include the sensitivity of developing and growing tissues, the longer life expectancy resulting in a larger window of opportunity for expressing radiation damage, and the large number of long-term survivors
- Several approaches have been used to decrease the morbidity of radiation delaying radiation using chemotherapy or surgery to avoid or reduce the dose of radiotherapy
- Despite these approaches, many children require radiation and remain at high risk for developing a multitude of serious long-term sequelae

# Radiation therapy options

- Multiple options for radiation delivery, including
- three dimensional conformal photon radiotherapy (3DCRT),
- intensity modulated radiation therapy (IMRT), and
- proton beam radiotherapy (PT)

Rombi et al., J Nucl Med Radiat Ther 2013, 4:4

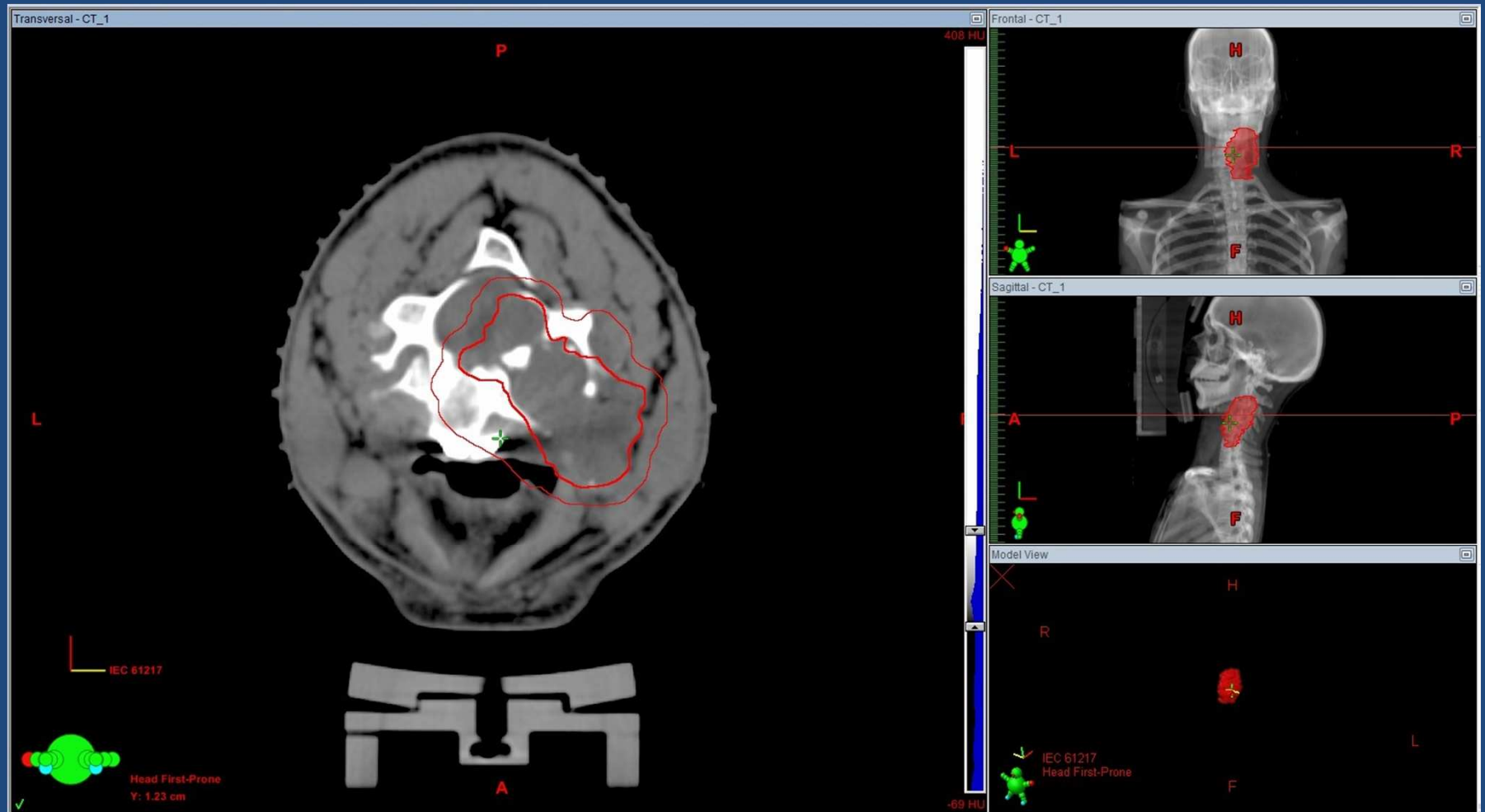
# Conventional RT: Chordoma

- Conventional two or three dimensional RT techniques using photons have a significant risk of damaging the brainstem and cranial nerves, and the lower doses historically used with these techniques have been associated with a high rate of local recurrence and treatment failure
- Limitations of photon therapy in the treatment of chordomas are illustrated by a series of 48 patients (20 with skull base lesions), 44 of whom had macroscopic disease following surgery
  - The local control rate with conventional photon radiation was only 27 percent, although 85 percent of patients achieved useful and prolonged palliation of pain. The median survival was 62 months.

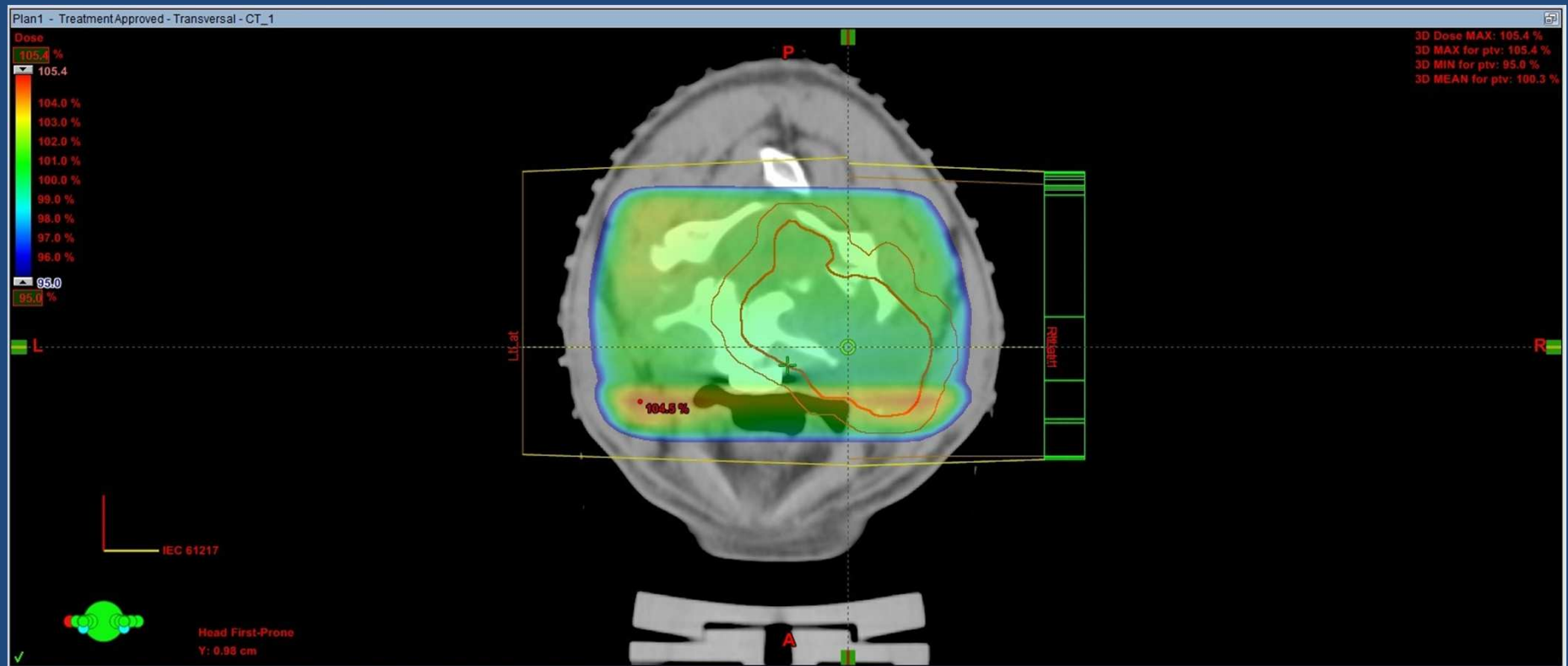
# **The Role of Irradiation in the Treatment of Chordoma of the Base of Skull and Spine**

Maurizio Amichetti, Dante Amelio, Barbara Rombi,  
Stefano Lorentini and Mariangela La Macchia  
*ATreP - Agenzia Provinciale per la Protonterapia  
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# Chordoma GTV

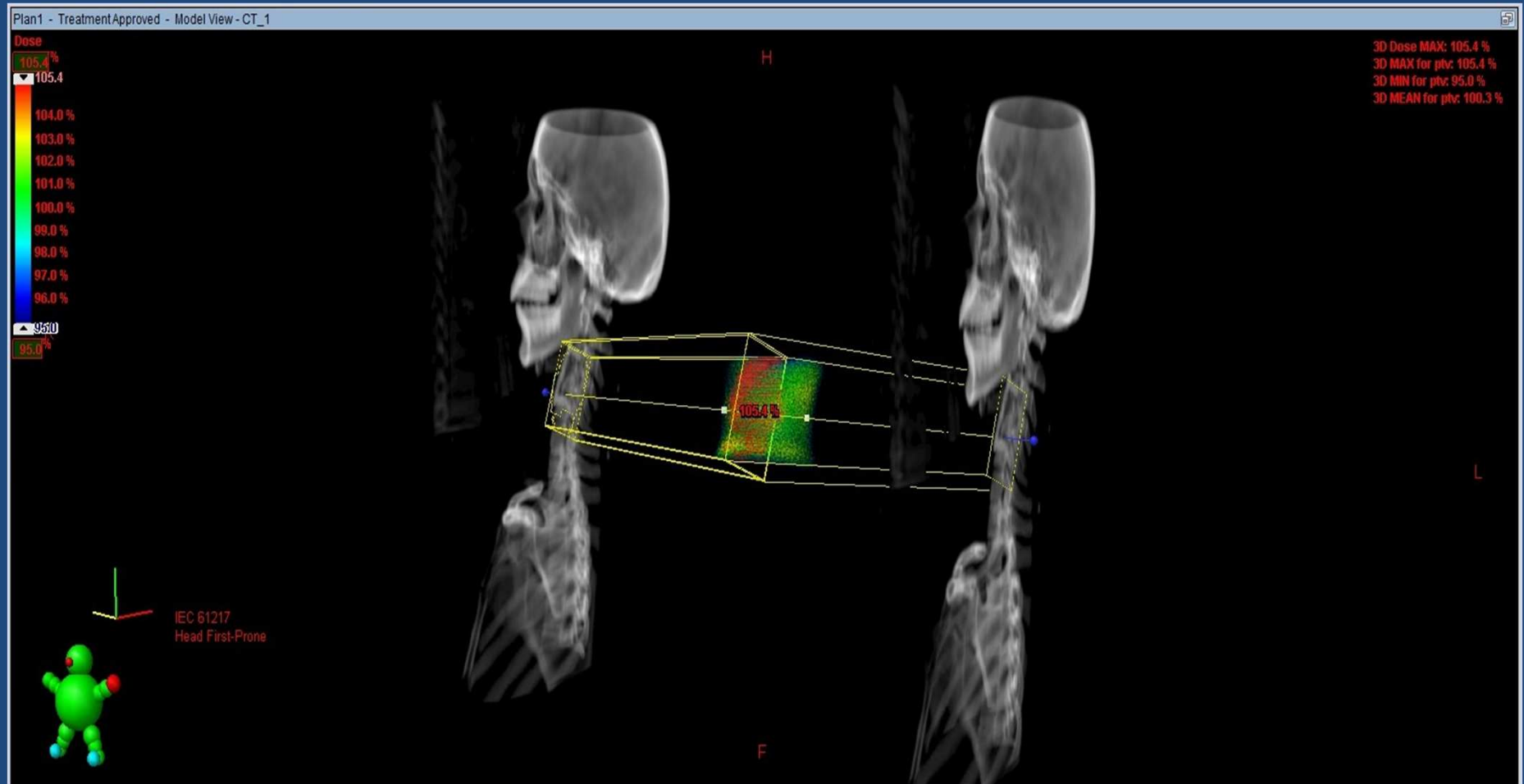


# Chordoma Dose Wash

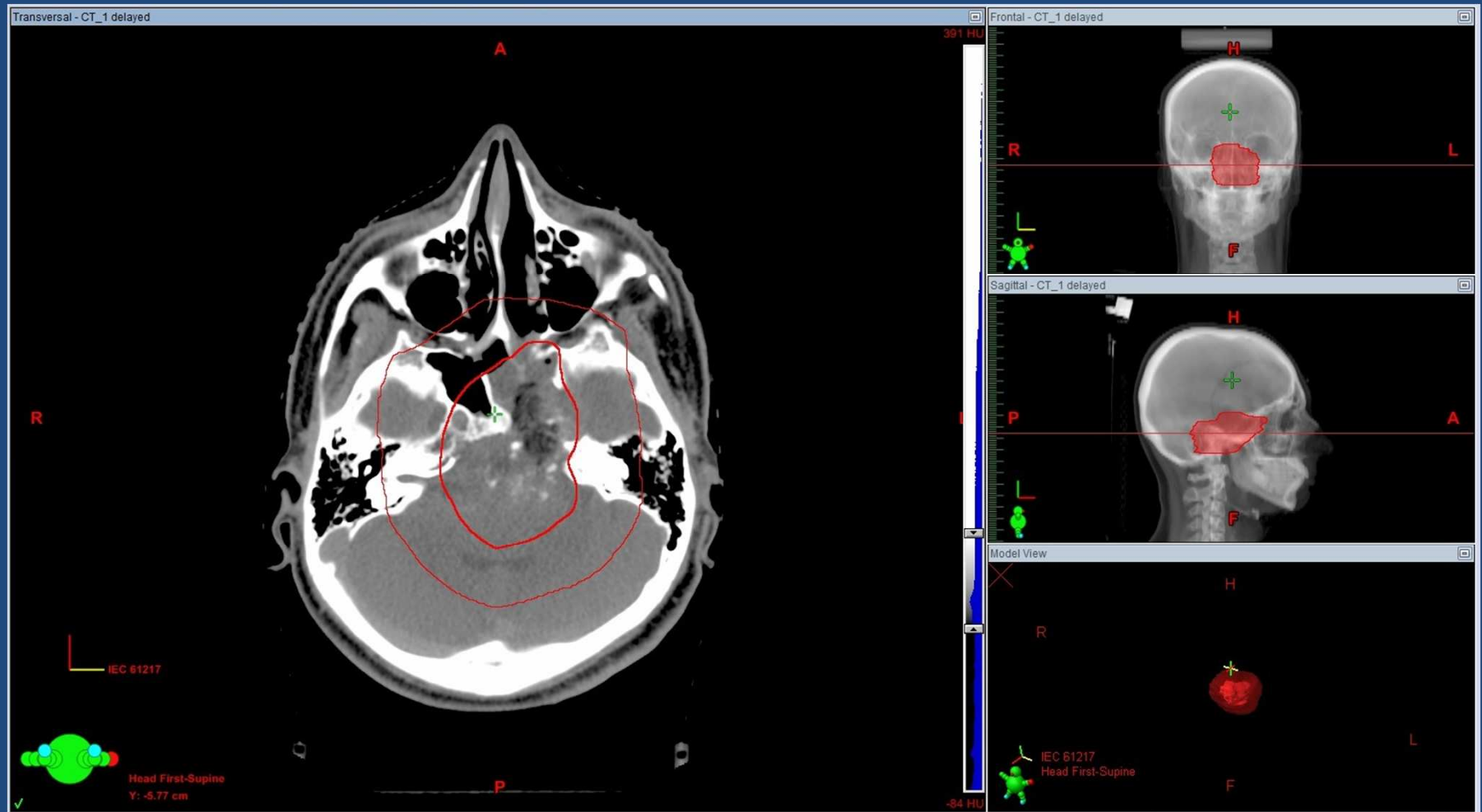




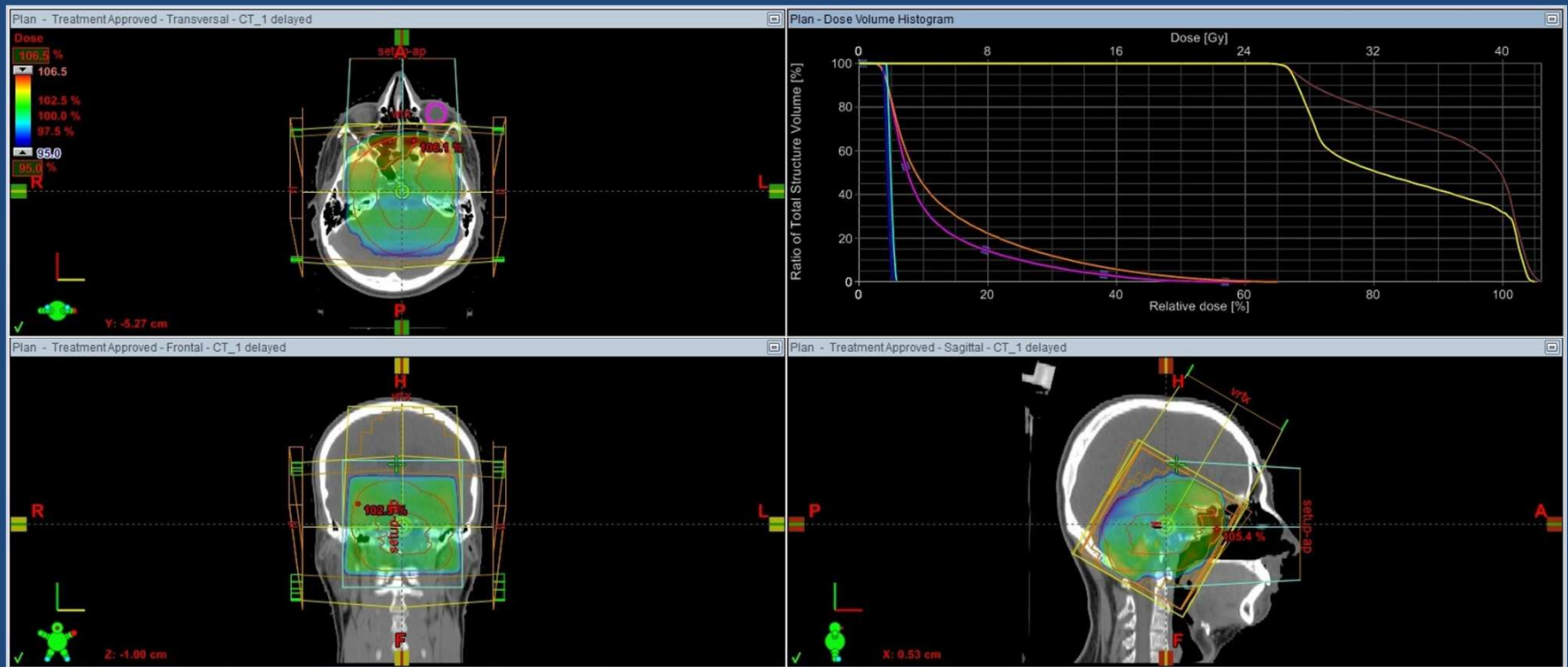
# Chordoma BEV



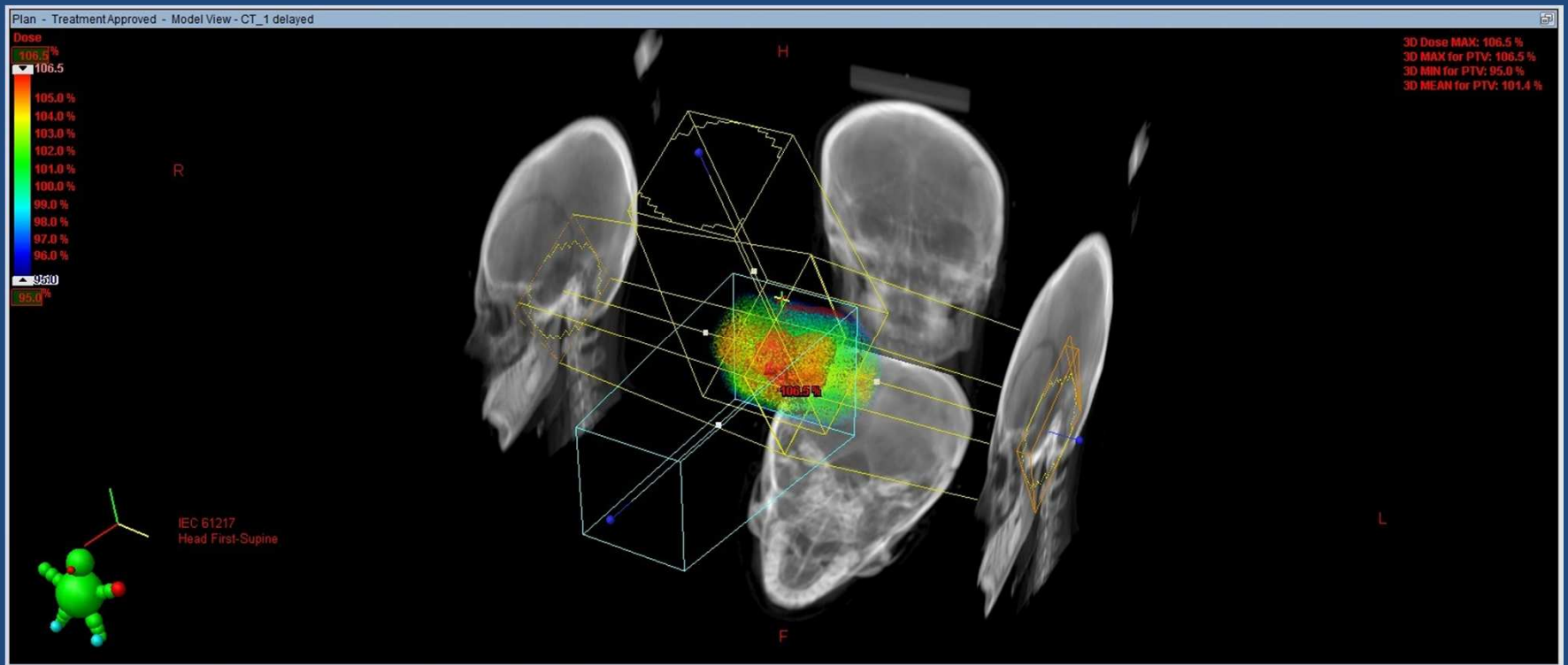
# Clival Chordoma GTV



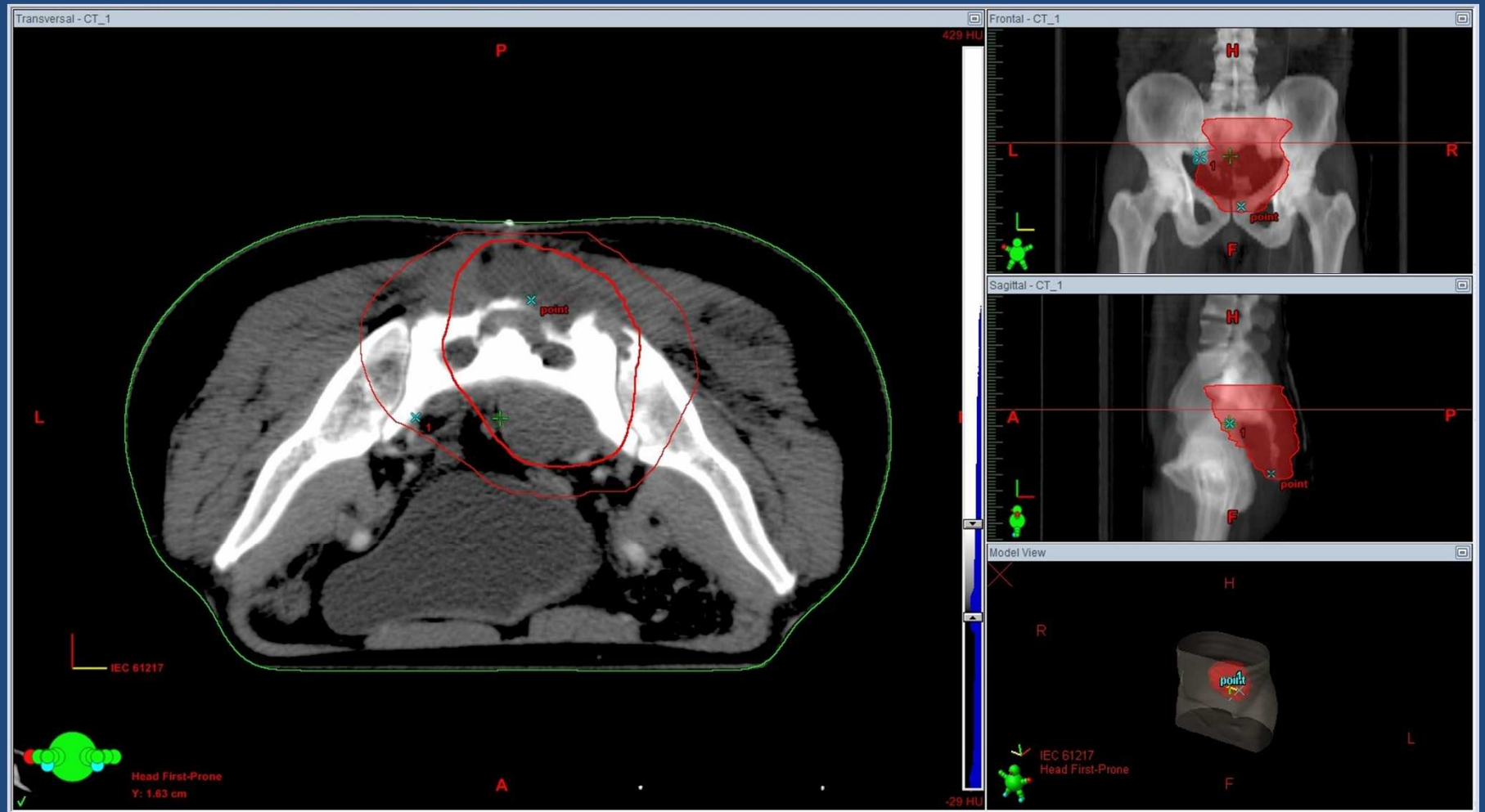
# Clival Chordoma Composite



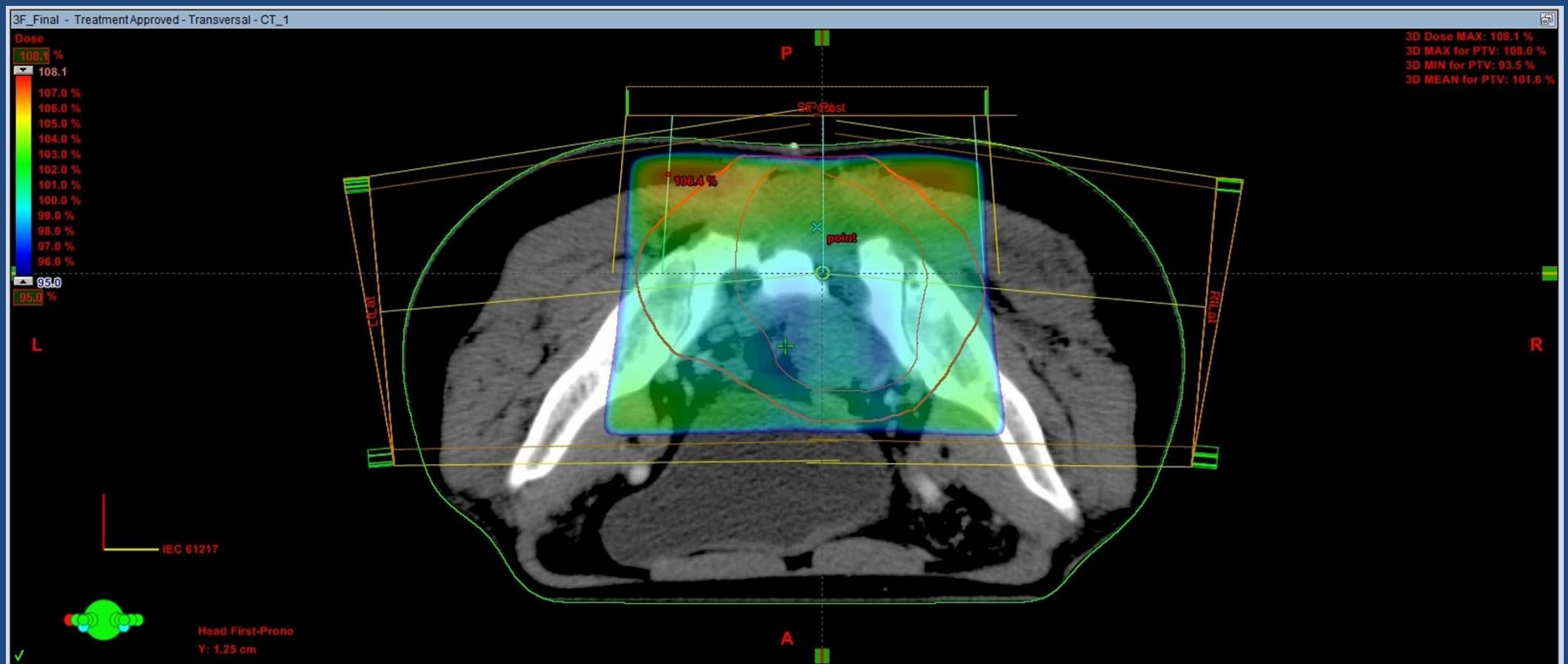
# Clival Chordoma BEV



# Sacral Chordoma GTV

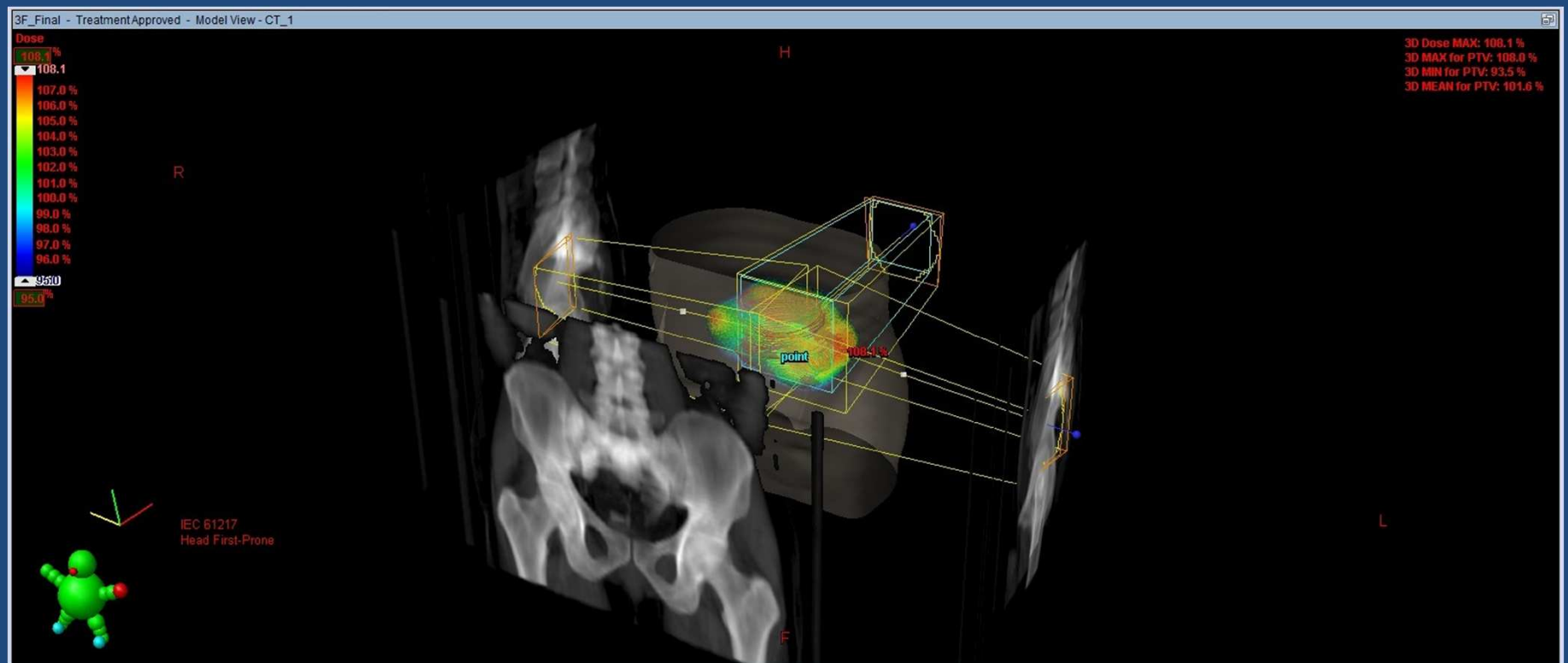


# Sacral Chordoma Dose Wash

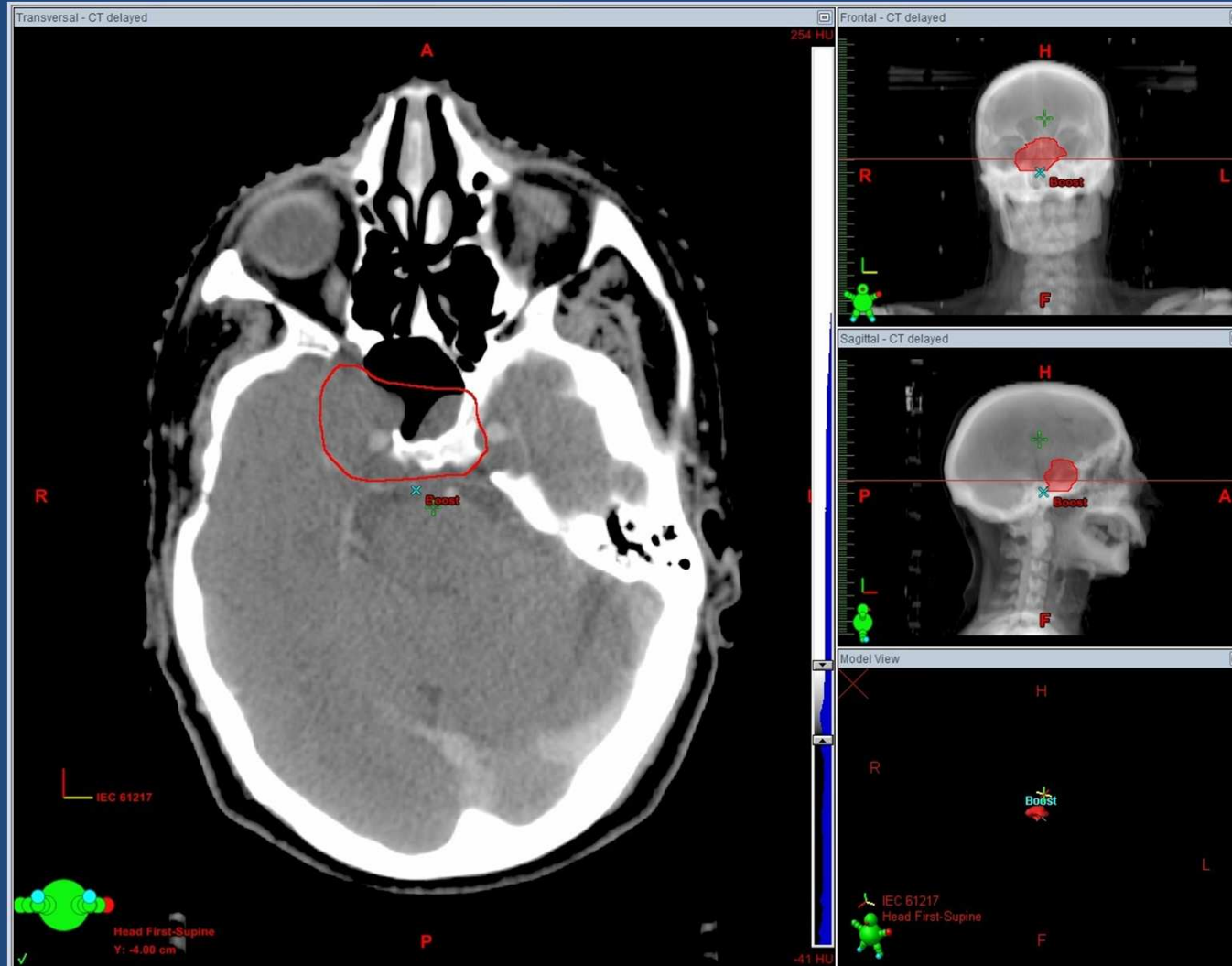




# Sacral Chordoma BEV

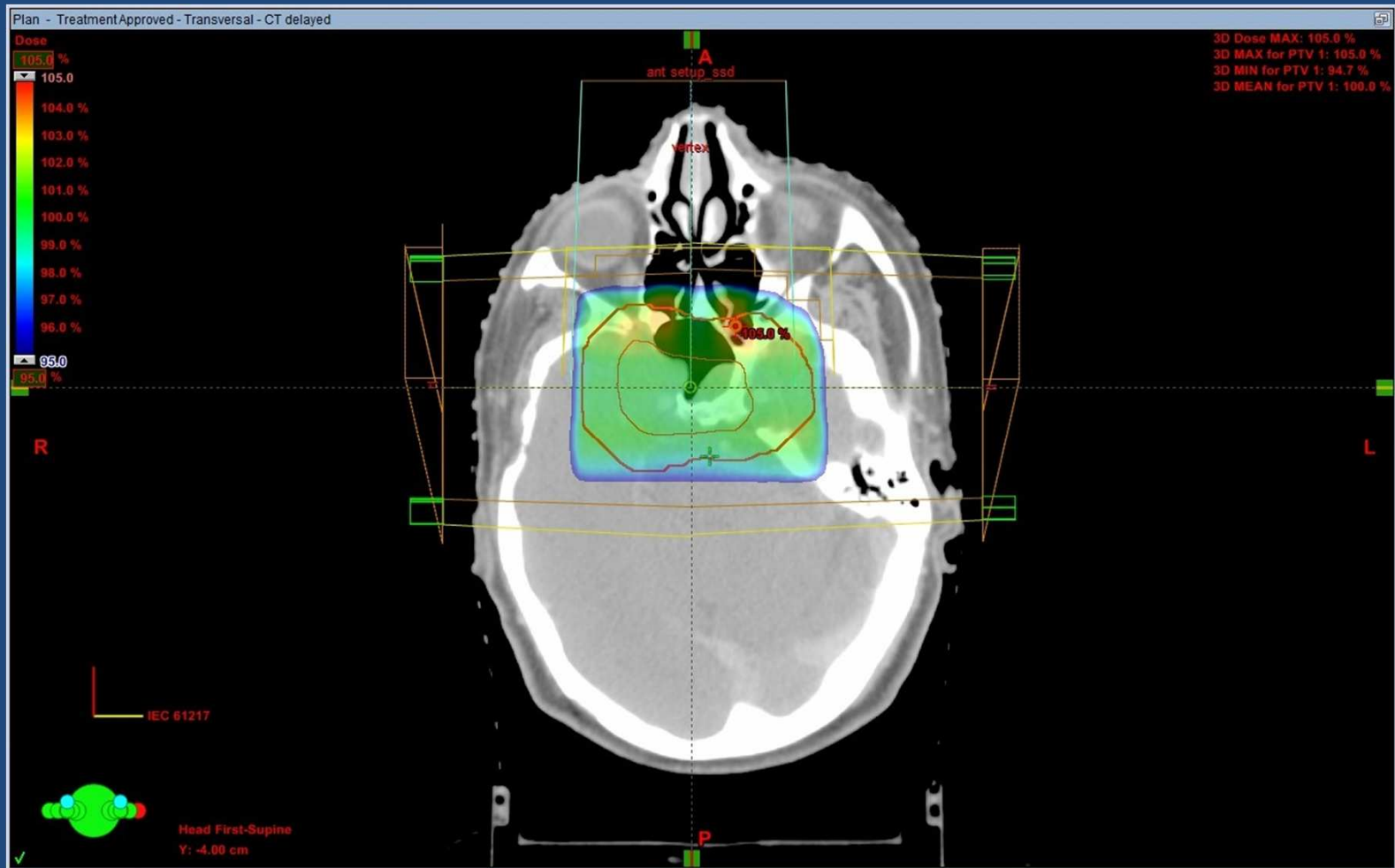


# Suprasellar Chordoma GTV

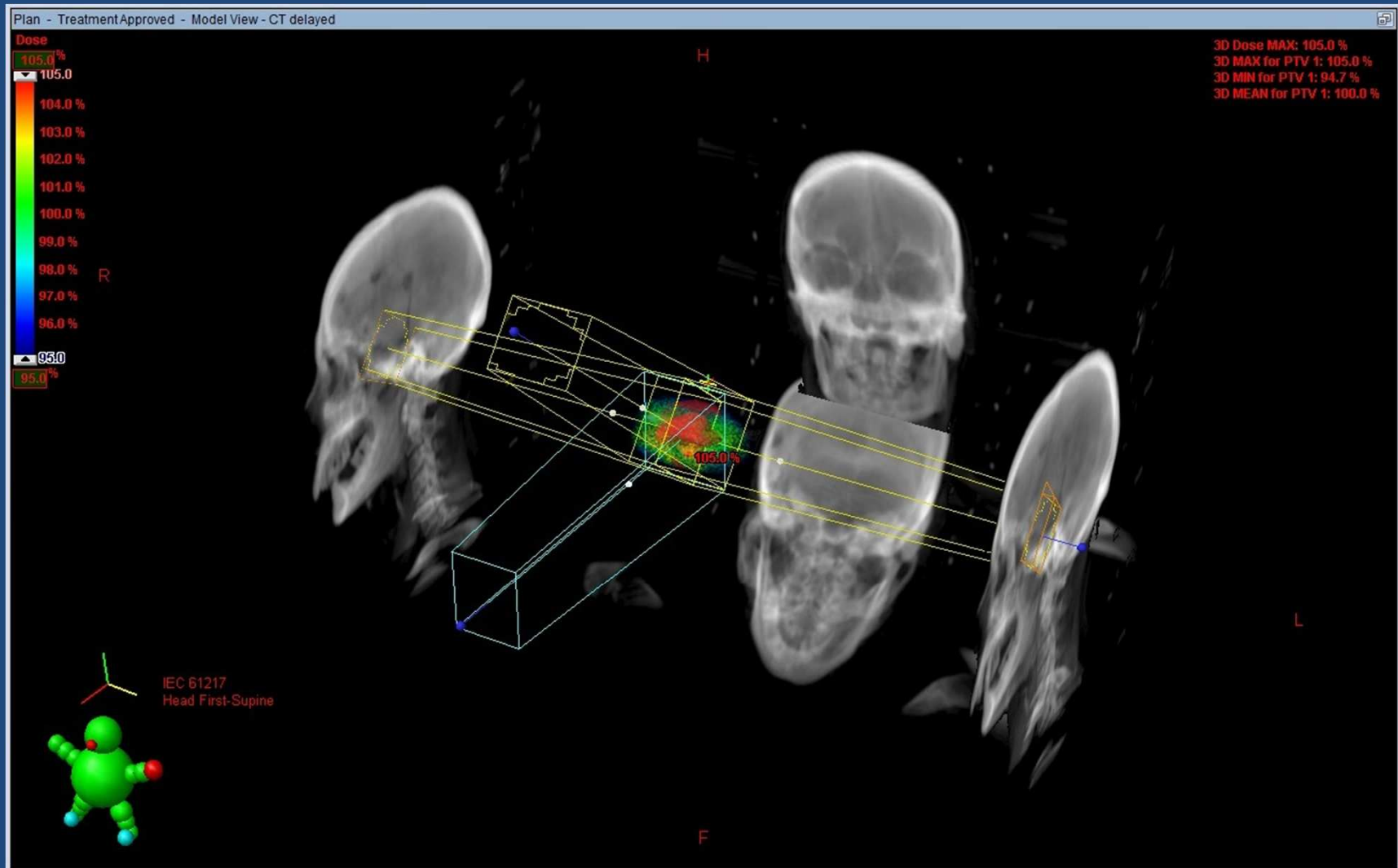




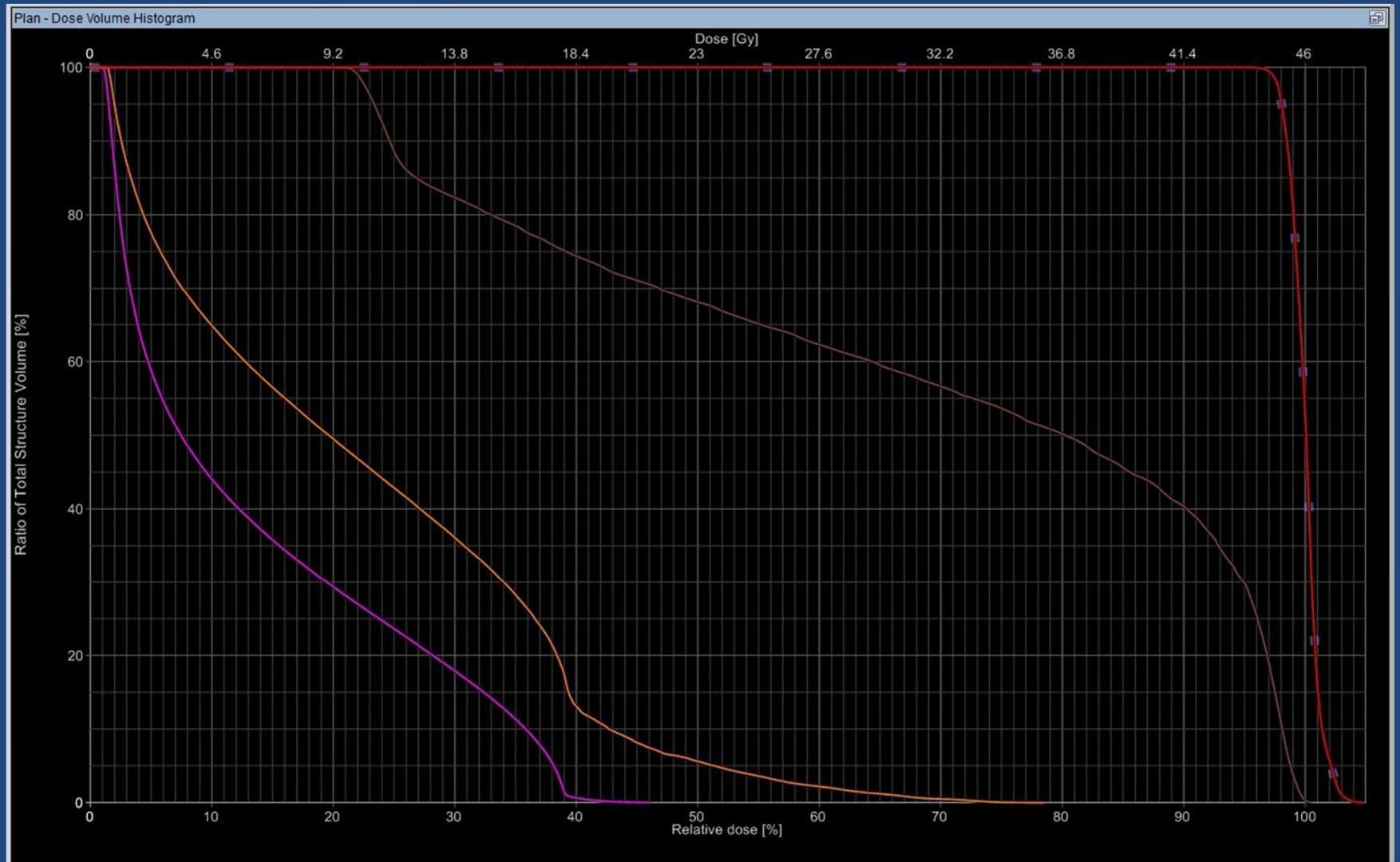
# Suprasellar Chordoma Dose Wash



# Suprasella Chordoma BEV



# Suprasellar Chordoma DVH



## Newer radiation techniques: Chordoma

- High dose focused radiation delivery techniques with particles (primarily protons) or photons (stereotactic radiosurgery [SRS], stereotactic radiation therapy [SRT], and intensity modulated radiation therapy [IMRT]) have allowed for higher doses of RT to be delivered to the tumor while sparing surrounding structures
- The most extensive data comes from proton beam therapy, but there are no randomized trials comparing these different contemporary techniques, and the advantages of proton beam therapy are primarily theoretical and anecdotal



# Proton Beam Therapy for Pediatric Chordomas: State of the Art

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<sup>2</sup>Clinic for Particle Therapy, West German Proton Therapy Center Essen (WPE), University Hospital Essen, Germany

## Abstract

Chordomas are a rare form of primary bone tumors arising from clivus, vertebra, and sacrum. Although it usually occurs in adults, children can be affected too. Multidisciplinary treatment is required and is particularly challenging because the chordoma's proximity to critical structures creates a high risk for significant adverse events. Standard procedure consists of extensive surgery followed by high-dose radiation therapy in excess of 70 Gy. Proton beam therapy has become one of the standard procedures to achieve high, local intensity while maximally sparing normal tissue in adults and children. Results achieved so far are promising and are superior to what has been achieved with surgery alone or conventional radiation therapy. When compared with modern photon radiation techniques, such as intensity-modulated radiation therapy, proton beam therapy may be of particular interest for children to provide high conformality while reducing the irradiated volume and therefore potentially minimizing the risk for secondary cancer induction. The role of chemotherapy remains to be defined.

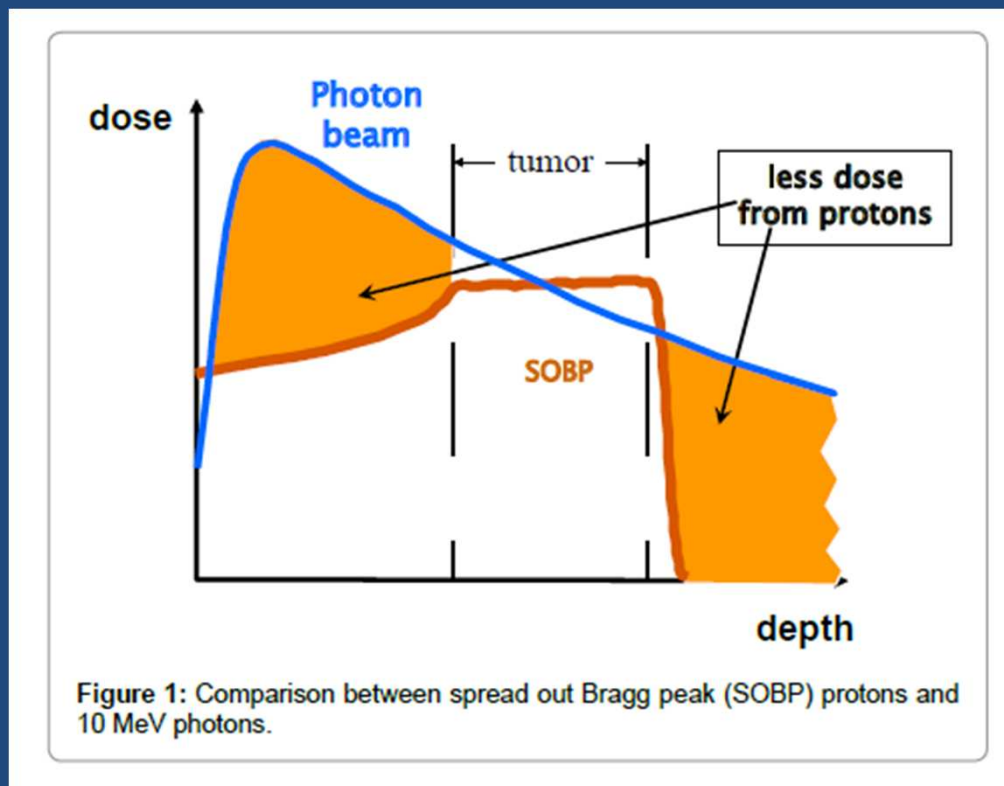
# Proton beam therapy

- Dosimetric studies continue to show the benefits of PT over these photons techniques and as a result, medical centers around the world are working to open more facilities and improve patient access
- Proton radiation therapy is a high-precision form of irradiation which enables optimal coverage of the tumor while maximally avoiding non-target tissues. As a result of its physical favorable characteristics, PT can treat the target with high homogeneity and conformality while relatively sparing the surrounding organs at risk (OAR); this dosimetric advantage should translate to reduced toxicity and a decreased incidence of radiation-induced secondary malignancies.

Rombi et al., J Nucl Med Radiat Ther 2013, 4:4

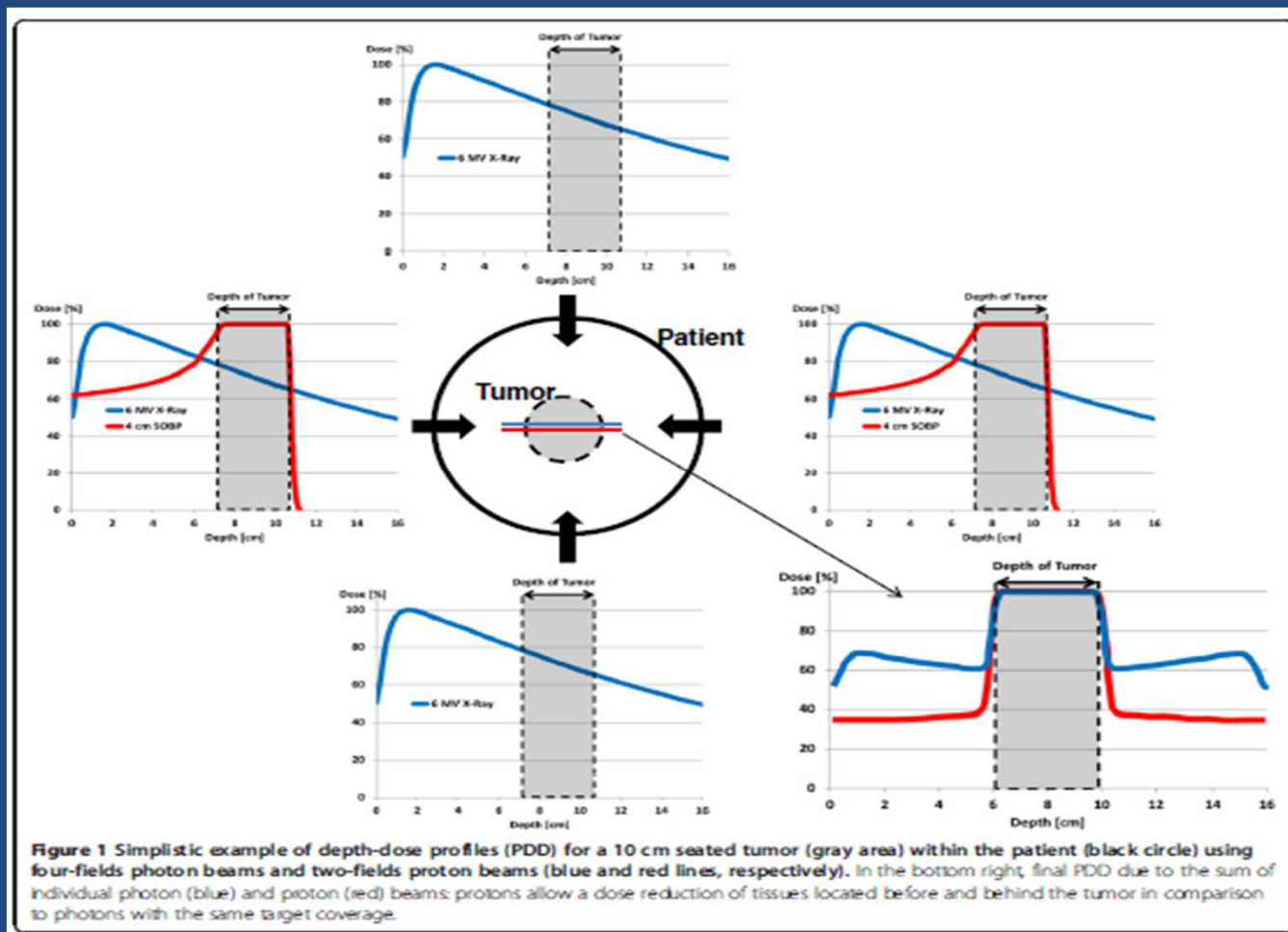


# Proton beam therapy



Rombi et al., J Nucl Med Radiat Ther 2013, 4:4

# Proton beam therapy





# Charged particle RT: Chordoma

- Charged particle RT - Proton beam RT is the most widely used charged ion technique. This approach appears to be more effective than earlier use of conventional photon RT with lower doses of radiation:
- Chordomas - A systematic review of the literature in patients with chordomas analyzed seven retrospective studies that included a total of 416 patients who were treated either with protons or with a combination of protons plus photons
- The radiation doses and schedules varied within and between series, but generally the total radiation dose was 70 Gy equivalents or higher. Clinical outcomes were available for all patients with a minimum follow up of two years. At a median follow up of 46 months, the five year local control and overall survival rates were 69 and 80 percent, respectively.

## Clinical Study

# Mesenchymal Chondrosarcoma in Children and Young Adults: A Single Institution Retrospective Review

Michael W. Bishop,<sup>1,2</sup> Jessica M. Somerville,<sup>3</sup> Armita Bahrami,<sup>4</sup> Sue C. Kaste,<sup>1,5,6</sup> Rodrigo B. Interiano,<sup>7</sup> Jianrong Wu,<sup>8</sup> Shenghua Mao,<sup>8</sup> Frederick A. Boop,<sup>9</sup> Regan F. Williams,<sup>7</sup> Alberto S. Pappo,<sup>1</sup> and Sandeep Samant<sup>3</sup>

<sup>1</sup> Department of Oncology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, USA

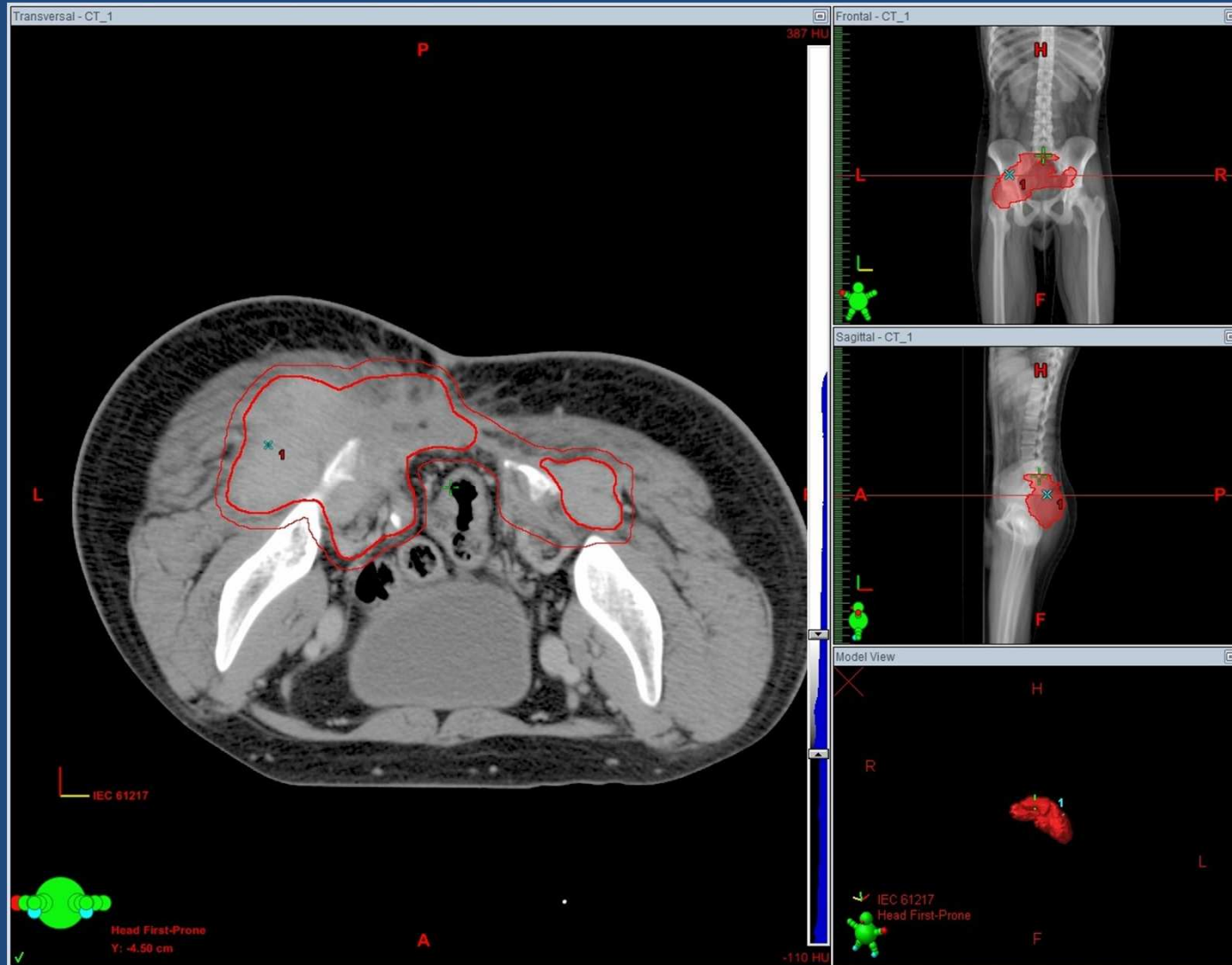
Received 29 January 2015; Revised 4 May 2015; Accepted 21 May 2015

TABLE 1: Characteristics, treatment, and outcome of children and adolescents with mesenchymal chondrosarcoma.

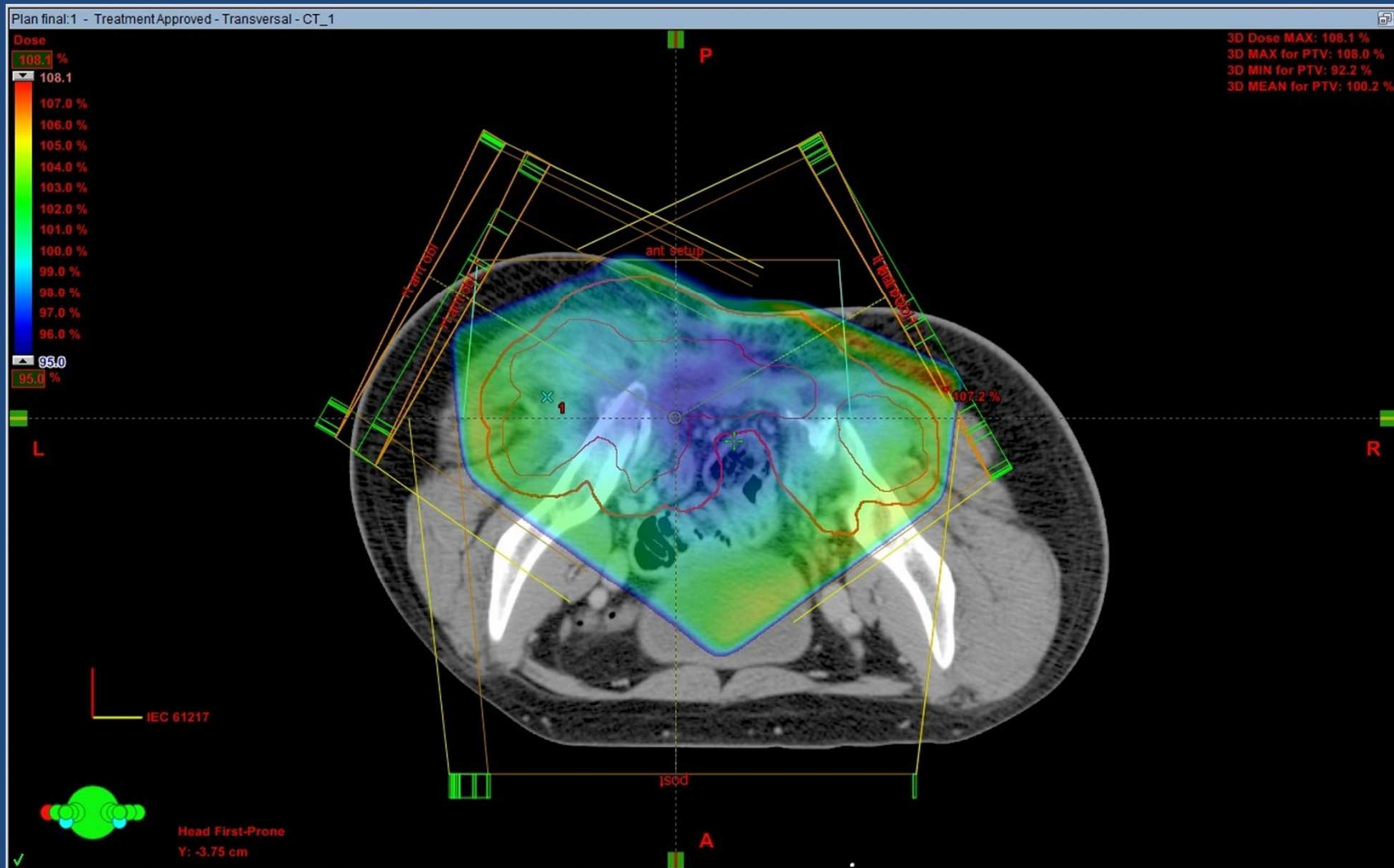
Patient	Age (yr)	Sex	Primary site	Size (cm)	Osseous versus extrasosseous	Neoadjuvant therapy	Response (RECIST)	Response (volumetric)	Extent of surgery	Adjuvant therapy	Outcome (yr)
1	15.2	F	Abdominal mesentery	12.7	Extrasosseous	—	—	—	CR	RT (55.2 Gy) CH (I, D)	NED (0.7)
2	14.5	F	Chest wall	2.5	Osseous	—	—	—	+margin	Brachytherapy (15 Gy) RT (45 Gy)	NED (8.7)
3	19.7	F	Pterygopalatine fossa	5.3	Extrasosseous	—	—	—	+margin	RT (59.4 Gy)	AWD (1.3)
4	13.9	F	Maxillary sinus	5.3	Osseous	—	—	—	+margin	CH (I, D) RT (55.8 Gy)	NED (0.3)
5	1.3	F	Paraspinal	6.0	Extrasosseous	—	—	—	Gross residual disease	RT (60.7 Gy) CH (I, C)	Died (8.1), renal failure
6	17.3	F	Maxilla	5.5	Osseous	CH (I, D, V) RT (50 Gy)	SD	SD	CR	RT (20 Gy)	NED (10.7)
7	11.7	M	Chest wall	10.4	Osseous	CH (I, D, V, E)	SD	SD	CR	CH (I, D, V, E) RT (55.8 Gy)	NED (5.3)
8	9.8	F	Orbit	2.5	Extrasosseous	CH (I, D) RT (45 Gy)	SD	SD	CR	CH (I, D)	NED (6.8)
9	17.4	F	Orbit	2.1	Extrasosseous	CH (I, D) RT (45 Gy)	SD	PR	CR	CH (I, D)	NED (6.1)
10	12.8	F	Intraspinal	3.1	Extrasosseous	CH (I, D) RT (45 Gy)	PD	SD	+margin	CH (I, D) RT (10.8 Gy)	AWD (4.3)
11	12.1	M	Nasal cavity	6.5	Extrasosseous	CH (I, D)*	SD	SD	+margin	RT (59.4 Gy)	NED (1.2)
12	16.5	M	Chest wall	2.5	Osseous	—	—	—	Primary resected**	CH (I, D)	DOD (1.3)

\*Patient received one cycle of neoadjuvant chemotherapy only; \*\*Primary tumor grossly resected, unable to be cleared of metastatic lung nodules. RT: radiotherapy; Gy: Gray; CH: chemotherapy; I: ifosfamide; D: doxorubicin; C: carboplatin; V: vincristine; E: etoposide; SD: stable disease; PR: partial response; CR: complete resection; NED: no evidence of disease; AWD: alive with disease; DOD: died of disease.

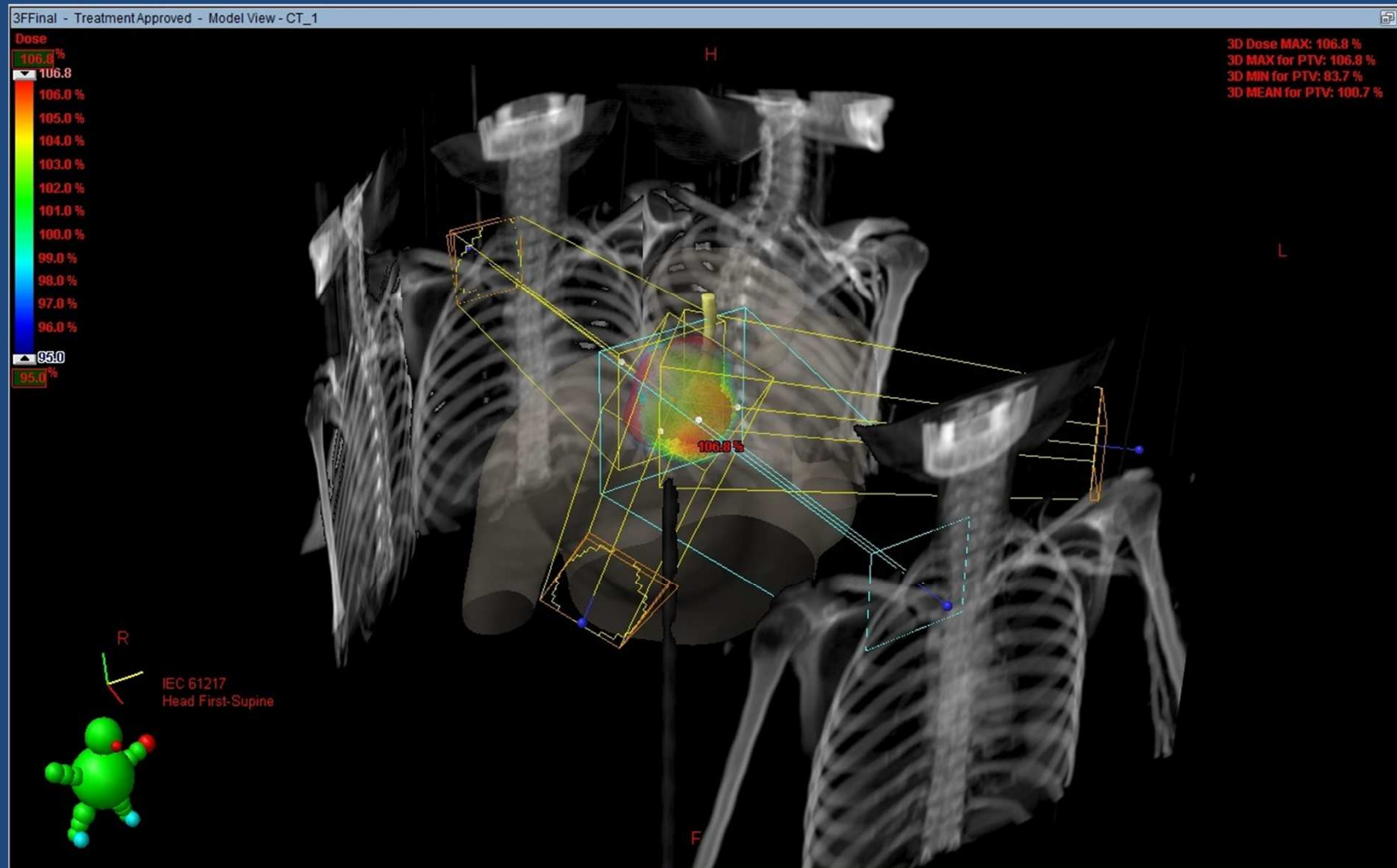
# Chondrosarcoma 1GTV



# Chondrosarcoma 1 Dose Wash

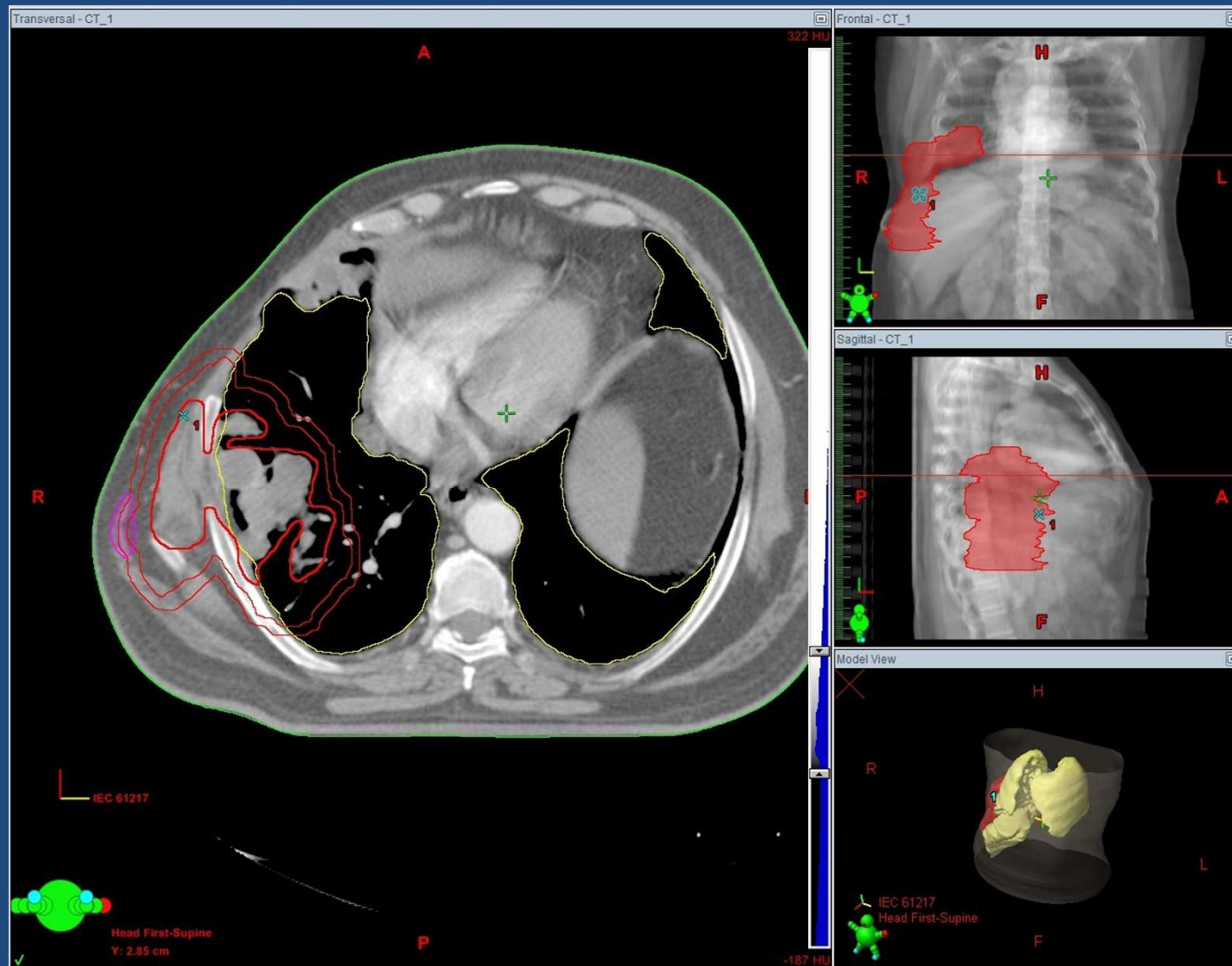


# Chondrosarcoma BEV

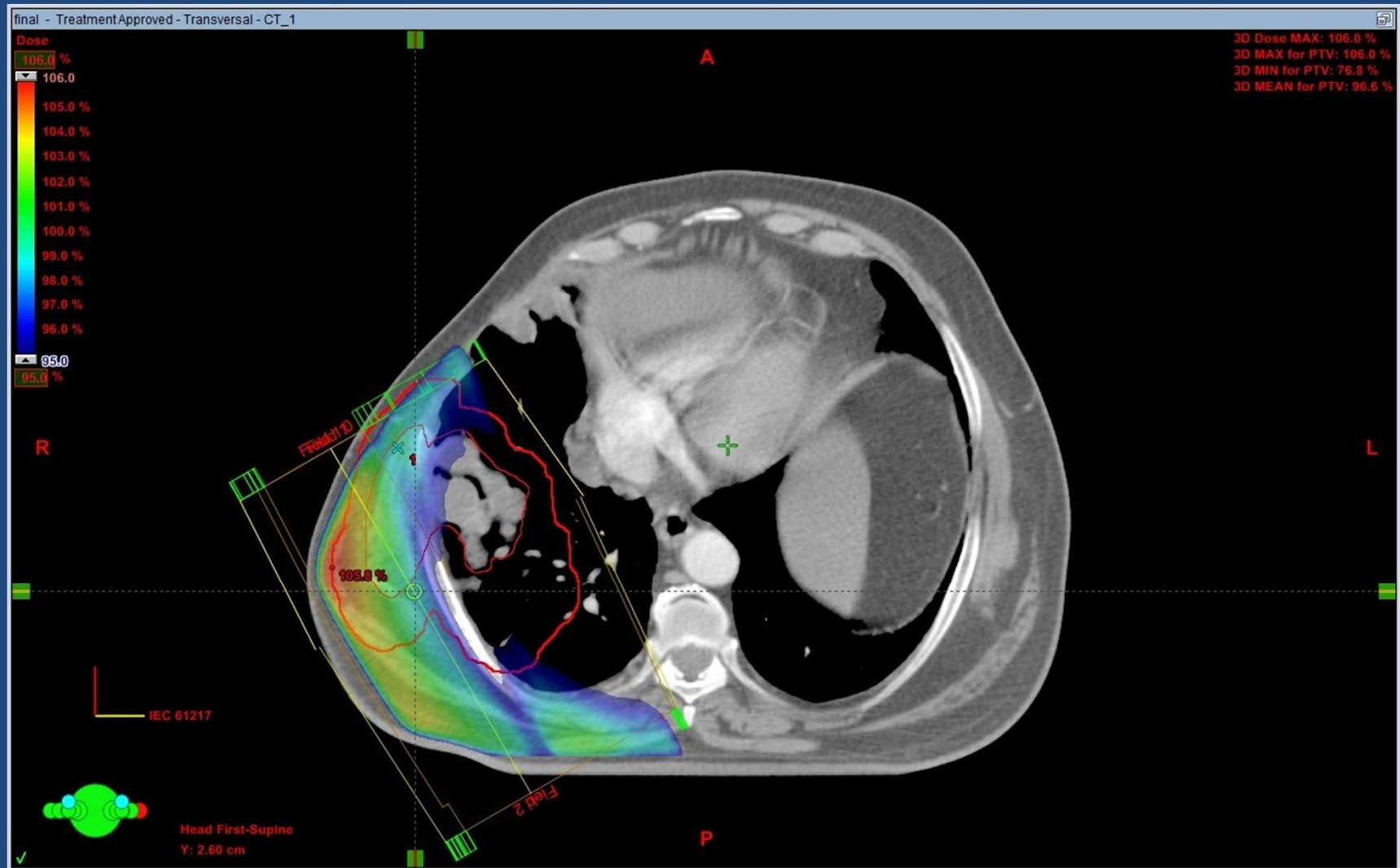




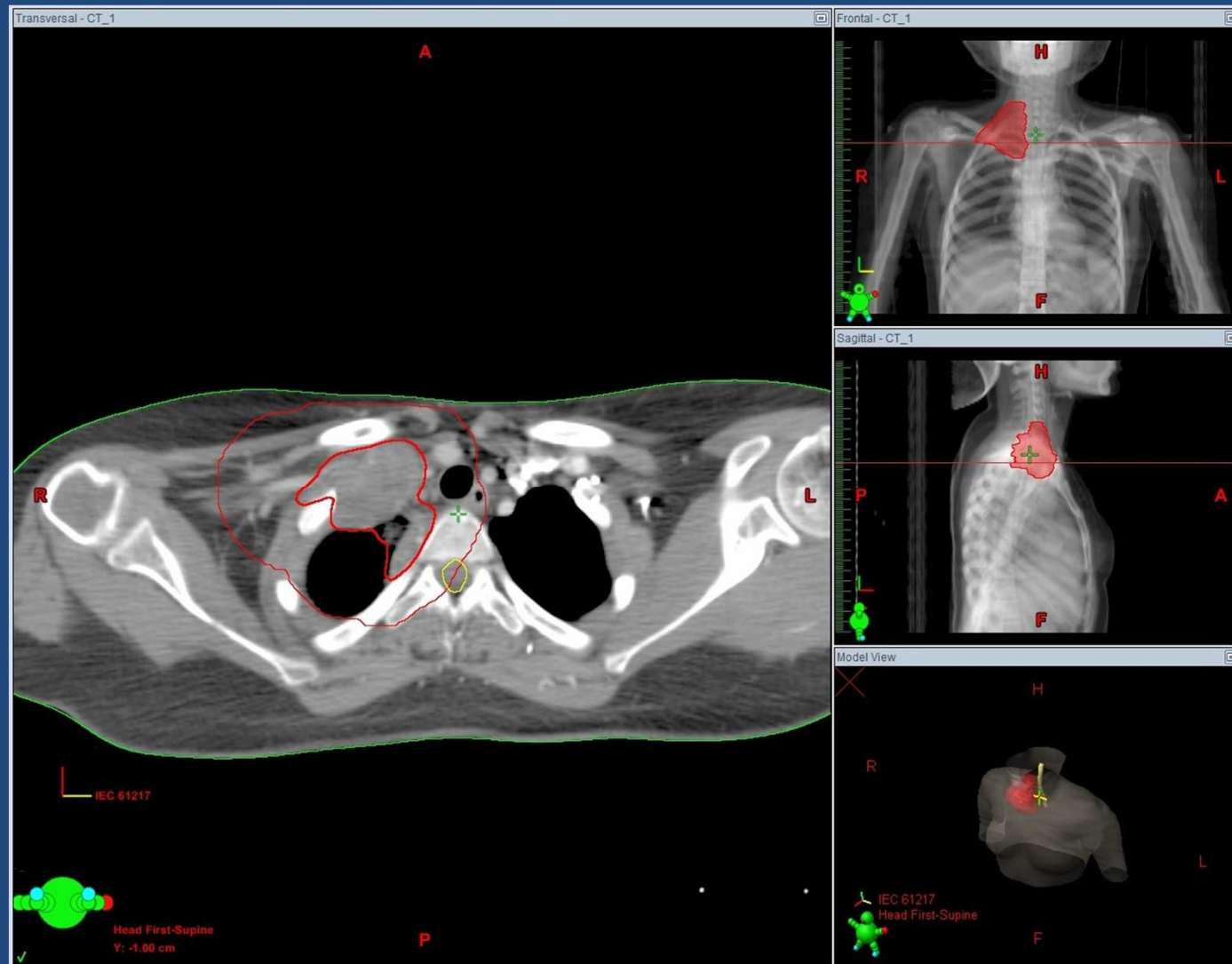
# Chondrosarcoma 2GTV



# Chondrosarcoma 2 Dose Wash

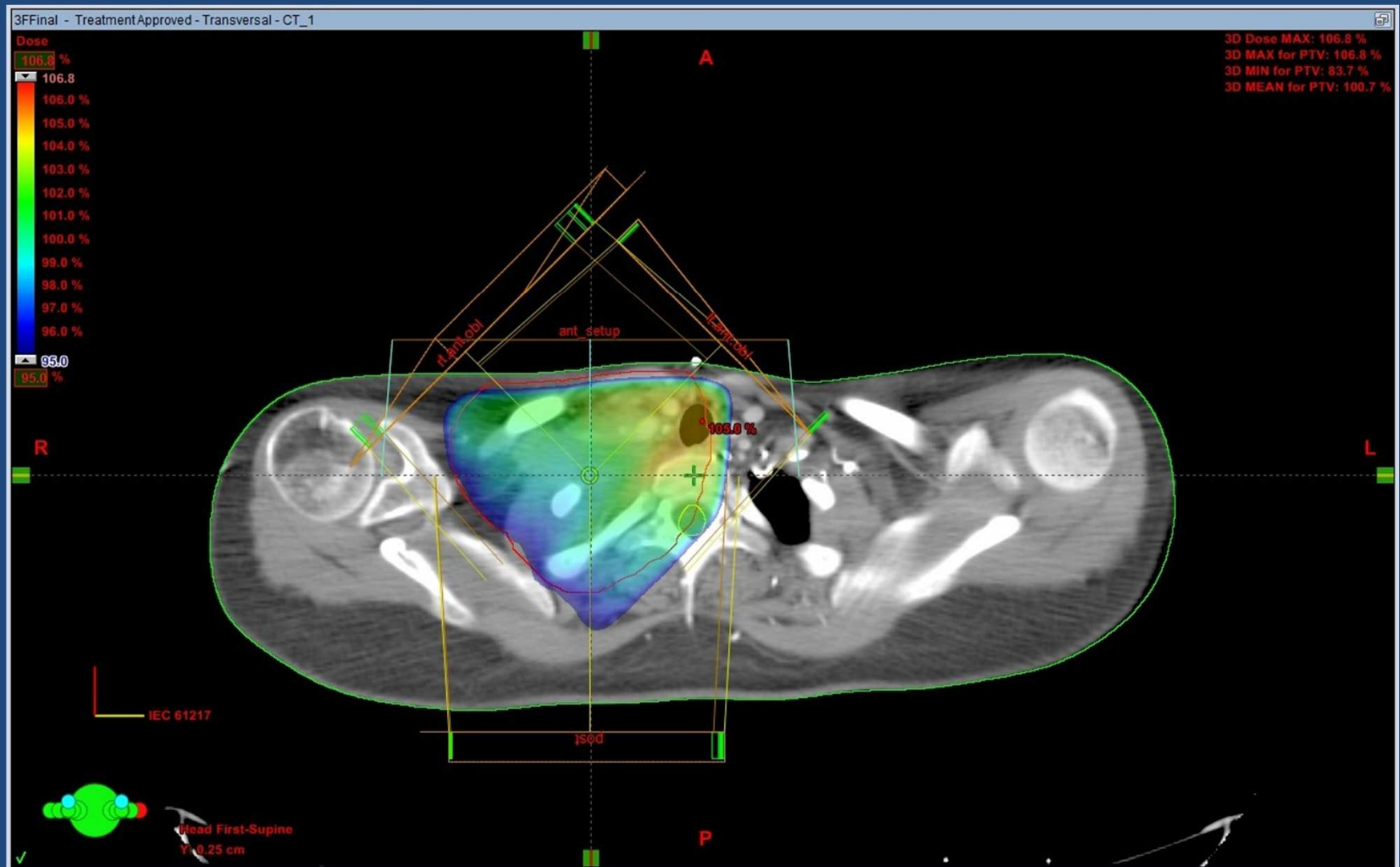


# Chondrosarcoma GTV

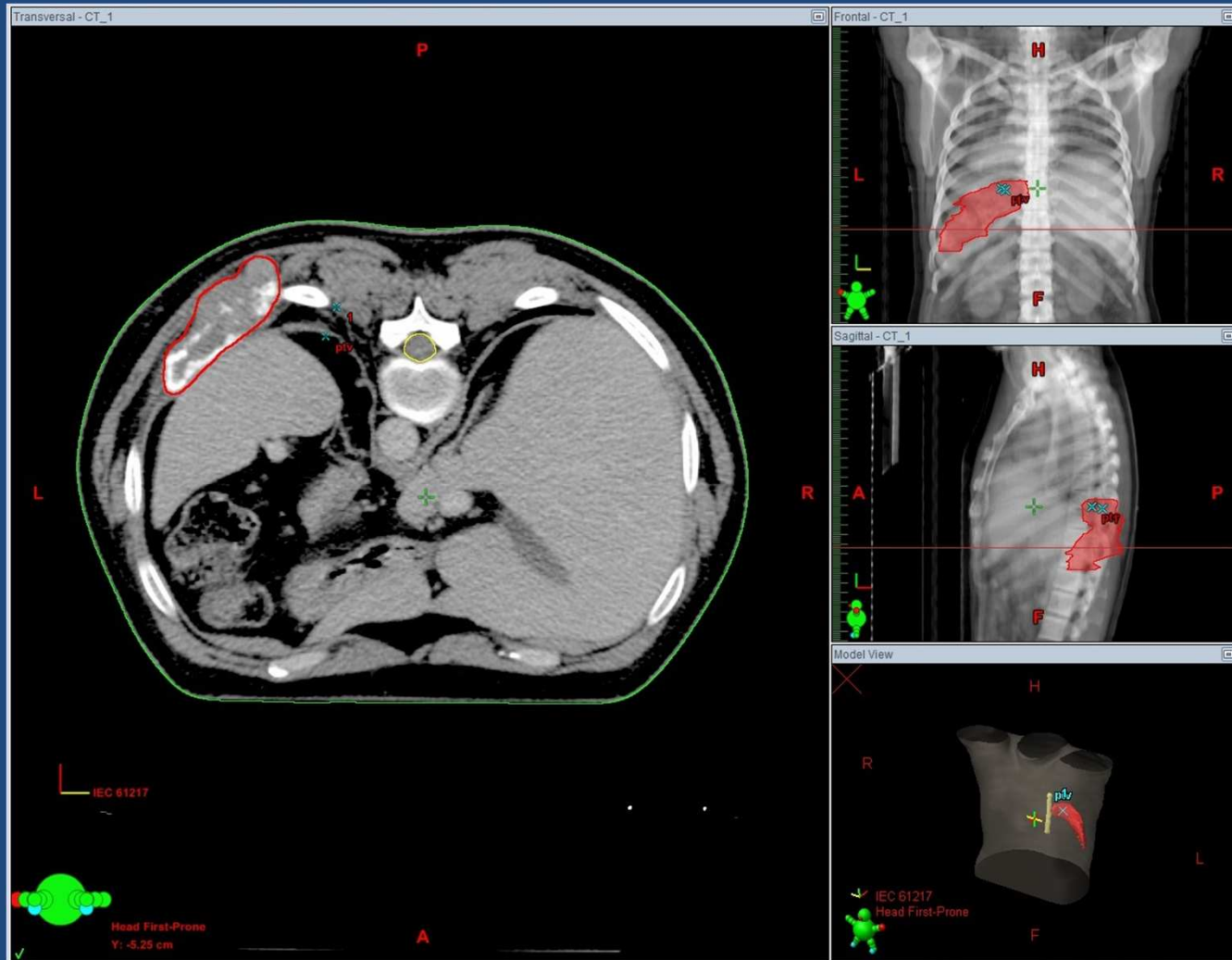




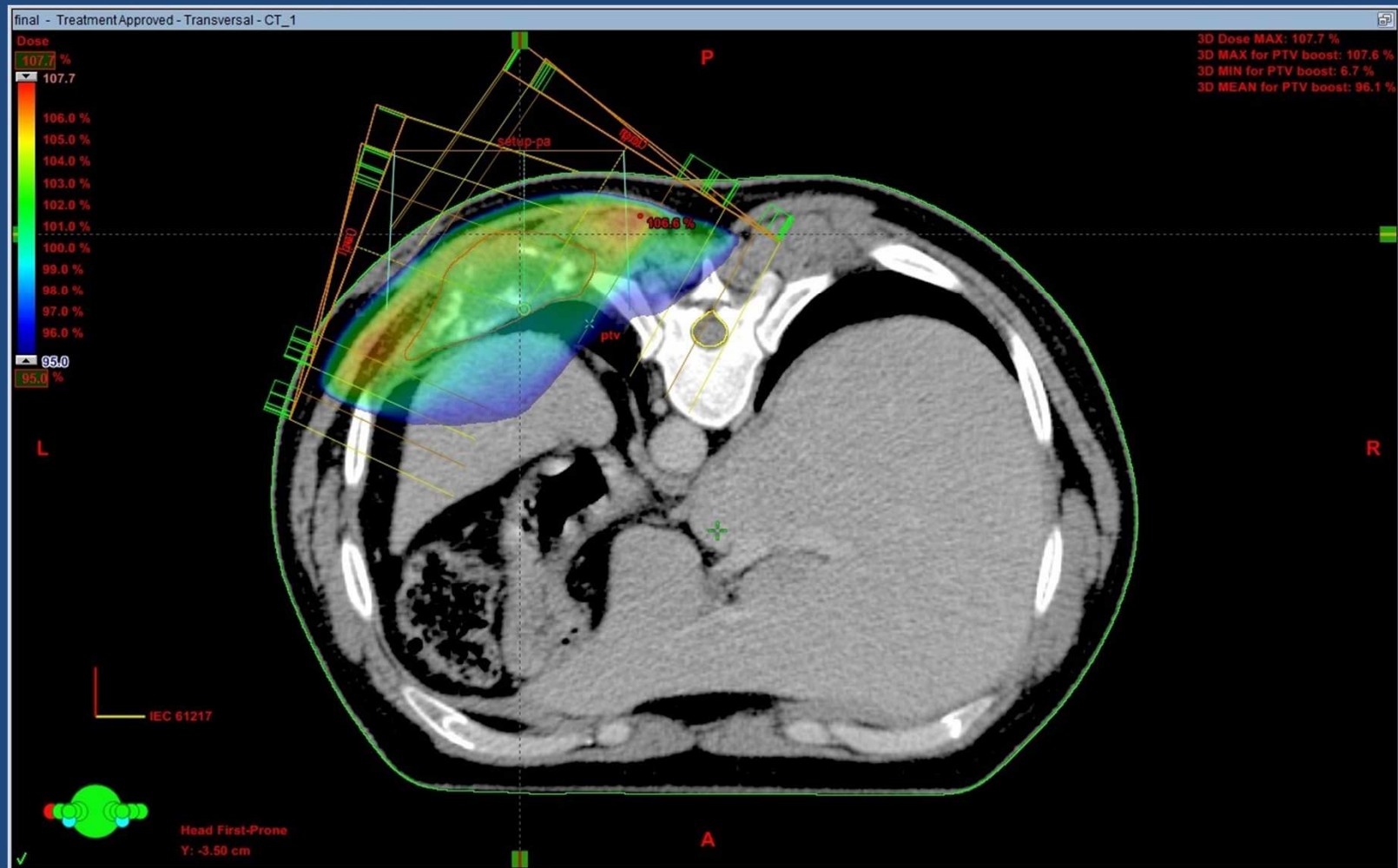
# Chondrosarcoma Dose Wash



# Chondrosarcoma 3 GTV



# Chondrosarcoma 3 Dose Wash



# Charged particle RT: Chondrosarcoma

- Chondrosarcomas - In patients with chondrosarcoma, the largest series comprised 200 patients treated at a single institution . The median total dose of radiation in that series was 72 Gy equivalents.
- The 10year local control and survival rates were 98 and 99 percent, respectively
- A subsequent review of the literature included that series plus 54 patients with chondrosarcoma identified in three other studies; the results in those series were similar

Clinical Investigation

# Spot-Scanning Proton Radiation Therapy for Pediatric Chordoma and Chondrosarcoma: Clinical Outcome of 26 Patients Treated at Paul Scherrer Institute

Barbara Rombi, MD,<sup>\*,†</sup> Carmen Ares, MD,<sup>\*</sup> Eugen B. Hug, MD,<sup>\*,§</sup> Ralf Schneider, MD,<sup>\*</sup> Gudrun Goitein, MD,<sup>\*</sup> Adrian Staab, MD,<sup>\*</sup> Francesca Albertini, PhD,<sup>\*</sup> Alessandra Bolsi, MSc,<sup>\*</sup> Antony J. Lomax, PhD,<sup>\*</sup> and Beate Timmermann, MD<sup>\*,†</sup>

*<sup>\*</sup>Center for Proton Therapy, Paul Scherrer Institute, Villigen, Switzerland; <sup>†</sup>ATreP (Provincial Agency for Proton Therapy), Trento, Italy; <sup>‡</sup>WestGerman Proton Therapy Center Essen, Germany; and <sup>§</sup>ProCure Proton Therapy Center, Somerset, New Jersey*

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# Other techniques

- Several other techniques have been used to deliver higher doses of photon radiation to central nervous system targets, while minimizing incidental exposure to normal critical structures. There are no randomized trials that compare SRS, SRT, or IMRT to proton beam or older photon techniques.
- SRS has been used in several retrospective series. A review of the literature identified 148 patients with chordomas treated in four series
- The 5 year survival rate ranged from 69 to 84 percent, at a median followup of 28 to 60 months. SRS is limited to tumors with a relatively small tumor volume.

# Summary of studies using PT in pediatric Chordomas and Chondrosarcoma

Author/Institution	#	Tumor Site (#)	Histology	RT Type (# pt)	Dose in CGE	5y-LC (%)	5y-OS (%)	F/U in months (range)
Benk (MGH) <sup>[49]</sup>	18	SB (15) C-spine (3)	All CH	P + Ph (18)	Median, 69.0	63%	68%*	Median, 72 (19-120)
Habrand (CPO) <sup>[50]</sup>	30	SB (16) C-spine (1) Both (13)	27 CH 3 CS	P + Ph (29) P (1)	Mean, 69.1 Mean, 65.3	77% (CH) 100% (CS)	81% (CH) 100% (CS)	Mean, 26.5 (5-102)
Hug (LLUMC) <sup>[51]</sup>	13	SB	10 CH 3 CS	P (6) P + Ph (4) P + Ph (3)	Median, 73.7 Median, 70.0	60% (CH) § 100% (CS) §	60% (CH)** 100% (CS) §	Mean, 40 (13-92)
Rombi (PSI) <sup>[52]</sup>	26	SB (17) Axial Skel (9)	19 CH 7 CS	P (All)	Mean, 74.0 Mean, 66.0	81%(CH) 80% (CS)	89% (CH) 75% (CS)	Mean, 46 (5-126)

\*: patients with cervical spine chordoma had a significant worse survival than other skull base patients ( $p=0.008$ );

\*\* : overall survival of the males was significantly superior to female patients ( $p=0.002$ );

§ :at last follow up

Abbreviations: #: number of; RT: radiotherapy; pt: patients; LC: local control; OS: overall survival; F/U: follow up; SB: skull base; CH: chordoma; CS: chondrosarcoma; Skel: skeleton; P: protons; Ph: photons; y: year.

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**Table 3** Summary of studies using PT in pediatric chordomas and chondrosarcomas

Author	<sup>†</sup>	Tumor site (no. of patients)	Histology	RT type (no. of patients)	Dose in Gy (RBE)	% of 5-y LC	% of 5-y OS	Follow-up in mo (range)
MGH Benk [1995]	18	SB (15) C-spine (3)	All CH	P + Ph (18)	Median, 69.0	63%	68%*	Median, 72 (19-120)
LLUMC Hug [2002]	13	SB (13)	10 CH 3 CS	P (6) P + Ph (4) P + Ph (3)	Median, 73.7 Median, 70.0	60% (CH) <sup>†</sup> 100% (CS) <sup>†</sup>	60% (CH) <sup>‡</sup> 100% (CS)	Mean, 37 (13-86)
PSI Rutz [2008]	10	SB (6) Axial Skeleton (4)	6 CH 4 CS	P	Median, 74.0 Median, 66.0	100% <sup>†</sup>	100% <sup>†</sup>	Median, 36 (8-77)
CPO Habrand [2008]	30	SB (16) C-spine (1) Both (13)	27 CH 3 CS	P + Ph (29) P (1)	Mean, 69.1 Mean, 65.3	77% (CH) 100% (CS)	81% (CH) 100% (CS)	Mean, 26.5 (5-102)
PSI Current Study	26	SB (17) Axial Skeleton (9)	19 CH 7 CS	P	Mean, 74.0 Mean, 66.0	81% (CH) 80% (CS)	89% (CH) 75% (CS)	Mean, 46 (5-126)

*Abbreviations:* CH = chordoma; CS = chondrosarcoma; LC = local control; OS = overall survival; P = protons; Ph = photons; RT = radiation therapy; SB = skull base.

\* Patients with cervical spine chordoma had significantly worse survival than the other skull base patients ( $P=.008$ ).

<sup>†</sup> At last follow-up.

<sup>‡</sup> Overall survival of males was significantly higher than that for females ( $P=.002$ ).



**Table 2.** Literature review of patient characteristics in proton beam therapy studies on pediatric chordomas and chondrosarcomas

Literature	Benk et al, 1995 <sup>66</sup>	Hug et al, 2002 <sup>8</sup>	Hoch et al, 2006 <sup>10</sup>	Habrand et al, 2008 <sup>17</sup>	Rombi et al, 2013 <sup>18</sup>	Rutz, 2008 <sup>61</sup>
No. of patients	18	13	73	30	26	10
Median age, y (range, y)	13 (4 to 18)	12 (1 to 19)	9.7 (1 to 18)	13.5 (6 to 17)	13.2 (3.7 to 20.8)	16 (10 to 20)
No. of male:female	7:11	6:7	31:42	NA	9:10	6:4
Histology (no. of patients)	CH (18)	CH (10); CS (3)	CH (73) Conventional (6) Chondroid (3) Poorly differentiated (5)	CH (27) CS, low-grade (3)	CH (19) CS (7)	CH (6) CS (4)
Tumor site (no. of patients)	SB (15); cervical spine (3)	SB (13)	SB (73)	SB (16); axial skeleton (1); cervical junction (13)	SB (17); axial skeleton (9)	Brain (1); SB (5); cervical spine (3); lumbar spine (1)
Tumor vol, mL (range, mL)	Median, 80 after surgery (13.9 to 282)	NA	NA	Mean, 26 (0 to 87)	Median, 161.7 (CH); median, 191.8 (CS).	NA
No. of patients with metastases before PT	0	NA	NA	NA	1	NA

**Abbreviations:** CH, chordomas; CS, chondrosarcomas; SB, skull base; no., number; y, year; vol., volume; mL, milliliter; PT, proton beam therapy; NA, not available

**Table 5.** Literature review of outcomes in proton beam therapy studies on pediatric chordomas and chondrosarcomas

Literature	Acute side effects (no. of patients)	Late effects (no. of patients)	High grade late toxicity <sup>a</sup> (no. of patients)	Metastases after PT (no. of patients)
Benk et al, 1995 <sup>66</sup>	NA	Pituitary insufficiency (2); single-sided hearing deficiency (3); brain injury (1); fibrosis of temporalis muscle (1)	Grade 3 (1) Grade 4 (1)	3
Hug et al, 2002 <sup>8</sup>	Skin erythema (NA); occasional headaches (NA); fatigue (NA); loss of appetite (NA); oropharyngeal mucositis (NA)	Right-sided motor weakness and ataxia (1); pituitary insufficiencies (8)	Grade 3 (1)	3
Hoch et al, 2006 <sup>10</sup>	NA	NA	NA	3
Habrand et al, 2008 <sup>17</sup>	Mucositis (10); epidermitis (14); headaches (10); nausea (9); focal alopecia (23)	Auditory toxicity (1); partial pituitary hormone failure (7)	Grade 3 (1)	NA
Rombi et al, 2013 <sup>18</sup>	Grade 2 toxicity (12)	Otitis media requiring drainage (2); unilateral hearing impairment(1); partial hypopituitarism (4); symptomatic nasal mucosal crusting (1)	None	NA
Rutz et al, 2008 <sup>61</sup>	Skin reactions (NA)  Focal alopecia (NA)	Insufficiency of the pituitary gland (1); focal alopecia (1); moderate auditory problems (1); neurosensory deficit in the left arm (1)	None	NA

**Abbreviations:** NA, not available; no., number; PT, proton beam therapy

<sup>a</sup>Grade toxicity is based on the Common Terminology Criteria for Adverse Events, version 4.0

# Protons in pediatric Chordomas and Chondrosarcoma - Summary

- Most recent study by Rombi et al., 26 patients were treated with spotscanning PT achieving 5-year LC of 81% and 80%, and 5-year OS rates of 89% and 75%, for chordomas and chondrosarcomas, respectively
- Furthermore, there were relatively few (19%) late complications and no high grade ( $\leq$  grade 2) late toxicities were noted.
  - otitis media requiring drainage;
  - unilateral hearing impairment;
  - hypopituitarism requiring hormonal replacement
  - symptomatic nasal mucosal crusting
- No secondary malignancies were observed during the follow-up

Rombi et al., J Nucl Med Radiat Ther 2013, 4:4

## Summary: Chordoma, Chondrosarcoma pediatric radiation therapy

- CH is an extremely rare disease in children
- Standard treatment usually consists of a maximal, but safely achievable, resection followed by high-dose radiation therapy
- PT is now considered as an important modality for radiation therapy in CH

## Summary: Chondroma, Chondrosarcoma pediatrics ration therapy

- Especially in children, PT offers a significant advantage over IMRT when looking at the high local control and survival rates while minimizing the risk of late side effects and SMN
- The different proton beam delivery techniques need to be individually chosen when balancing benefits and drawbacks of each modality

# Osteosarcoma: Radiotherapy

- With the improvements in RT techniques over time, there has been renewed interest in the use of RT for patients whose tumors respond to chemotherapy and in whom surgery would be debilitating
- One report described a 5 year local control rate of 56 percent among 31 patients with nonmetastatic extremity osteosarcoma who refused surgery and were instead treated with radiotherapy (median dose 60 Gy)

# Osteosarcoma: Radiotherapy

- The 5 year metastasis free survival rate was 91 percent, and there were no local failures among the 11 patients who responded well to chemotherapy (ie, had both a radiographic and biochemical response with normalization of serum alkaline phosphatase)
- Among patients who achieved local control, 86 percent had "excellent" limb function. However, this single study does not represent sufficient data to recommend the use of RT as a replacement for surgery in patients with resectable tumors



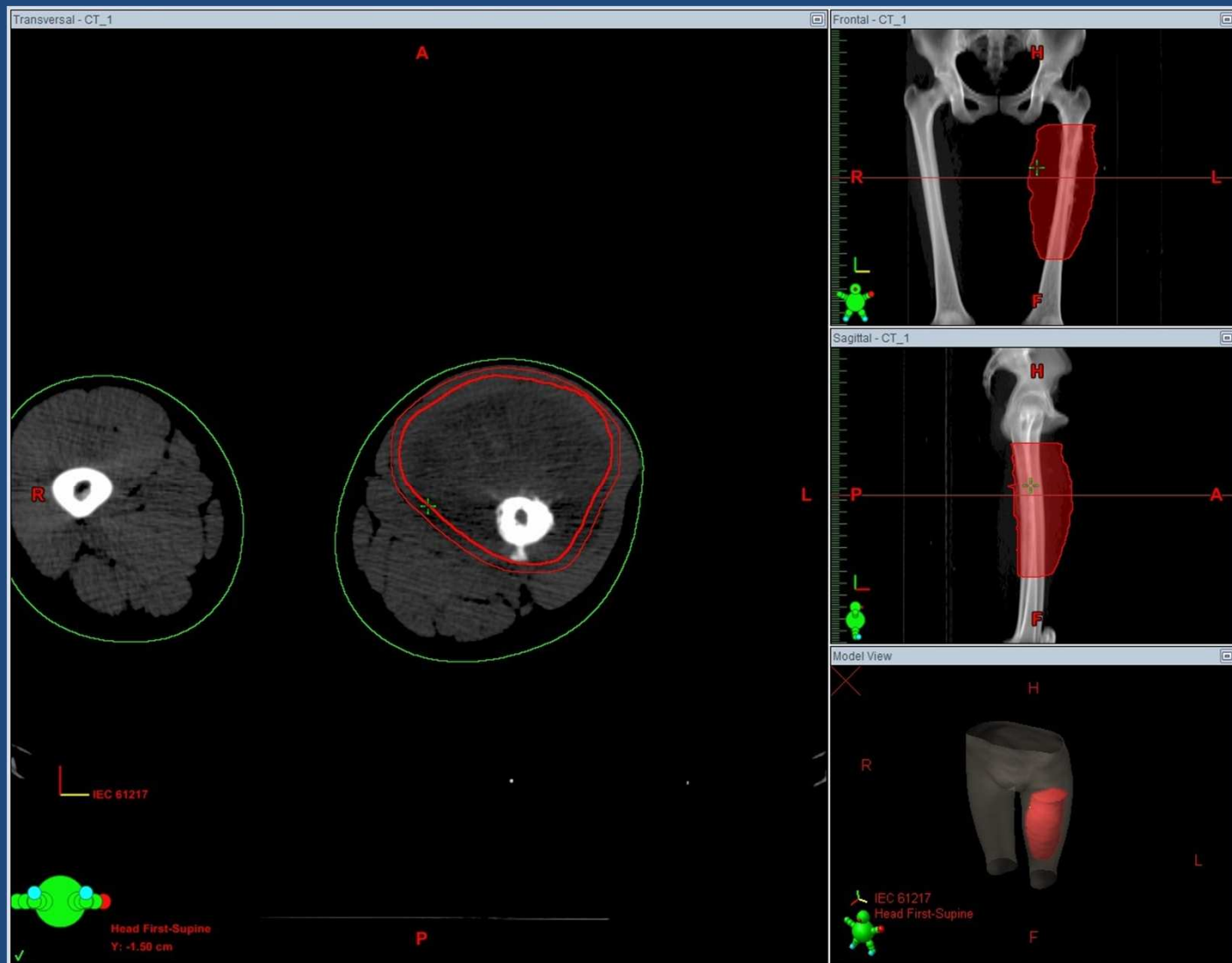
# Proton-Based Radiotherapy for Unresectable or Incompletely Resected Osteosarcoma

I. Frank Ciernik, MD<sup>1,2</sup>; Andrzej Niemierko, PhD<sup>1,3,4</sup>; David C. Harmon, MD<sup>3,5</sup>; Wendy Kobayashi, BA<sup>1</sup>; Yen-Lin Chen, MD<sup>1,3,4</sup>; Torunn I. Yock, MD<sup>1,3,4</sup>; David H. Ebb, MD<sup>3,6</sup>; Edwin Choy, MD, PhD<sup>3,5</sup>; Kevin A. Raskin, MD<sup>3,7</sup>; Norbert Liebsch, MD, PhD<sup>1,3,4</sup>; Francis J. Hornicek, MD, PhD<sup>3,7</sup>; and Thomas F. DeLaney, MD<sup>1,3,4</sup>

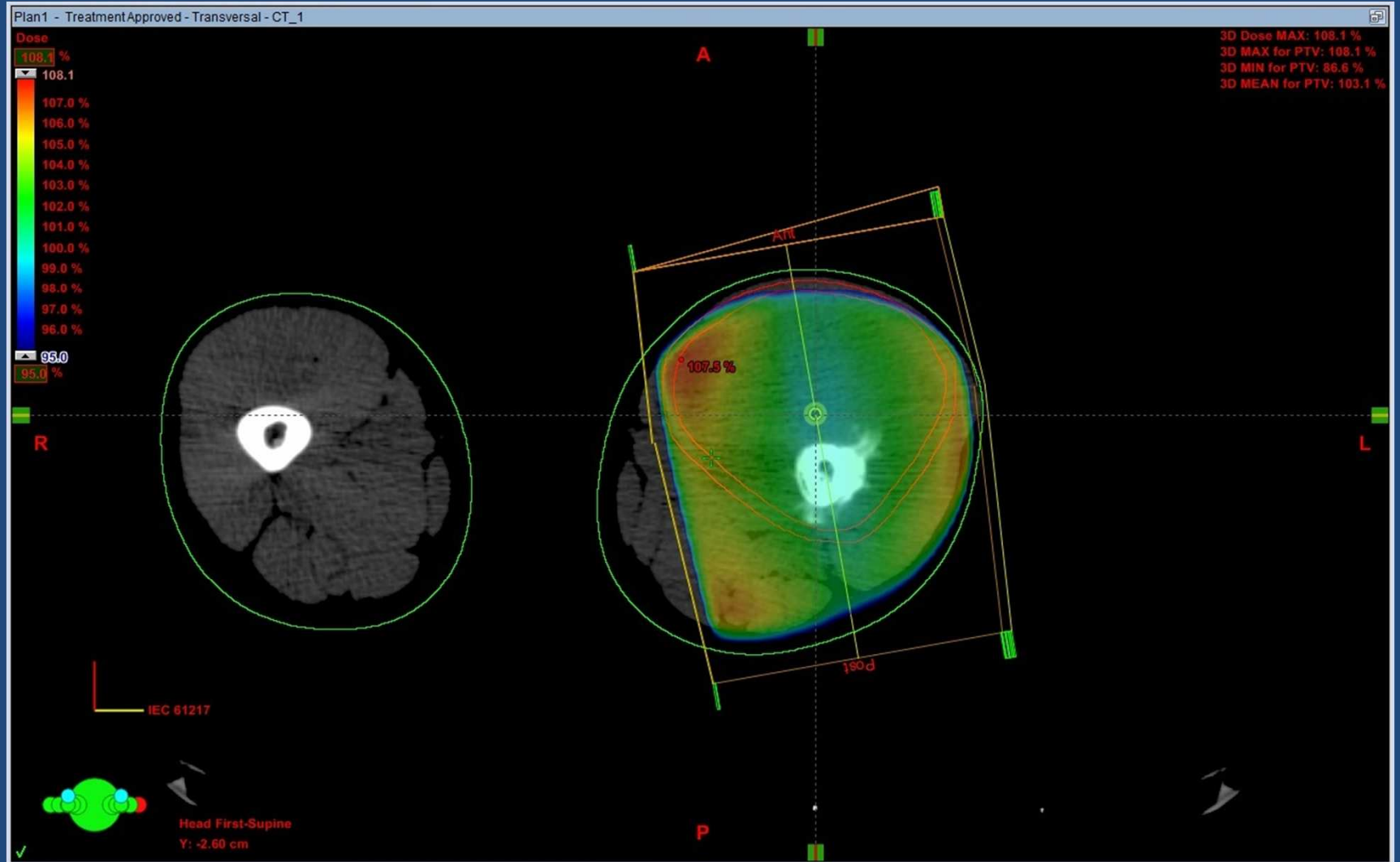
**RESULTS:** Fifty-five patients with a median age of 29 years (range, 2-76 years) were offered proton therapy. The mean dose was 68.4 gray (Gy; standard deviation, 5.4 Gy). Of the total dose, 58.2% (range, 11%-100%) was delivered with protons. Local control after 3 and 5 years was 82% and 72%, respectively. The distant failure rate was 26% after 3 and 5 years. The 5-year DFS was 65%, and the 5-year OS was 67%. The extent of surgical resection did not correlate with outcome. Risk factors for local failure were  $\geq 2$  grade disease ( $P < .0001$ ) and total treatment length ( $P = .008$ ). Grade 3 to 4 late toxicity was seen in 30.1 % of patients. One patient died from treatment-associated acute lymphocytic leukemia, and 1 from secondary carcinoma of the maxilla. **CONCLUSIONS:** Proton therapy to deliver high radiotherapy doses allows locally curative treatment for some patients with unresectable or incompletely resected OSA. *Cancer* 2011;117:4522-30. © 2011 American Cancer Society.



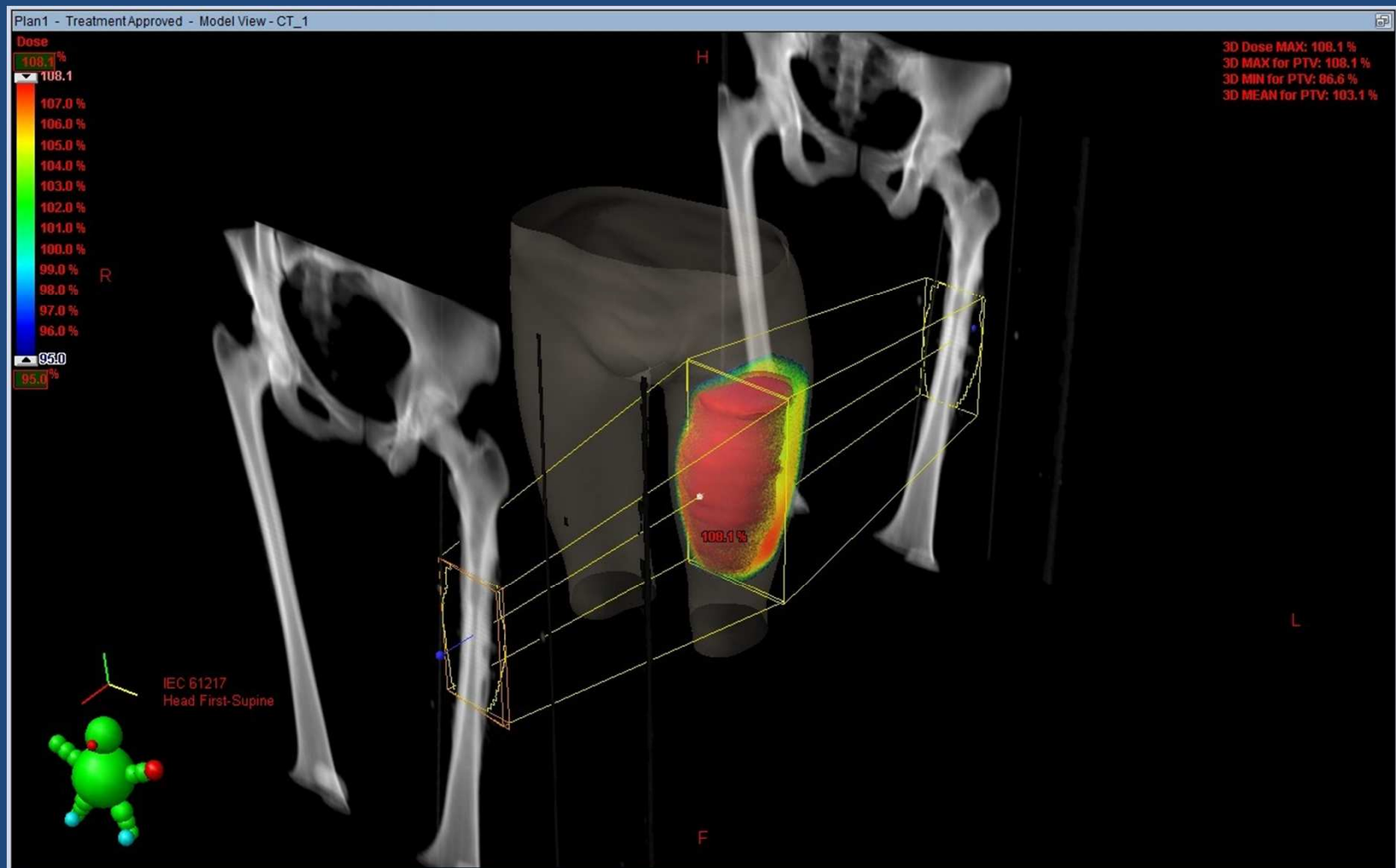
# Osteosarcoma 2 GTV



# Osteosarcoma 2 Dose Wash



# Osteosarcoma BEV



# Conclusions

- There is a definite role of radiotherapy in pediatric chordomas and chondrosarcomas.
- The role of radiation in pediatric osteosarcomas is fast emerging due to exploitation of higher RBE of protons
- With the advent of protons, the fears of secondary malignancies and late side effects are relatively less.
- The potential limitations of proton beam therapy include high installation and maintenance cost. Also it needs to be hospital based facility rather than experimental labs.(because children require anesthesia)

Thank You!

