HITRI plus
Heavy Ion Therapy Research Integration

Ewing and Rhabdomyosarcoma

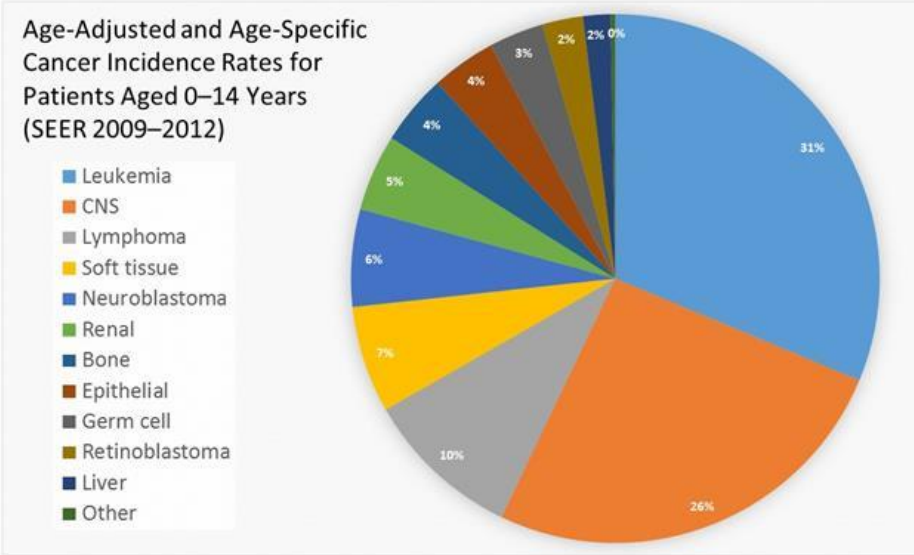
C. LÜTGENDORF-CAUCIG

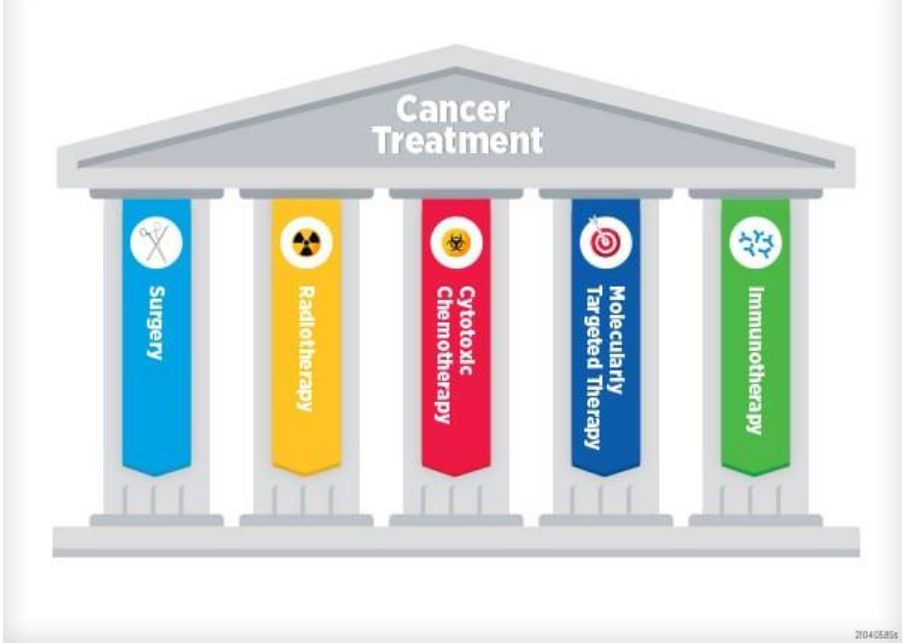
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

PEDIATRIC SARCOMAS

- **Paediatric cancers are:**
  - Rare
  - Heterogeneous group of malignancies
  - Increasing incidence since the 1970ies
  - Increasing OS since the 1970ies
  - Soft tissue sarcomas 7% and bode 4% of all paediatric cancers

- ***BUT***
  - Increasing incidence of therapy associated late toxicity health conditions
  - psycho social burden for survivors and their families
  - Financial burden for the health system



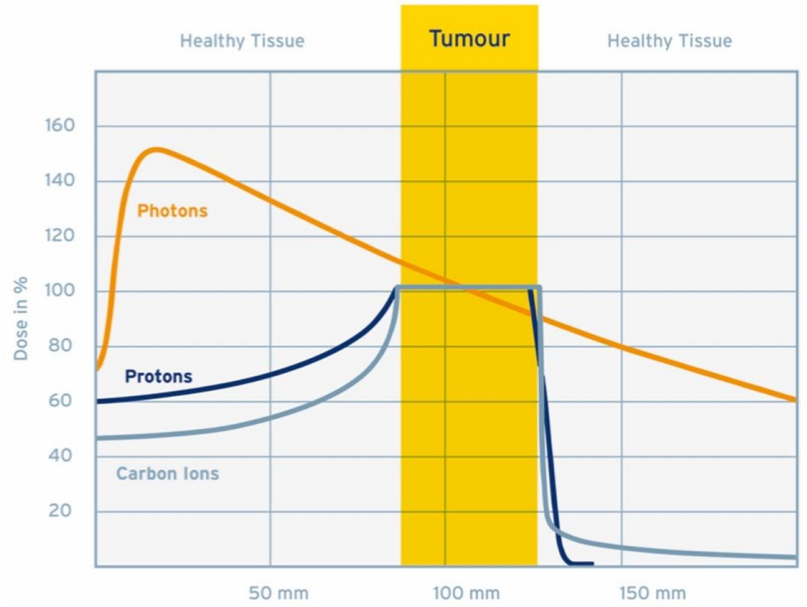


The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Chronic Health Conditions in Adult Survivors of Childhood Cancer

Kevin C. Oeffinger, M.D., Ann C. Mertens, Ph.D., Charles A. Sklar, M.D.,



"Among survivors, the cumulative incidence of a chronic health condition reached 73.4% (95% CI, 69.0 to 77.9) 30 years after the cancer diagnosis, with a cumulative incidence of 42.4% (95% CI, 33.7 to 51.2) for severe, disabling, or life-threatening conditions or death due to a chronic condition."

N Engl J Med 2006;355:1572-82.

EPTN, PTCOCG, PROS consensus

Proton therapy for pediatric malignancies: Fact, figures and costs. A joint consensus statement from the pediatric subcommittee of PTCOG, PROS and EPTN

Damien C. Weber [a,*], Jean Louis Habrand [b], Bradford S. Hoppe [c], Christine Hill Kayser [d], Nadia N. Laack [e], Johanes A. Langendijk [f], Shannon M. MacDonald [g], Susan L. McGovern [h], Luke Pater [i], John P. Perentesis [j], Juliette Thariat [b], Beate Timmerman [k], Torunn I. Yock [g], Anita Mahajan [e]

[a] *Center for Proton Therapy, Paul Scherrer Institute, ETH Domain, Villigen PSI, Switzerland;* [b] *Centre de lutte contre le cancer François-Baclesse, Caen, France;* [c] *Department of Radiation Oncology, University of Florida College of Medicine, Gainesville;* [d] *Department of Radiation Oncology, University of Pennsylvania, Philadelphia;* [e] *Department of Radiation Oncology, Mayo Clinic, Rochester, USA;* [f] *Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, The Netherlands;* [g] *Department of Radiation Oncology, Massachusetts General Hospital, Boston;* [h] *Department of Radiation Oncology, MD Anderson Cancer Center, Houston;* [i] *Department of Radiation Oncology, University of Cincinnati;* [j] *Cincinnati Children's Hospital Medical Center, University of Cincinnati, USA;* [k] *WPE, University Hospital Essen, Germany*

Conclusions

Many studies still suggest that the predominant cause for early death among cancer survivors remains the primary tumor; however, it is also known survivors have many treatment related sequelae that impair their QOL in many domains. Through almost all dosimetric and model based evaluation, clinical outcomes for PT should be favorable with an improved QOL, organ function, development with a reduction in the risk of SMNs. Several decades of

MODERN THERAPY CONCEPTS IN PEDIATRIC CANCERS

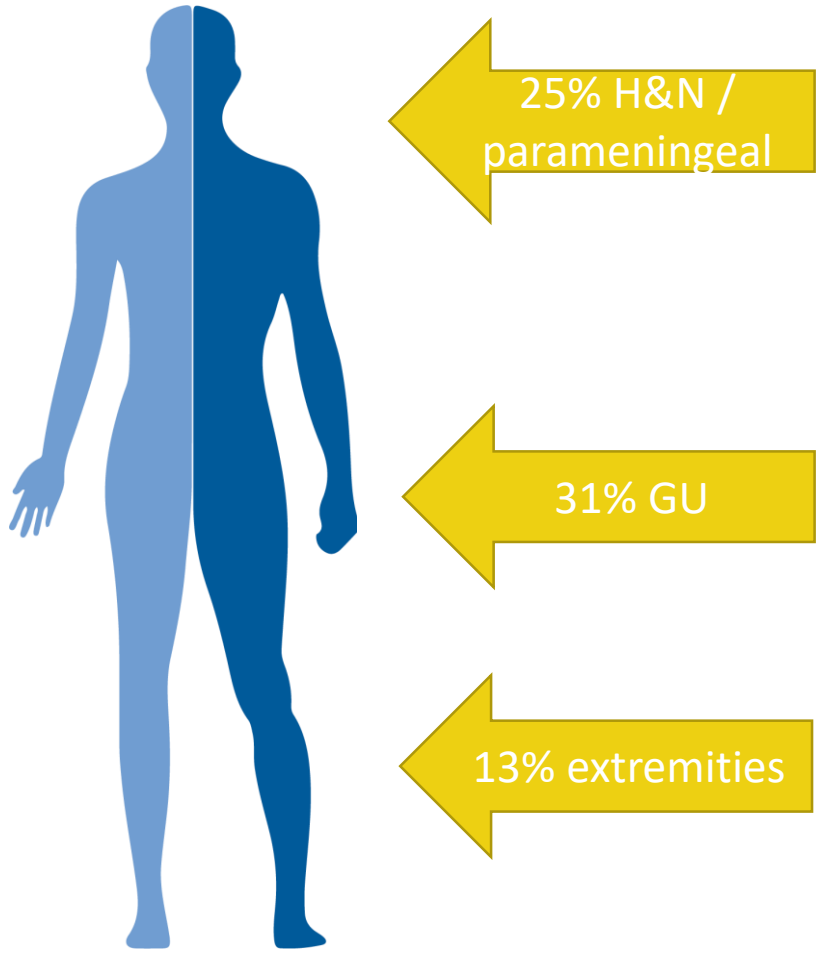
- **Maintaining excellent local control and overall survival while reducing long term toxicity / morbidity**

  - International standardized therapy concepts and stud protocols
  - Interdisciplinary strategies
  - Multimodal therapy approach
  - Risk-adapted Therapy strategies
  - Response guided therapy strategies
  - ***Use Protontherapy whenever available!***

RHABDOMYOSARCOMA

- Childhood rhabdomyosarcoma is a soft tissue malignant tumor of mesenchymal origin
- Incidence
  - 2.7% of cancer cases among children aged 0 to 14 years
  - 1.4% of cancer cases among adolescents 15 to 19 years

  → Fifty percent of these cases are seen in the first decade of life
- Genetic risk factors:
  - Li-Fraumeni cancer susceptibility syndrome (with germline *TP53* mutations); DICER1 syndrome; NF1; Costello syndrome (with germline HRAS mutations); Beckwith-Wiedemann syndrome Noonan syndrome
- Histological characterization:
  - embryonal, alveolar, spindle cell/sclerosing, and pleomorphic (WHO 2020)
- Molecular characterization :
  - *FOXO1* gene fusions pos. vs. *FOXO1* gene fusions neg.



Other less common primary sites include the trunk, chest wall, perineal/anal region, and abdomen, including the retroperitoneum and biliary tract

RHABDOMYOSARCOMA – PROGNOSTIC FACTORS

- Age (between 1 to 9 years)
- Site of origin Tumor size (tumors <5cm)
- Respectability
- Histological subtype (embryonal vs. alveolar)
- Molecular subtype (*FOXO1* fusion neg)
- Metastases at diagnose (nodal, distant)
- Response to therapy

Primary Site	Number of Patients	Survival at 5 Years (%)
Orbit[a]	82	97
Head and neck (nonparameningeal)[b]	164	83
Cranial parameningeal[c]	204	69.5
Genitourinary (excluding bladder/prostate)[b]	158	89
Localized bladder/prostate[d]	322	84
Localized extremity[e]	643	67
Trunk, abdomen, perineum, etc.[f]	147	67
Biliary[g,h]	25	76.5–78

RHABDOMYOSARCOMA – PROGNOSTIC FACTORS

Group	Incidence	Definition
I	Approximately 15%	Localized disease, completely resected (regional lymph nodes not involved).
II	Approximately 16%	Localized disease, grossly resected with microscopic residual disease or regio grossly resected with or without microscopic residual disease. (a) Localized di grossly resected tumor with microscopic residual disease, regional nodes not i Regional disease with involved nodes, completely resected with no microscop disease (including most distal node is histologically negative). (c) Regional di involved nodes, grossly resected with evidence of microscopic residual and/or involvement of the most distal regional node in the dissection.
III	Approximately 50%	Localized or regional disease, biopsy only or incomplete resection with gross disease.
IV	Approximately 20%	Distant metastatic disease present at onset. Although not limited to these, the f considered evidence of metastatic disease: (a) presence of positive cytology in positive cytology in pleural or abdominal fluids, (c) presence of implants on p peritoneal surfaces. (Note: Regional lymph node involvement and adjacent organ infiltration are not considered metastatic disease. Presence of a pleural effusion or ascites, without positive cytological evaluation, is not considered evidence of metastatic disease.)

Soft Tissue Sarcoma Committee of the Children's Oncology Group: Surgical-Pathological Group System

Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low Risk	A	Negative	I	Any	N0	Both Favourable
Standard Risk	B	Negative	I	Any	N0	One or both Unfavourable
	C	Negative	II, III	Favourable	N0	Any
High Risk	D	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very High Risk	G	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Risk Group assignment is determined at diagnosis

Soft Tissue Sarcoma Committee of the Children's Oncology Group: Rhabdomyosarcoma Risk Group Classification

RHABDOMYOSARCOMA – TREATMENT OPTION

- All children with rhabdomyosarcoma require multimodality therapy with systemic chemotherapy, in conjunction with either surgery, radiation therapy (RT), or both modalities to maximize local tumor control
- surgical resection is performed before chemotherapy if it will not result in disfigurement, functional compromise, or organ dysfunction. If this is not possible, only an initial biopsy is performed.

- Group I: about 15% of patients; complete tumor resection → OP+CHT
- Group II: about 20% of patients; CHT and local tumor bed irradiation
- Group III: about 50% of patients; initial CHT + definitive RT or STR + RT or no GTR / no response to CHT + CHT
- Group IV: about 15% of patients; CHT + RT to the primary tumor and metastatic disease sites when feasible

PARAMENINGEAL RMS

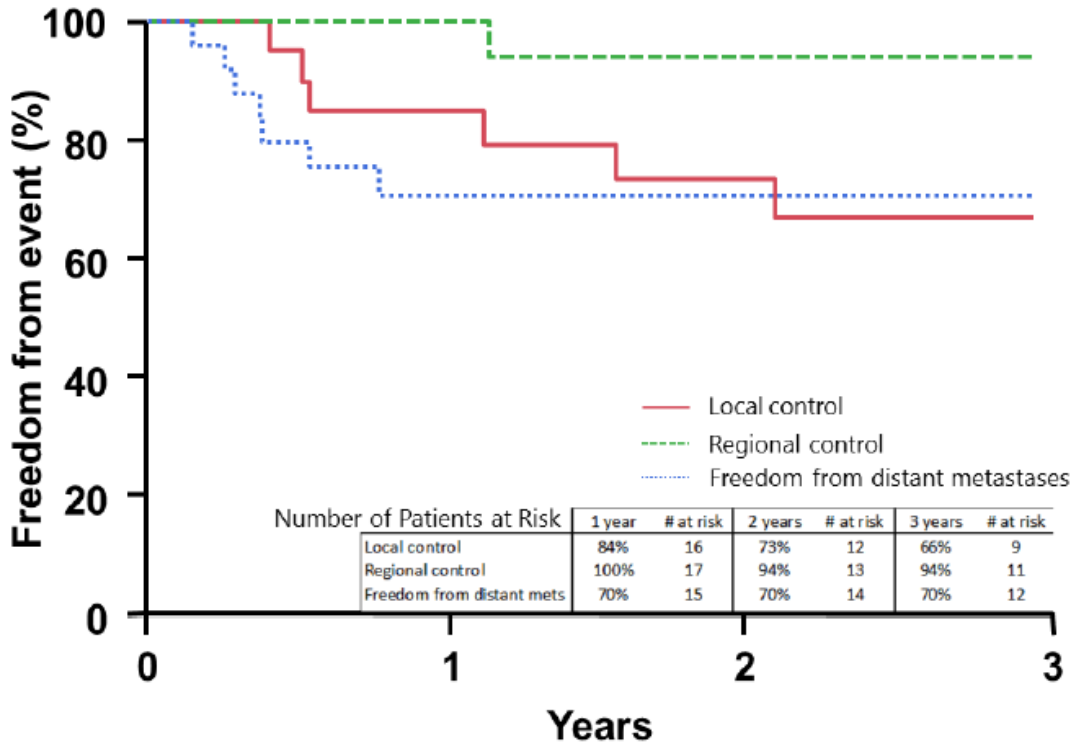
Patterns of Failure in Parameningeal Alveolar Rhabdomyosarcoma

Bradley J, Univ. FL, Jacksonville. Feb.2020,

- Retrospective institutional analysis
- 24 pts; median age 3.5 years (range, 1–20)
- node-negative (67%), intracranial extension (54%).
- Median total dose 50.4GyRBE (range, 41.4–59.4)
- CHT according to COG, EpSSG or St Judes RMS 13

- Median FUP 2.4 yrs.
- 3-year LC 66%, LRC 94%, DFS 40%, OS 60%,
- Median time to any failure 0.5a (range, 0.2–2.1).

- ***Failures***
  - mainly local and leptomeningeal
  - All local recurrence within CTV
  - No patients developed distant metastases outside of the CNS



Bradley JA, et al. Patterns of Failure in Parameningeal Alveolar Rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. 2020 Feb 7. [Epub ahead of print]

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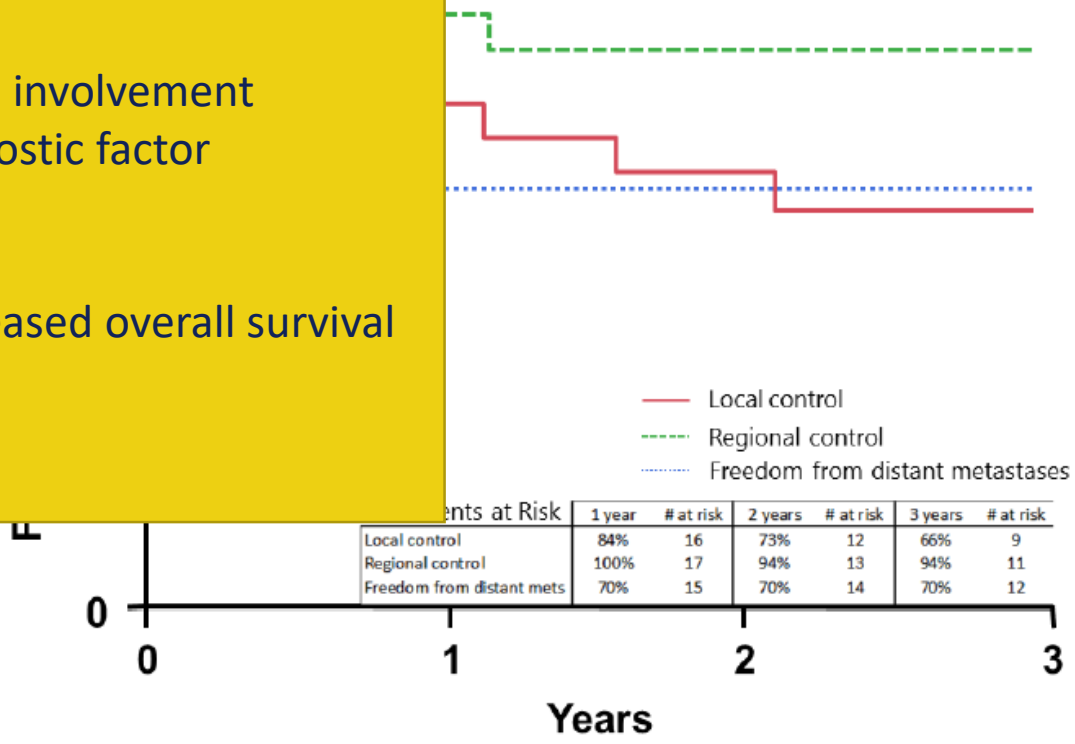
- Median FUP 2
- 3-year LC 66%
- Median time t

- ***Failures***
  - mainly local and leptomeningeal
  - All local recurrence within CTV
  - No patients developed distant metastases outside of the CNS

Confirms :
Alvelolar histology higher risk for LN involvement
Intracranial extension poor prognostic factor

However:
Regional failure did not translate into decreased overall survival



Bradley JA, et al. Patterns of Failure in Parameningeal Alveolar Rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. 2020 Feb 7. [Epub ahead of print]

CASE HISTORY

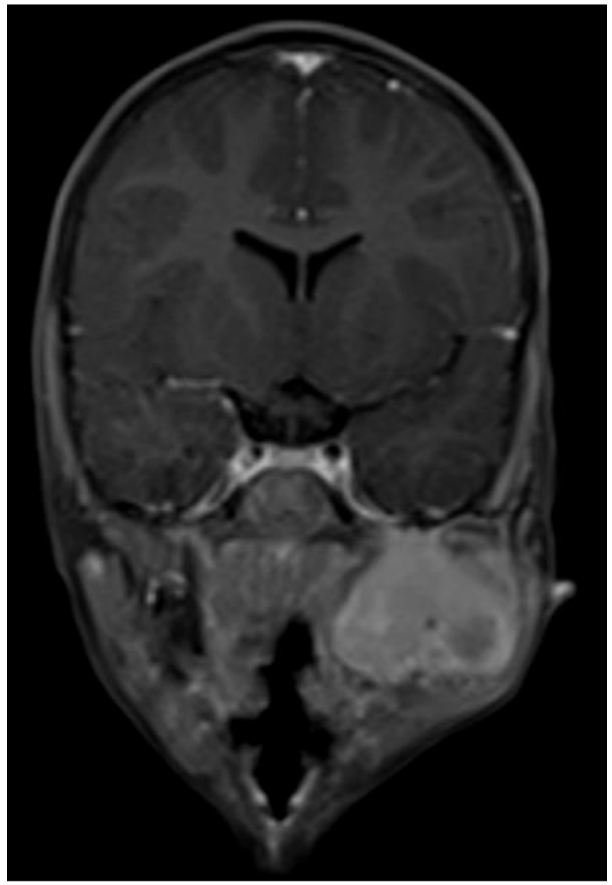
male, **4** years

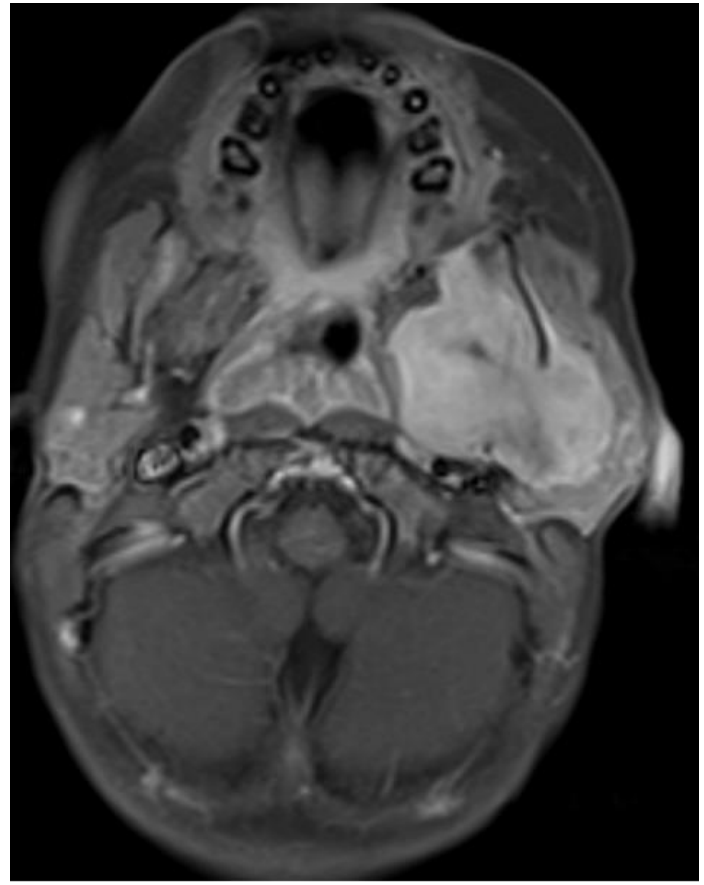
Dx 02/2019

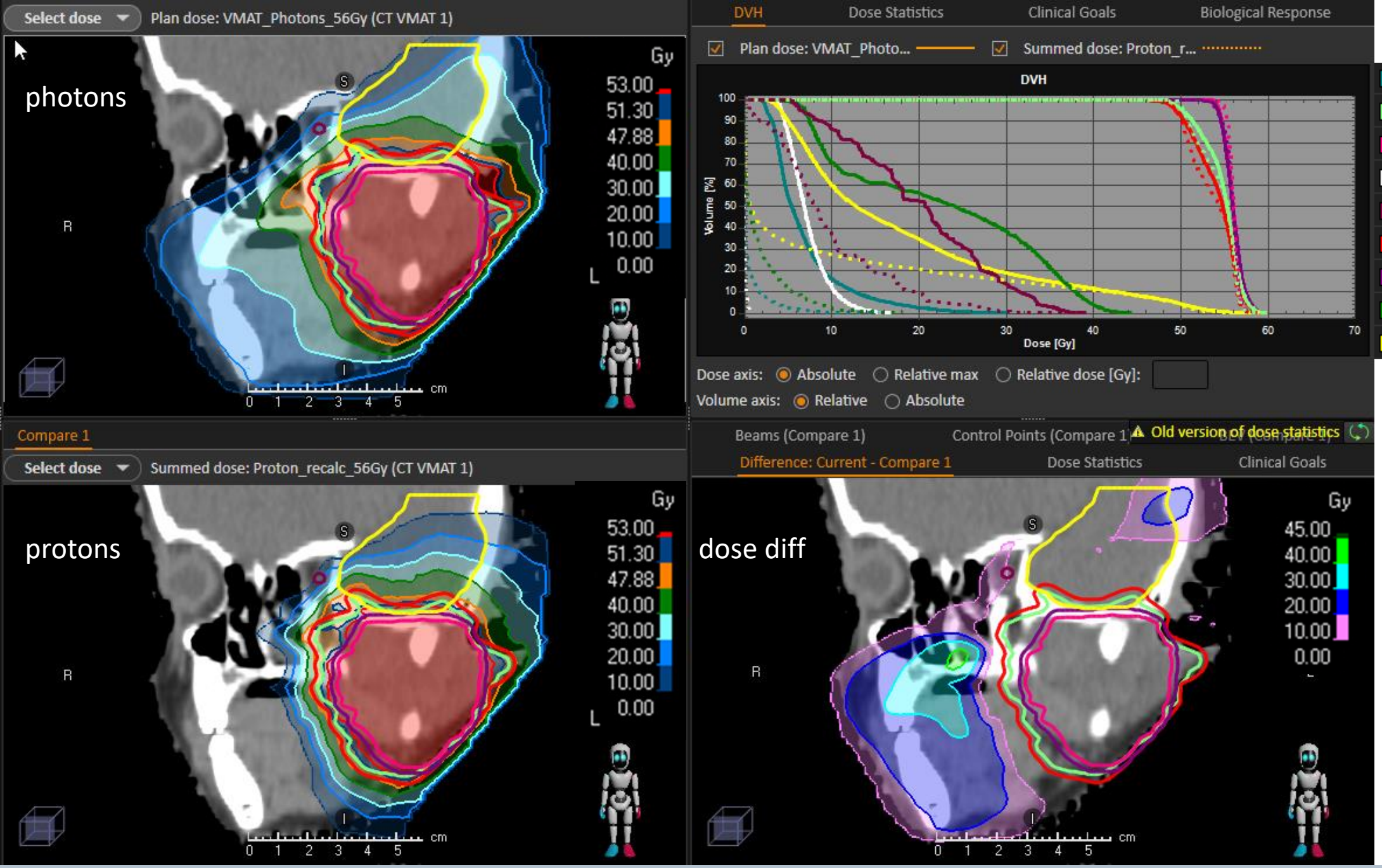
Parameningeal rhabdomyosarcoma, embryonal

- St.p. biopsy 02/2019
- St.p. chemotherapy according to EpSSG RMS 2005

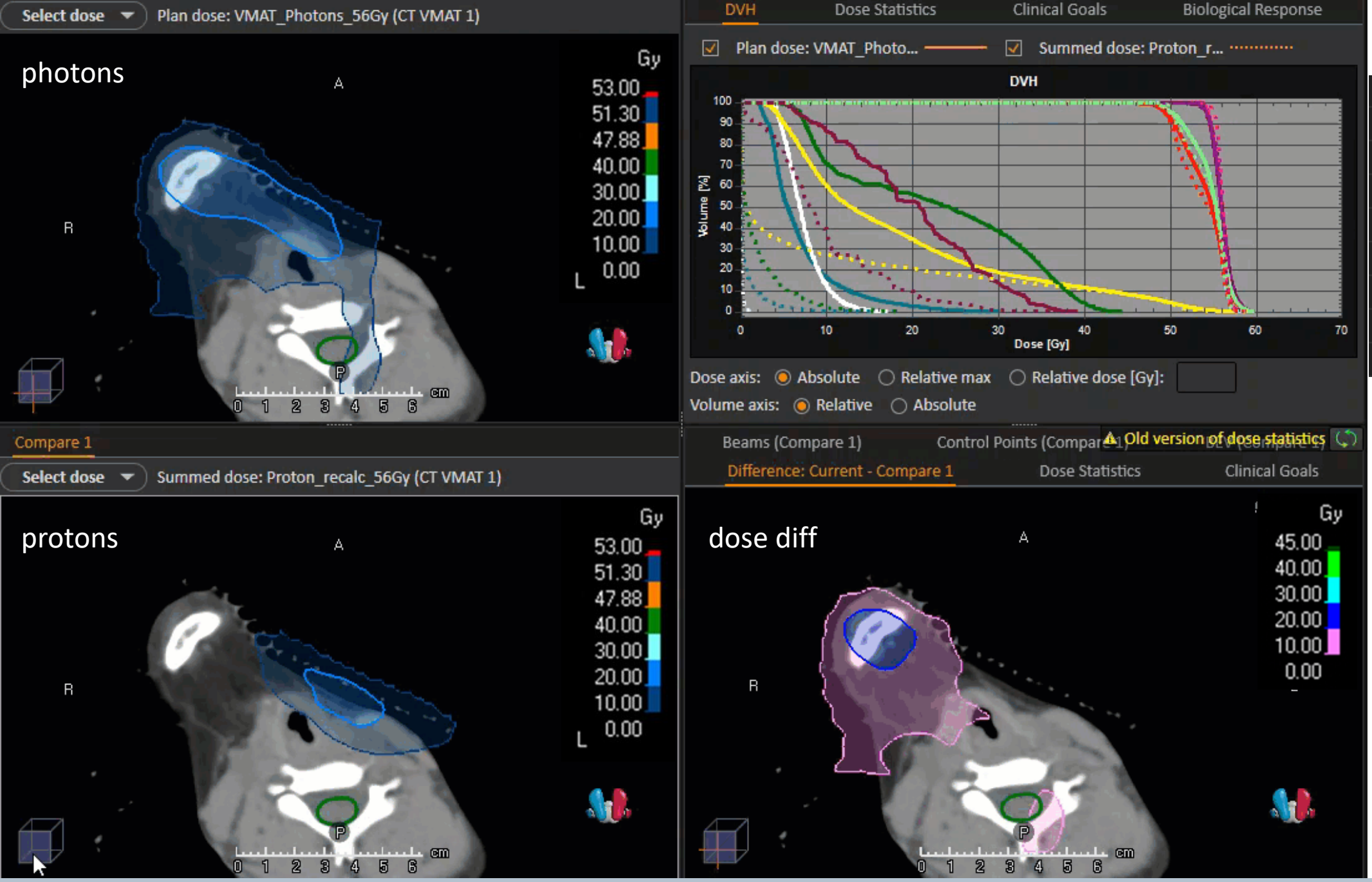
- Re-evaluation on week 9 → minor response
- No surgery → PBT
- SIB: PTV1 50.4Gy, PTV2 55.4Gy







solid DVH: photons
dashed DVH: protons



solid DVH: photons
dashed DVH: protons

- brainstem
- CTV1
- CTV2
- hippocampusLEFT
- opticusLEFT
- PTV1
- PTV2
- spinalcord
- templobeLEFT

Video

Note: Runs automatically in presentation mode.

CASE HISTORY

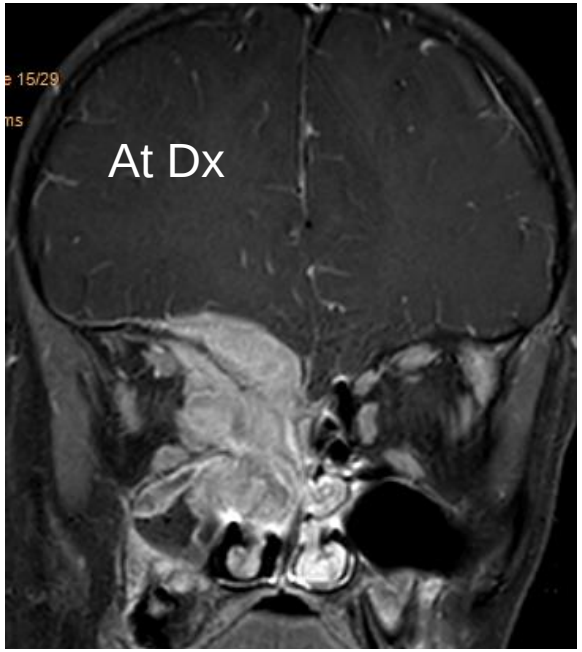
female, 10 years

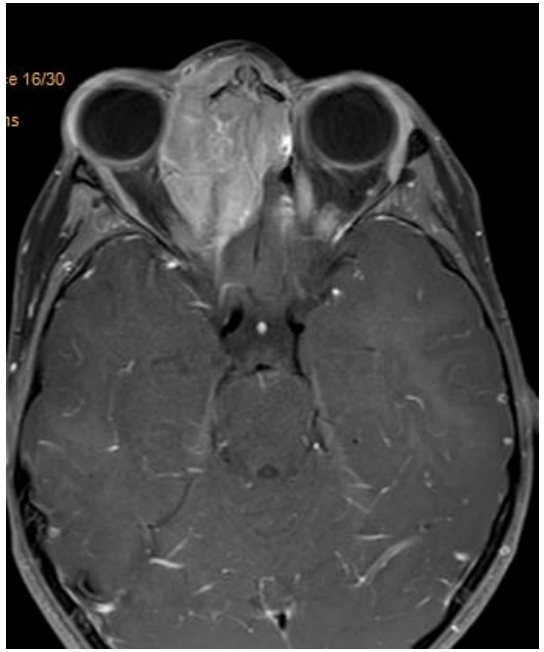
Dx 10/2021

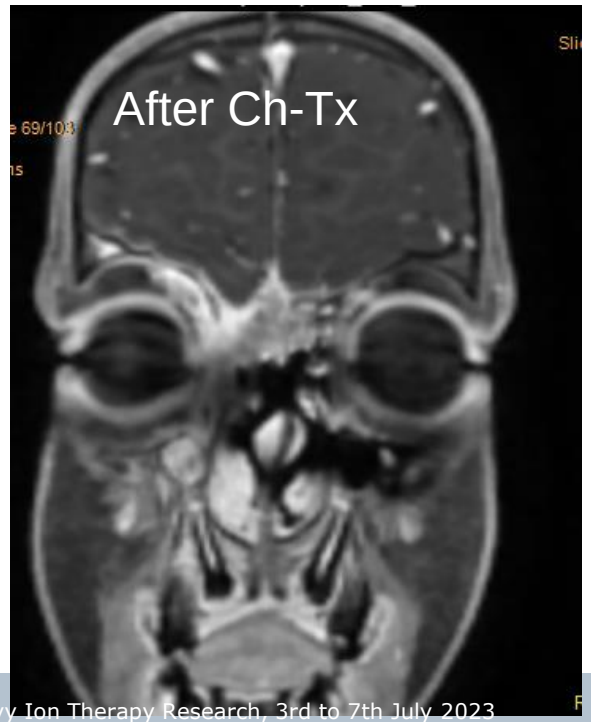
Parameningeal RMS with initial infiltration of the right orbit, maxillary sinus, frontal sinus and ethmoid sinus;
Localized disease, IRSIII
St.p. biopsy 10/2021
Pathology: Alveolar Rhabdomyosarcoma, FOXO1 positive

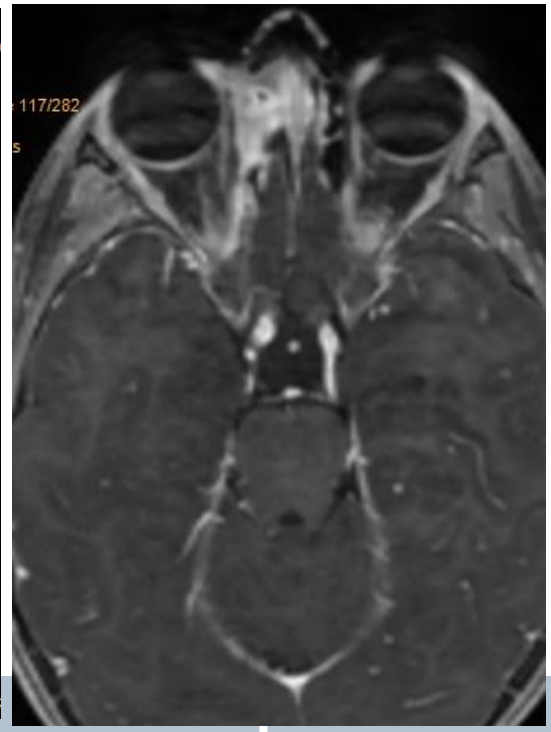
CSF, BM neg; nodes neg.

- chemotherapy according protocol Far RMS; d1 14.10.2021
- Re-evaluation on week 9 → good response
- No surgery → consolidating PBT
- PTV1 54.0Gy, PTV2 59.4Gy

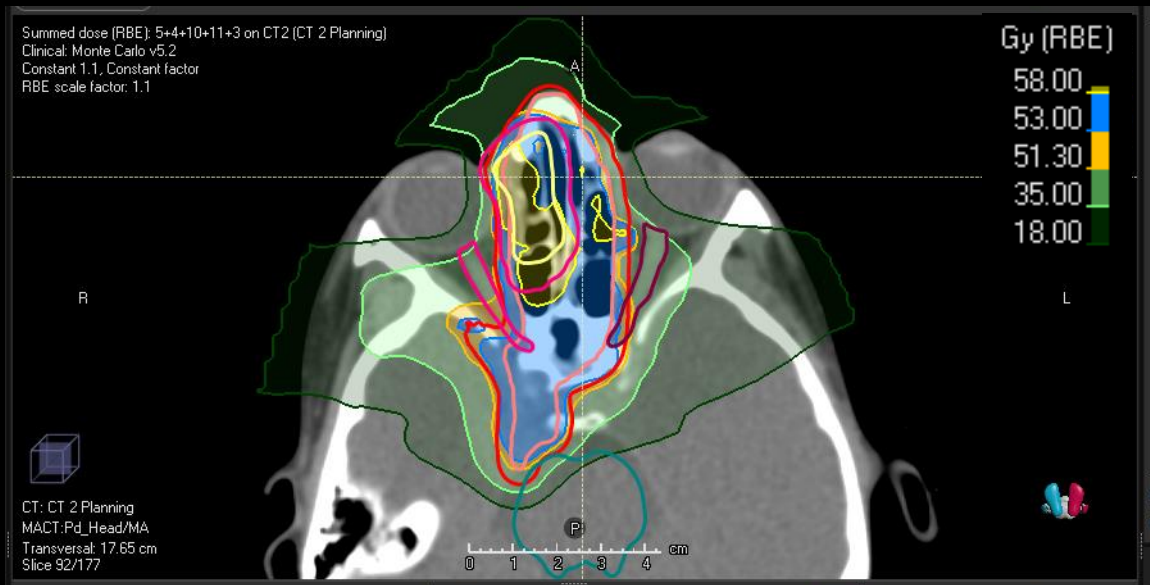


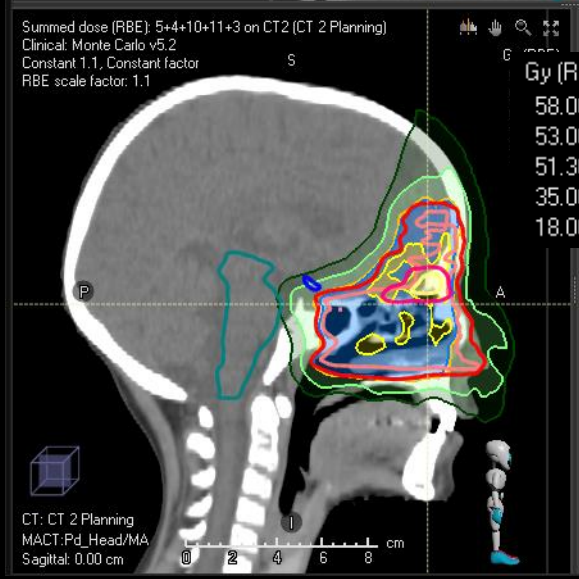


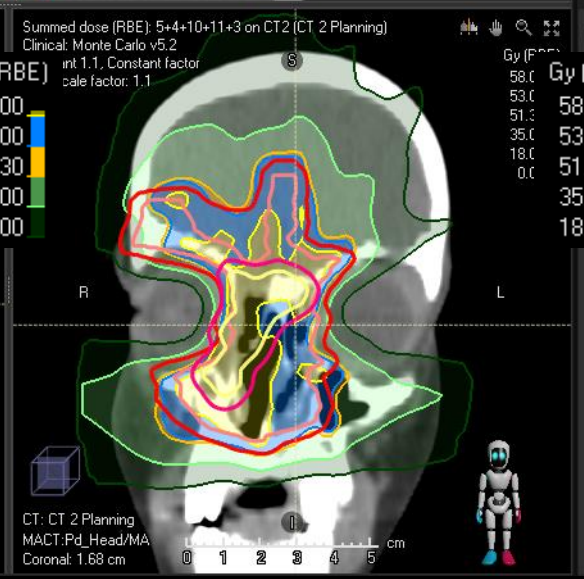




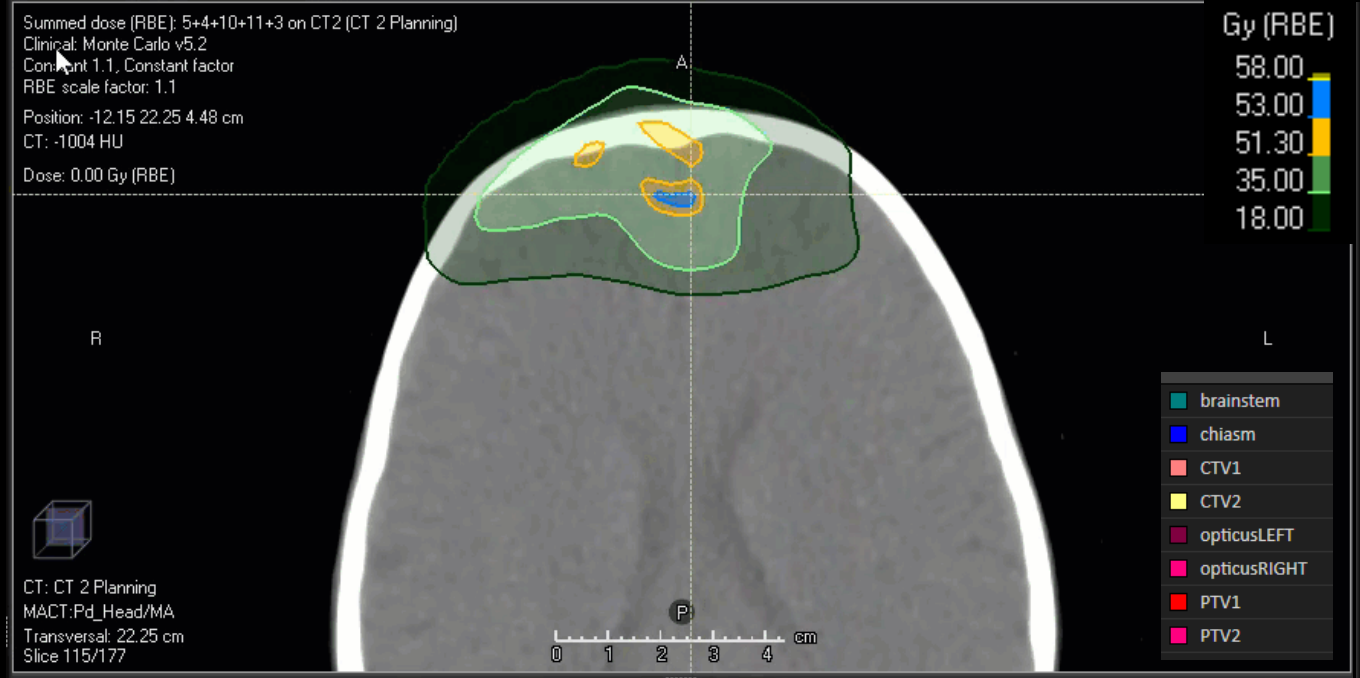
Note: Use of Protons results in minimal additional dose to normal tissues in process of boost-dose increase

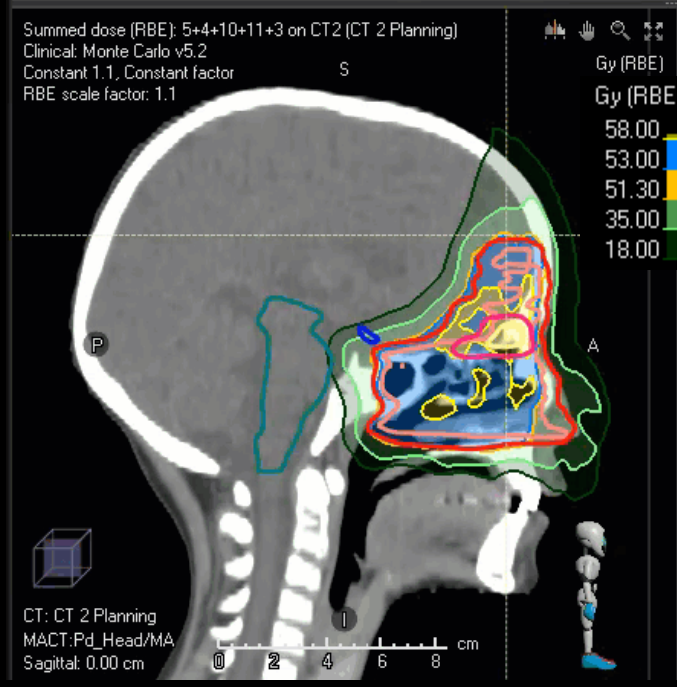


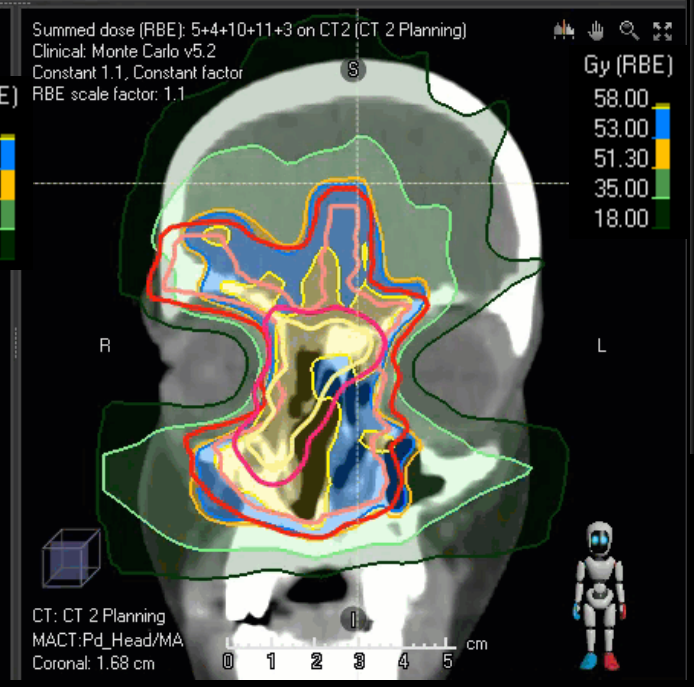


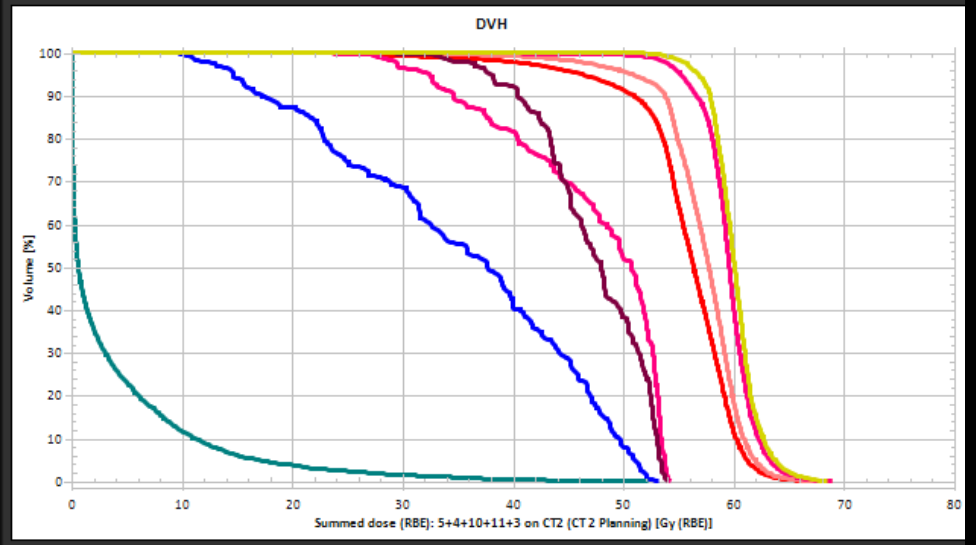


	ROI vol. [cm³]	Dose [Gy (RBE)] D99	D98	D95	Average	D50	D2	D1
brainstem	26.13	0.01	0.02	0.03	3.68	0.61	26.89	34.36
chiasm	0.46	10.89	12.28	14.65	35.36	37.72	51.95	52.16
CTV1	86.35	42.03	45.89	50.89	57.22	57.77	63.16	64.05
CTV2	12.25	54.47	55.41	56.84	60.16	60.13	65.17	66.24
opticusLEFT	0.63	33.52	34.93	37.99	47.33	47.99	53.59	53.81
opticusRIGHT	0.70	27.92	29.36	32.42	47.19	50.78	53.92	54.03
PTV1	150.03	33.67	39.83	46.35	55.66	56.38	62.58	63.47
PTV2	27.53	52.31	53.75	55.21	59.53	59.62	64.60	65.70









Dose axis: Absolute | Relative max | Relative dose [Gy (RBE)]:
Volume axis: Relative | Absolute

Dose stati... | Clinical g... | Biological... | Plan frac... | Beams (C... | Control p... | BEV (Curr...

ROI statistics | POI statistics

ROI	ROI vol. [cm³]	Dose [Gy (RBE)] D99	D98	D95	Average	D50	D2	D1
brainstem	26.13	0.01	0.02	0.03	3.68	0.61	26.89	34.36
chiasm	0.46	10.89	12.28	14.65	35.36	37.72	51.95	52.16
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opticusLEFT	0.63	33.52	34.93	37.99	47.33	47.99	53.59	53.81
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PTV1	150.03	33.67	39.83	46.35	55.66	56.38	62.58	63.47
PTV2	27.53	52.31	53.75	55.21	59.53	59.62	64.60	65.70

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ORBITAL EMBRYONAL RMS

45 GyRBE for group III orbital embryonal rhabdomyosarcoma

- prospective outcome study
- 30 pts; median age 4.8a (range, 1–11.4)
- Median total dose 45Gy (36 GyRBE+9 GyRBE)
- Median FUP 4.0 a (range, 0.5–9.5)

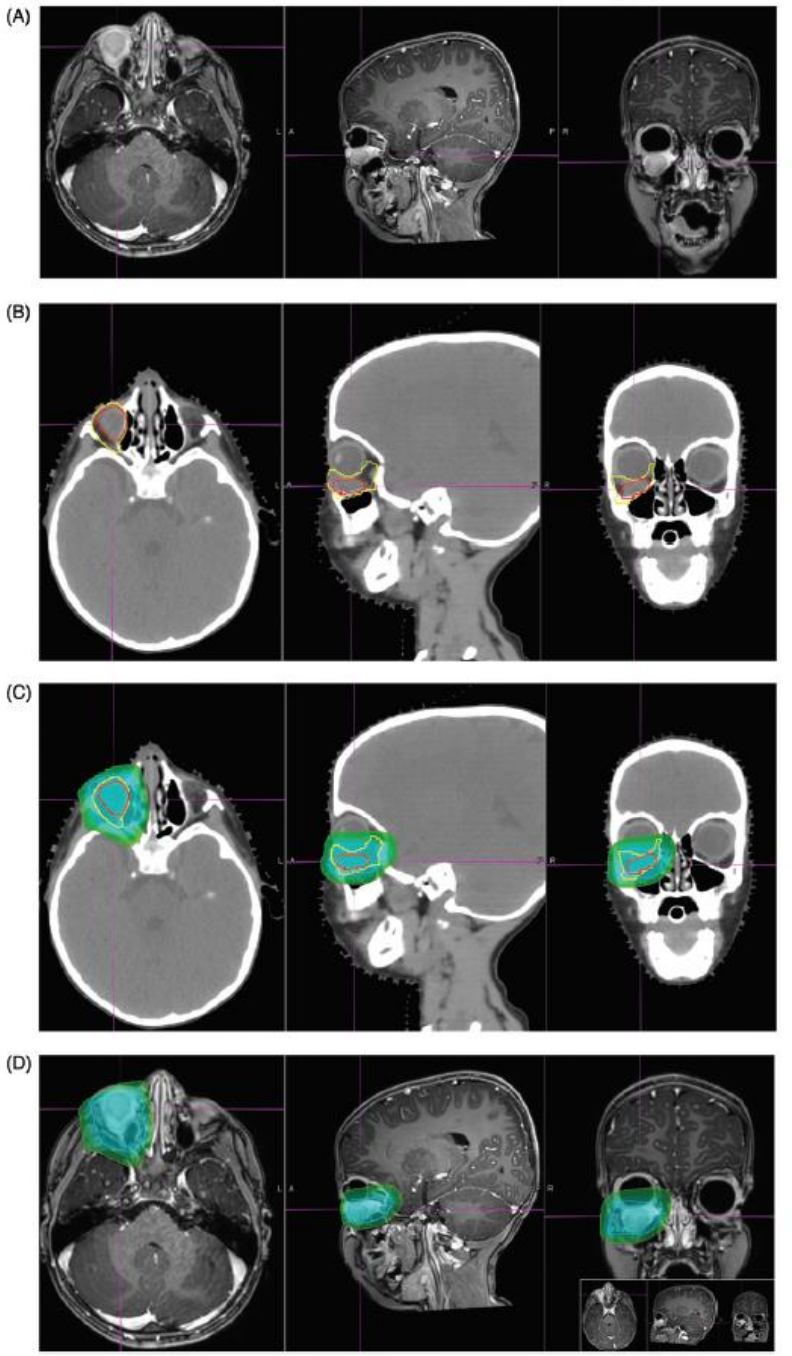
Results:

- 5a LC 97%,PFS 97%, OS 100%

- "Serious" late toxicity

2/30 – reduced visual acuity: 18 pts with cataracts (15 required surgery or laser treatment, 2 of 15 cataract with reduced visual acuity)

4 pts severe keratoconjunctivitis, 4 pts severe dry eye, 1 chron. sinusitis



Indelicato DJ, et al. 45 GyRBE for group III orbital embryonal rhabdomyosarcoma. Acta Oncol. 2019 Oct;58(10):1404-1409.

PELVIC RMS

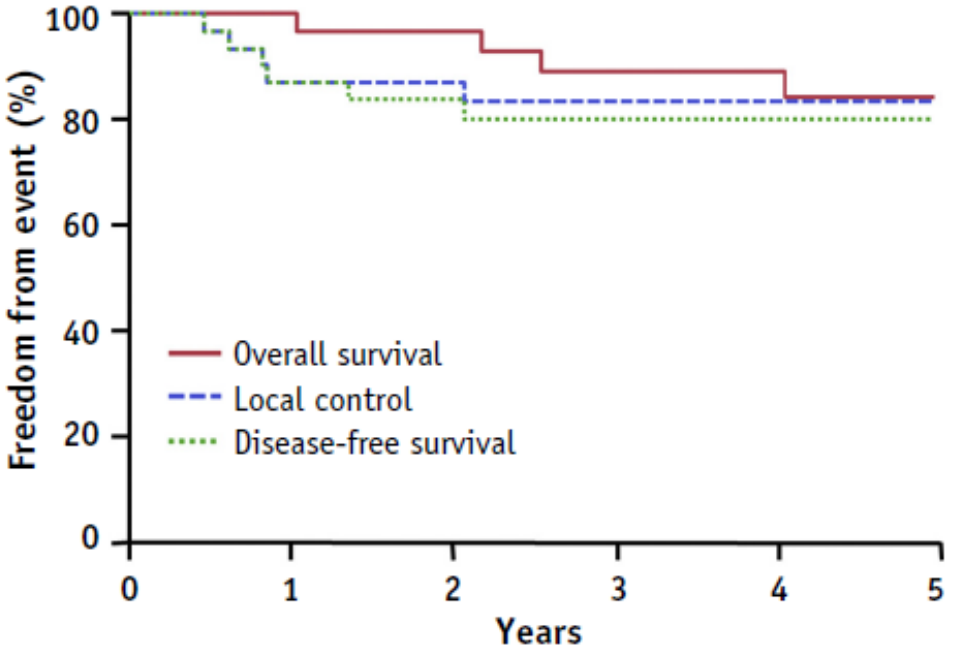
Outcomes Following Proton Therapy for Group III Pelvic Rhabdomyosarcoma

D. Indelicato, U. FL, USA, 2020

- prospective outcome study
- 31 pts; median age 2.6a (range, 1-20)
- 24 embryonal RMS, 7 alveolar RMS
- Median total dose
  - PTV1=36 GyRBE (range, 30.6-43.2)
  - PTV2=50.4 GyRBE (range, 36-59.4)
- Median FUP 2.9a

Results:

- **5a LC 83%**, PFS 80%, OS 84%
  - Pts <3 years old had better LC (100% vs 68%; P<.02),
  - embryonal histology had better OS (96% vs 54%; P < .02)



RT related toxicity:

- >2 toxicity: 1 leg length discrepancy, 1 stress fracture of S1, 1 gonadal failure.

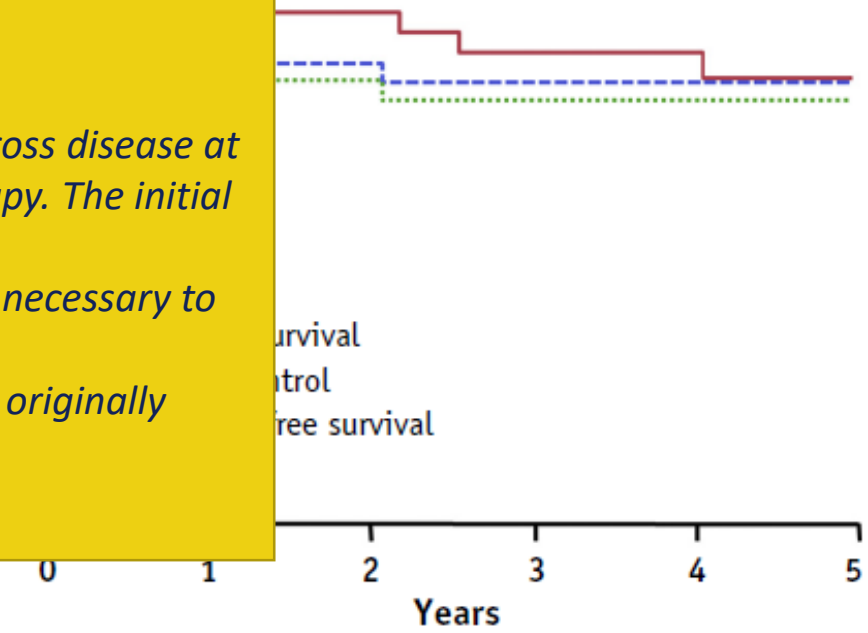
Indelicato DJ, et al. Outcomes following Proton Therapy for Group III Pelvic Rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. 2020 Jan 24. [Epub ahead of print]

PELVIC RMS

Outcomes Following Proton Therapy for Group III Pelvic Rhabdomyosarcoma

- prospective outcome st
- 31 pts; median age 2.6a
- 24 embryonal RMS, 7 a
- Median total dose
  - PTV1=36 GyRBE (ran
  - PTV2=50.4 GyRBE (ra
- Median FUP 2.9a

Note:
Reduced Volume definition:
"The gross tumor volume (GTV) was defined by the gross disease at the time of radiation, following induction chemotherapy. The initial clinical target volume (CTV1)
was defined as the GTV + 10 mm, further modified as necessary to encompass all surfaces
originally in contact with the tumor and all soft tissue originally infiltrated by disease."



Results:

- 5a LC 83%, PFS 80%, OS 84%
  - Pts <3 years old had better LC (100% vs 68%; P<.02),
  - embryonal histology had better OS (96% vs 54%; P < .02)
  - No sign difference between combined-modality local therapy versus definitive radiation.

RT related toxicity:

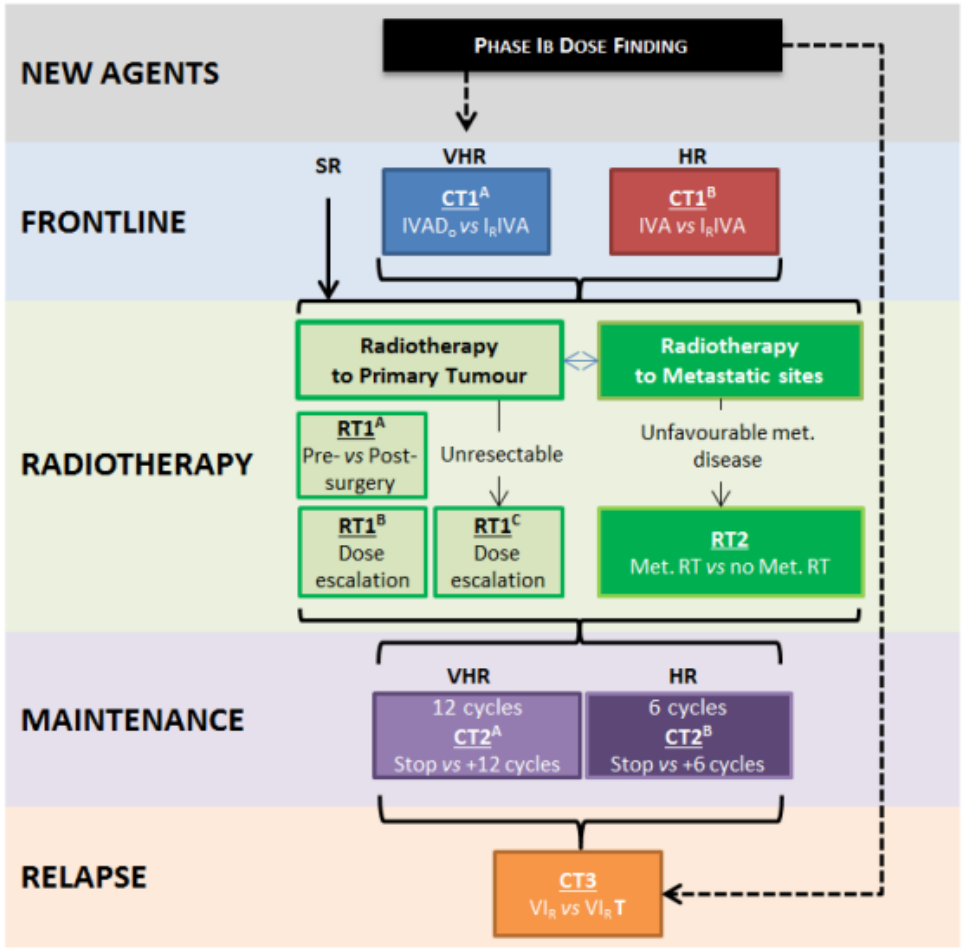
- >2 toxitity: 1 leg length discrepancy, 1 stress fracture of S1, 1 gonadal failure.

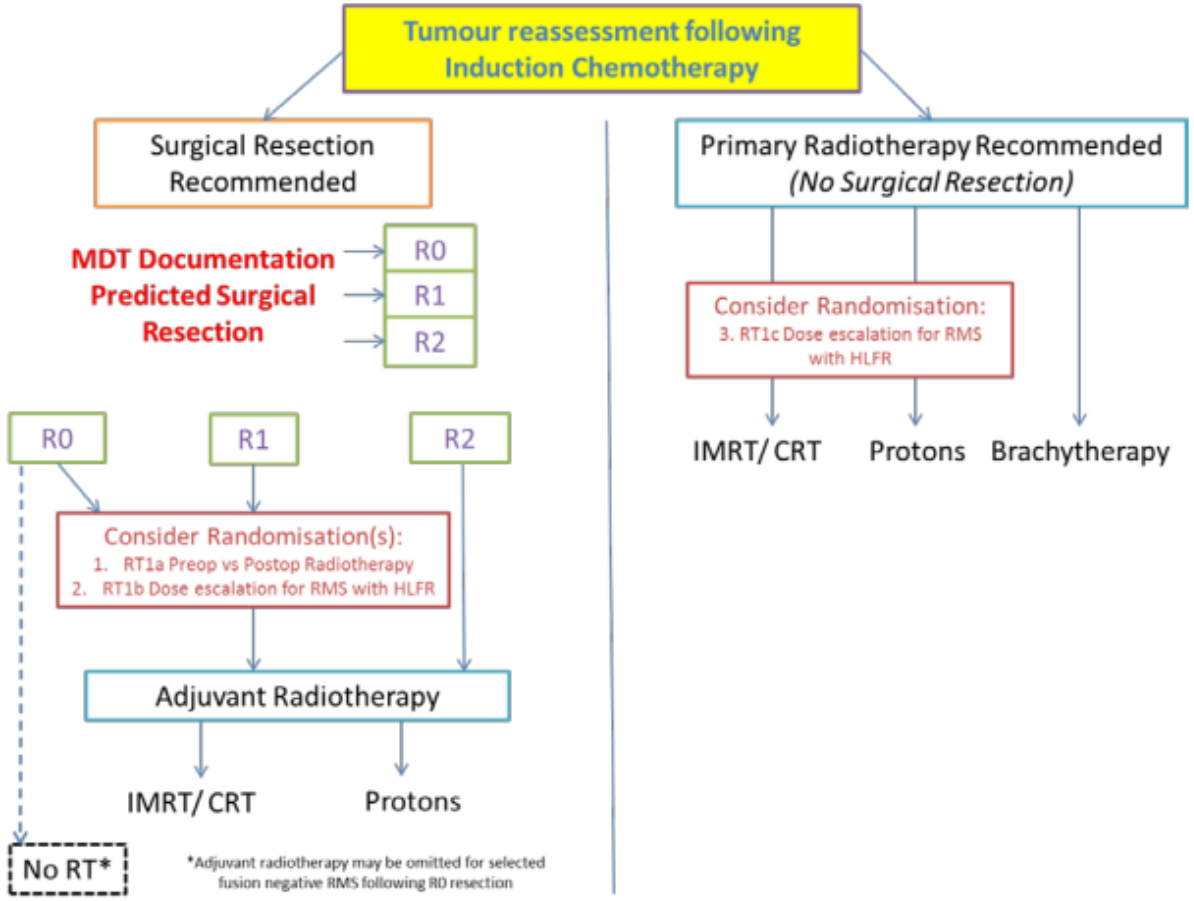
Indelicato DJ, et al. Outcomes following Proton Therapy for Group III Pelvic Rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. 2020 Jan 24. [Epub ahead of print]

RHABDOMYOSARCOMA – RADIOTHERAPY (FAR-RMS)

TRIAL SCHEMA

Figure 1: Overall Trial Schema





DOSES: PATIENTS WITH RESECTABLE DISEASE

Resectable pre or post-op radiotherapy SLFR standard dose:

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVp_Pre_4140	41.4 Gy	23	1.8 Gy

Resectable pre or post-op radiotherapy HLFR standard dose:

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVp_Pre_4140	41.4 Gy	23	1.8 Gy

Resectable pre or post-op radiotherapy HLFR escalated dose:

Two phase technique:

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
1	PTVp_Pre_4140	41.4 Gy	23	1.8 Gy
2	PTVp_Post_5040	9.0 Gy	5	1.8 Gy

OR Simultaneous integrated boost (SIB):

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVp_Pre_4250	42.5 Gy	28	1.518 Gy
	PTVp_Post_5040	50.4 Gy	28	1.8 Gy

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DOSES: PATIENTS WITH UN-RESECTABLE DISEASE

Unresectable complete response (to induction chemotherapy) standard dose:

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVp_Pre_4140	41.4 Gy	23	1.8 Gy

Unresectable incomplete response (to induction chemotherapy) HLFR standard dose:

Two phase technique:

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
1	PTVp_Pre_4140	41.4 Gy	23	1.8 Gy
2	PTVp_Post_5040	9.0 Gy	5	1.8 Gy

OR Simultaneous integrated boost (SIB):

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVp_Pre_4250	42.5 Gy	28	1.518 Gy
	PTVp_Post_5040	50.4 Gy	28	1.8 Gy

Unresectable incomplete response (to induction chemotherapy) HLFR escalated dose:

Two phase technique:

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
1	PTVp_Pre_4140	41.4 Gy	23	1.8 Gy
2	PTVp_Post_5940	18.0 Gy	10	1.8 Gy

OR Simultaneous integrated boost (SIB):

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVp_Pre_4250	42.5 Gy	28	1.518 Gy
	PTVp_Post_5810	58.1 Gy	28	2.075 Gy

Unresectable incomplete response (to induction chemotherapy) SLFR standard dose:

Two phase technique:

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
1	PTVp_Pre_4140	41.4 Gy	23	1.8 Gy
2	PTVp_Post_5040	9.0 Gy	5	1.8 Gy

OR Simultaneous integrated boost (SIB):

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVp_Pre_4250	42.5 Gy	28	1.518 Gy
	PTVp_Post_5040	50.4 Gy	28	1.8 Gy

FaR-RMS Protocol_ v1.b_11-Nov-2019

DOSES: NODAL RADIOTHERAPY

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVn_Pre_4140	41.4 Gy	23	1.8 Gy

Nodal radiotherapy, in case of bulky macroscopic residual involved lymph nodes after induction chemotherapy:

Two phase technique:

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
1	PTVn_Pre_4140	41.4 Gy	23	1.8 Gy
2	PTVn_Post_5040	9.0 Gy	5	1.8 Gy

OR Simultaneous integrated boost (SIB):

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVn_Pre_4250	42.5 Gy	28	1.518 Gy
	PTVn_Post_5040	50.4 Gy	28	1.8 Gy

FaR-RMS Protocol_ v1.b_11-Nov-2019

DOSES: METASTATIC RADIOTHERAPY

Metastatic radiotherapy:

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVm_Pre_4140	41.4 Gy	23	1.8 Gy

Metastatic radiotherapy, in exceptional case of bulky macroscopic residual metastatic disease after induction chemotherapy:

Two phase technique:

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
1	PTVm_Pre_4140	41.4 Gy	23	1.8 Gy
2	PTVm_Post_5040	9.0 Gy	5	1.8 Gy

OR Simultaneous integrated boost (SIB):

Phase	Target volume	Dose prescription	Fractions	Dose/Fraction
Single phase	PTVm_Pre_4250	42.5 Gy	28	1.518 Gy
	PTVm_Post_5040	50.4 Gy	28	1.8 Gy

FaR-RMS Protocol_ v1.b_11-Nov-2019

EWING SARCOMA AND UNDIFFERENTIATED SMALL ROUND CELL SARCOMAS OF BONE AND SOFT TISSUE

- **Ewing sarcoma** originates from a primordial bone marrow–derived mesenchymal stem cell
- **Older terms** such as peripheral primitive neuroectodermal tumor, Askin tumor (Ewing sarcoma of chest wall), and extraosseous Ewing sarcoma (often combined in the term Ewing sarcoma family of tumors) refer to this same tumor

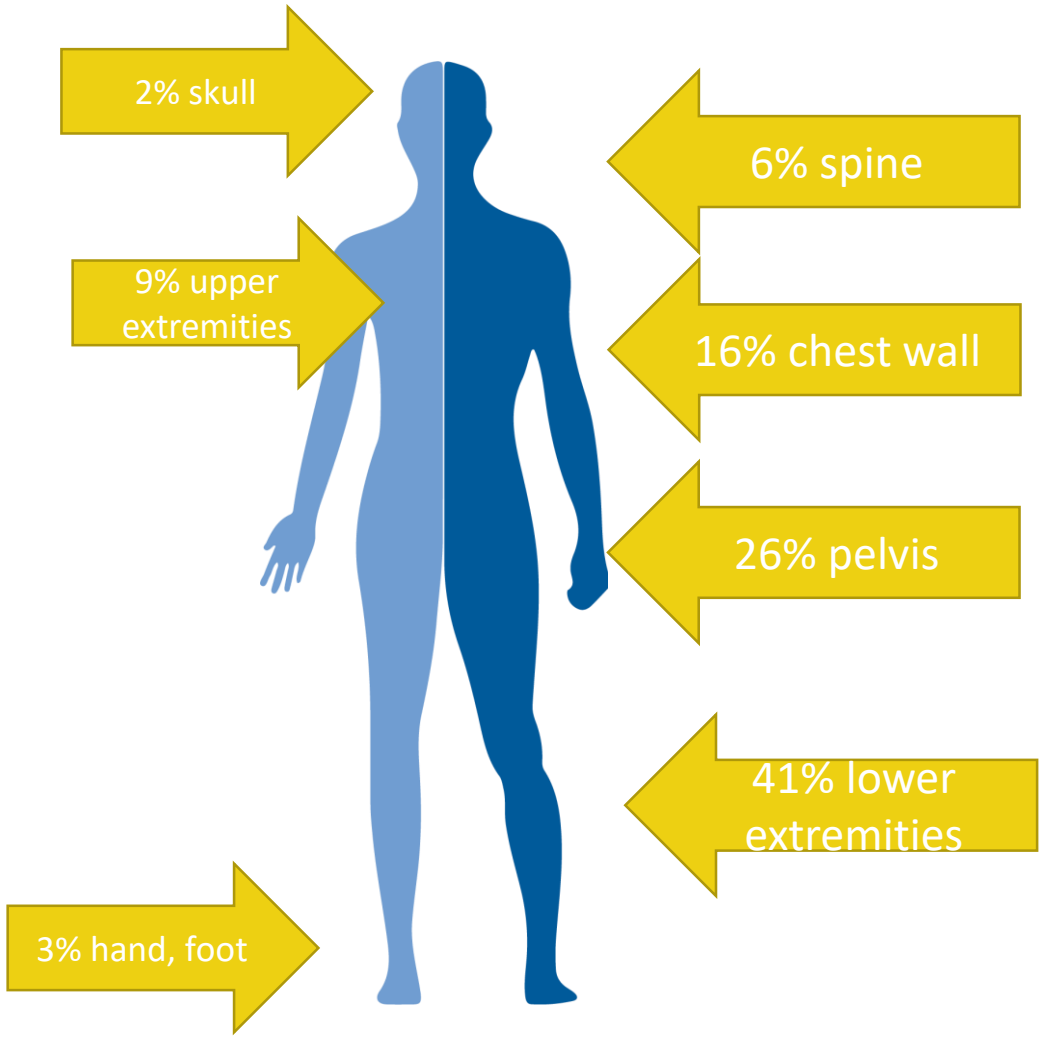
- Before the widespread availability of genomic testing, Ewing sarcoma was identified by the appearance ***of small round blue cells on light microscopic examination, along with positive staining for CD99 by immunohistochemistry***
- *The detection of translocation involving the EWSR1 gene on chromosome 22 band q12 and any one of a number of partner chromosomes is the key feature in the diagnosis of Ewing sarcoma*
- **CAVE: WHO classification 2020** to introduce a new chapter on undifferentiated small round cell sarcomas of bone and soft tissue. This chapter consists of Ewing sarcoma and three main categories
  - Undifferentiated Small Round Cell Sarcomas With BCOR Genetic Alterations.
  - Undifferentiated Small Round Cell Sarcomas With CIC Genetic Alterations.
  - Undifferentiated Small Round Cell Sarcomas With EWSR1::non-ETS Fusions.

  → There is agreement that these tumors are sufficiently different from Ewing sarcoma. These tumors should be stratified and analyzed separately from Ewing sarcoma with the common translocation, even if they are treated with similar therapy.

EWING SARCOMA

- 5-year survival rate has increased from 59% to a range of 75% to 80% for children <15 years and from 20% to 65% for children <15 to 19 years
- median age of patients with Ewing sarcoma is 15 years, and more than 50% of patients are adolescents
- Primary tumor location: osseous and extraosseous (trunk, extremities, head/neck, retroperitoneum, other)

Characteristic	Extraosseous Ewing Sarcoma	Skeletal Ewing Sarcoma	*P* Value
Mean age (range), years	20 (0–39)	16 (0–39)	<.001
Male	53%	63%	<.001
White race	85%	93%	<.001
Axial primary sites	73%	54%	<.001
Pelvic primary sites	20%	27%	.001



EWING SARCOMA
PROGNOSTIC FACTORS

Pretreatment factors

- **Site of tumor:** Patients with **Ewing sarcoma** in the distal extremities have the best prognosis. Patients with **Ewing sarcoma** in the proximal extremities have an intermediate prognosis, followed by patients with central or pelvic sites
- **Extraskeletal versus skeletal primary tumors:** extra-skeletal primary tumors statistically significant better prognosis than did patients with skeletal primary tumors.
- **Tumor size or volume:** Cutoffs of a volume of 100 mL or 200 mL and/or single dimension greater than 8 cm are used to define larger tumors.
- **Age:** Infants and younger patients have a better prognosis than do patients aged 15 years and older
- **Sex:** Girls with **Ewing sarcoma** have a better prognosis than do boys with **Ewing sarcoma**
- Increased LHD and mets are adverse prognostic factors

Response to initial therapy factors

- minimal or no residual viable tumor after presurgical chemotherapy have a significantly better EFS
- decreased PET uptake after chemotherapy correlated with good histological response and better outcome.

EWING SARCOMA BONE AND SOFT TISSUE TREATMENT

*The successful treatment of patients with **Ewing sarcoma** requires systemic chemotherapy in conjunction with surgery and/or radiation therapy for local tumor control*

Chemotherapy: Multidrug chemotherapy for **Ewing sarcoma** always includes vincristine, doxorubicin, ifosfamide, and etoposide.

Local therapy (surgery and RT): Treatment approaches for **Ewing sarcoma** and therapeutic aggressiveness must be adjusted to maximize local control while also minimizing morbidity.
Surgery is the most commonly used form of local control.
RT is an effective alternative modality for local control in cases where the functional or cosmetic morbidity of surgery is deemed too high by experienced surgical oncologists.

Treatment Group	Standard Treatment Options
Localized **Ewing sarcoma**	Chemotherapy
	Local-control measures:
	— Surgery
	— Radiation therapy
	High-dose chemotherapy with autologous stem cell rescue
Metastatic **Ewing sarcoma**	Chemotherapy
	Surgery
	Radiation therapy
Recurrent **Ewing sarcoma**	Chemotherapy (not considered standard treatment)
	Surgery (not considered standard treatment)
	Radiation therapy (not considered standard treatment)
	High-dose chemotherapy with stem cell support (not considered standard treatment)
	Other therapies (not considered standard treatment)

EWING SARCOMA BONE AND SOFT TISSUE RADIOTHERAPY

Radiation therapy is usually employed in the following cases:

- Patients who do not have a surgical option that preserves function and cosmesis.
- Patients whose tumors have been excised but with inadequate margins.
- Preoperative radiation therapy if gross-total resection is possible but without adequate margins (and preservation of function and cosmesis).

- Standard radiation dose varies between 45.0Gy and 55.8Gy (12Gy-15Gy whole lung RT)

TREATMENT OUTCOME IN EWING SARCOMA
DOSE – EFFECT RELATIONSHIP

Author	Localisation	n	RT dose	Outcome
Worawongsakul et al. 2022	Pelvis ES	47	Total dose 59.4 GyRBE	3 year local control 80.2%
Uezono et al. 2020	Pelvis ES	35	Definite RT: 54 – 64.8 GyRBE	3 year local control 92%
Talleur et al. 2016	all localisations	45	Adjuvant RT 50.4 Gy Definitive RT (< 8 cm) 55.8 Definitve RT (> 8cm) 64.8 Gy	10 year local failure rate: 4%, no faliure in the escalated dose group
Ahmed et al. 2017	Pelvis ES	48	Median dose 55.8 Gy (range 48-63 Gy)	Definite RT with doses >56 Gy had the lowest incidence of local failure
Laskar et al. (ASTRO 2019)	All sites (except chest wall and intracranial)	95	Randomisation 55.8 vs. 70.2 Gy	Local control 70.2 Gy group: 79.2% 55.8 Gy group: 55.3 %

EWING SARCOMA: PROGNOSTIC FACTORS

1. Patient/ Tumor factors:

- Tumour size (</> 5-10 cm negatively impacts outcome)
- Tumor site (pelvic localisation is worse when compared to extremities)

2

Indictions for dose escalation

- Tumor localisation (pelvis)
- Large initial tumor volume (> 8 cm)
- Poor histological response to chemotherapy
- Inoperable / incomplete resected tumors

CASE HISTORY

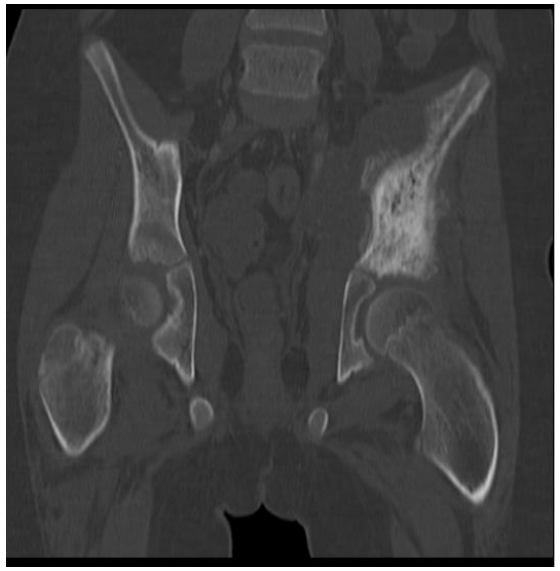
male, 15 years

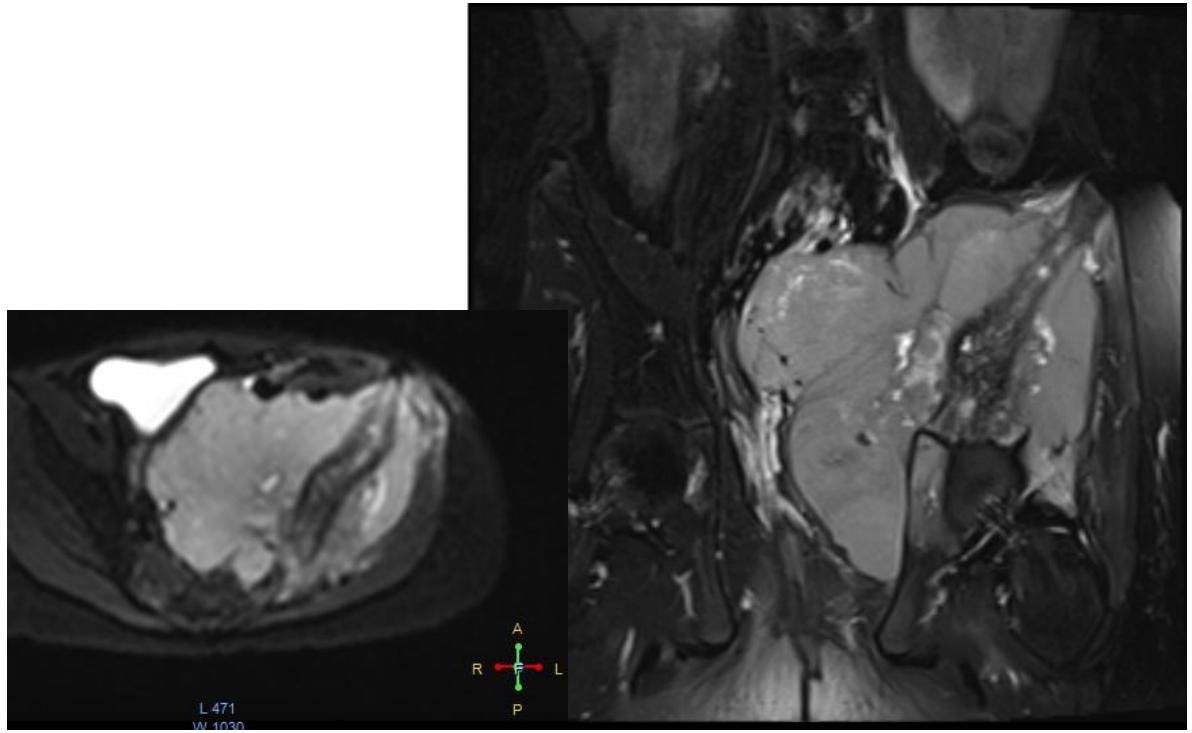
Dx 01/2019

Ewing Sarcoma os ileum sin.

- St.p. biopsy 01/2019
- St.p. chemotherapy according to Euro Ewing protocol
- Re-staging after 6 cycles: tumor regression

- St.p. tumor resection 06/2019 with intraoperative extra-corporal photon radiation of the pelvic bone with 100Gy
- Adjuvant PBT treatment 54.0Gy_1.8Gy





PENIS

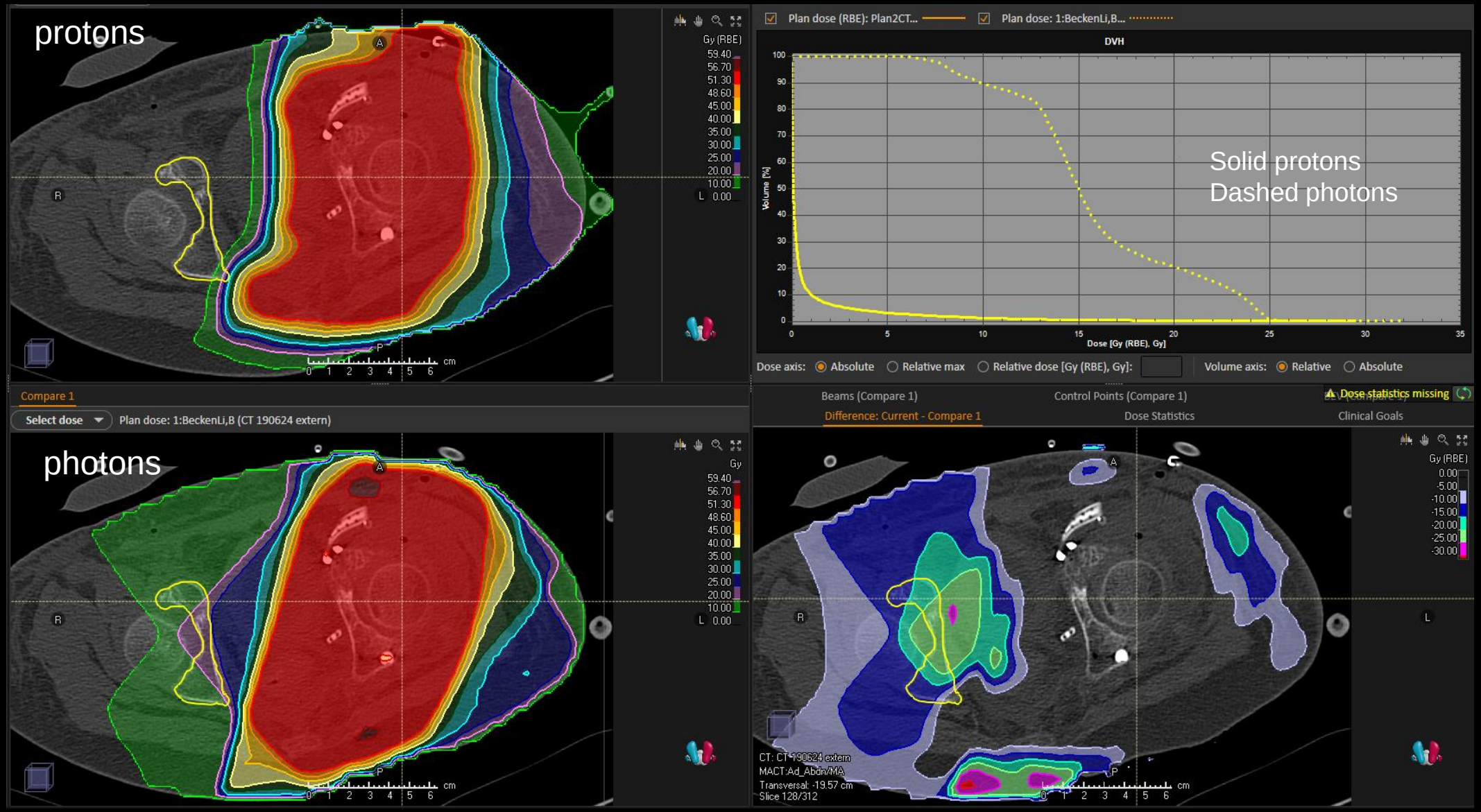

protons
Max Dose 57.58 Gy (RBE)
Gy (RBE)
59.40
56.70
51.30
48.60
45.00
40.00
35.00
30.00
25.00
20.00
10.00
L 0.00
A
P
cm
0 1 2 3 4 5 6


Plan dose (RBE): Plan2CT...
Plan dose: 1:BeckenLi,B...
DVH
Volume [%]
Dose [Gy (RBE)]
0
10
20
30
40
50
60
70
80
90
100
Solid protons
Dashed photons
Dose axis: Absolute Relative max Relative dose [Gy (RBE)], Gy]:
Volume axis: Relative Absolute

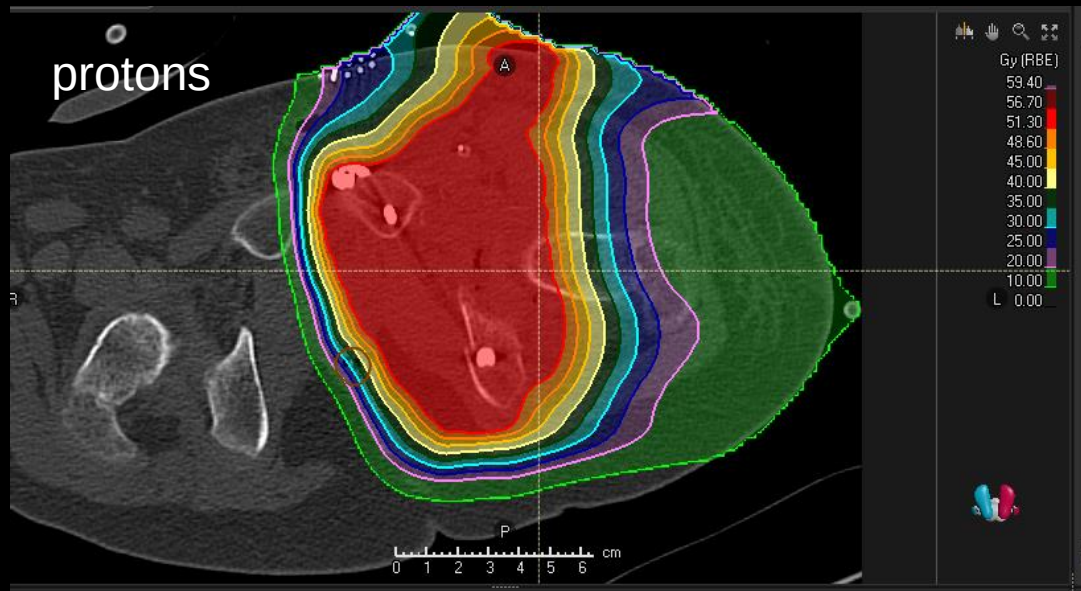

Plan dose: 1:BeckenLi,B (CT 190624 extern)
photons
Gy
59.40
56.70
51.30
48.60
45.00
40.00
35.00
30.00
25.00
20.00
10.00
L 0.00
A
P
cm
0 1 2 3 4 5 6

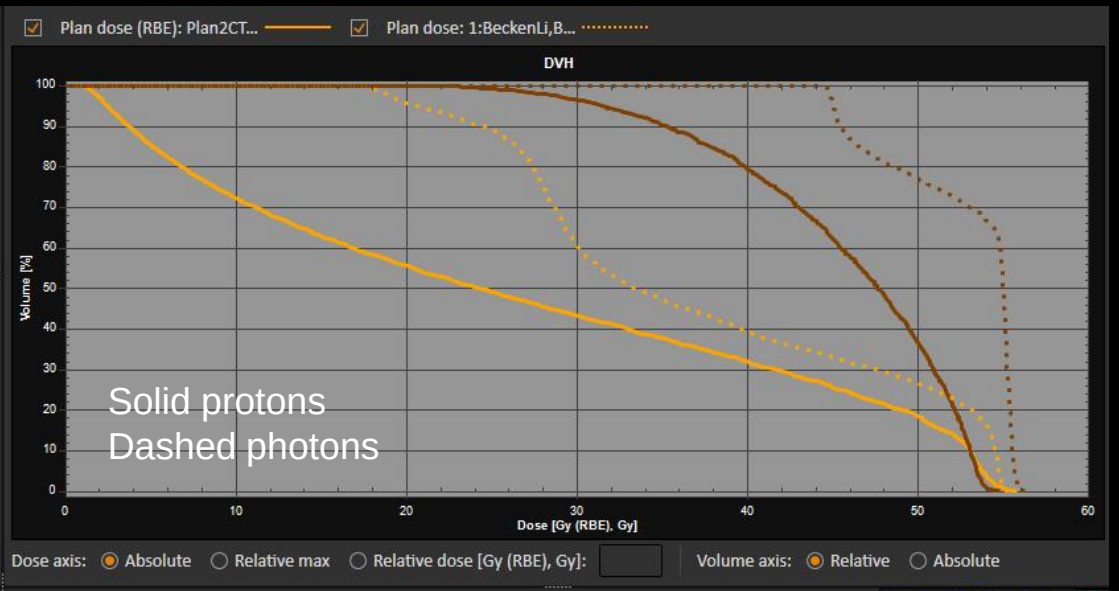

Beams (Compare 1)
Control Points (Compare 1)
Dose statistics missing
Difference: Current - Compare 1
Dose Statistics
Clinical Goals
Position: -6.45 -25.73 -8.20 cm
CT: -1023 HU
Dose difference: 0.00 Gy (RBE)
Gy (RBE)
0.00
-5.00
-10.00
-15.00
-20.00
-25.00
-30.00
A
R
L
P
CT: CT 190624 extern
MACT:Ad_Abdn/MA
Transversal: -25.73 cm
Slice 40/312
cm
0 1 2 3 4 5 6

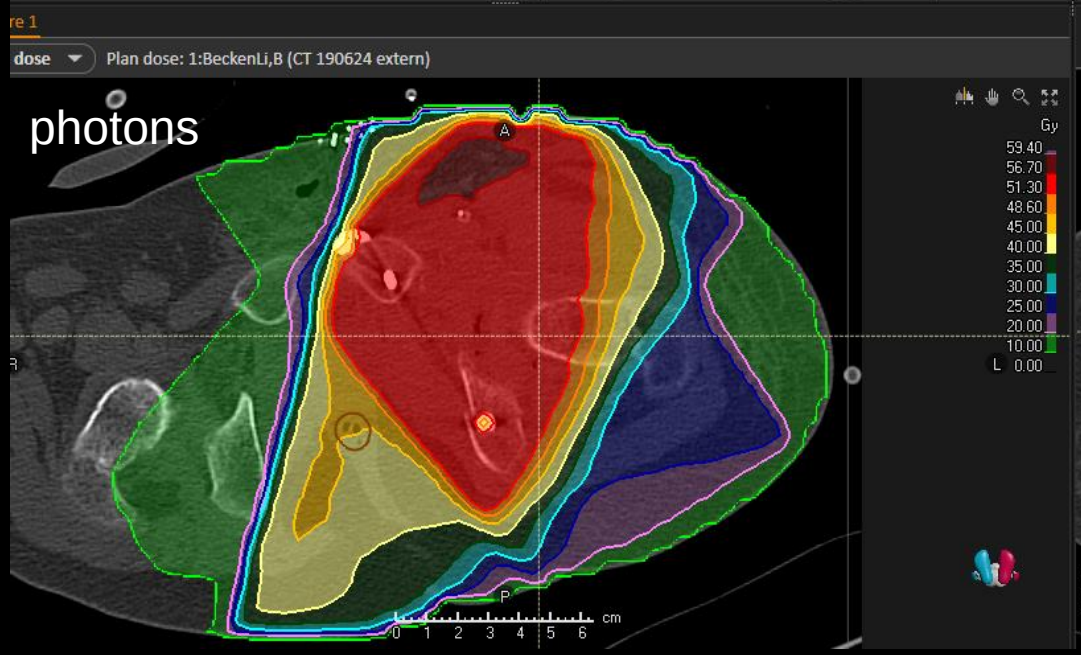
ACETABULUM

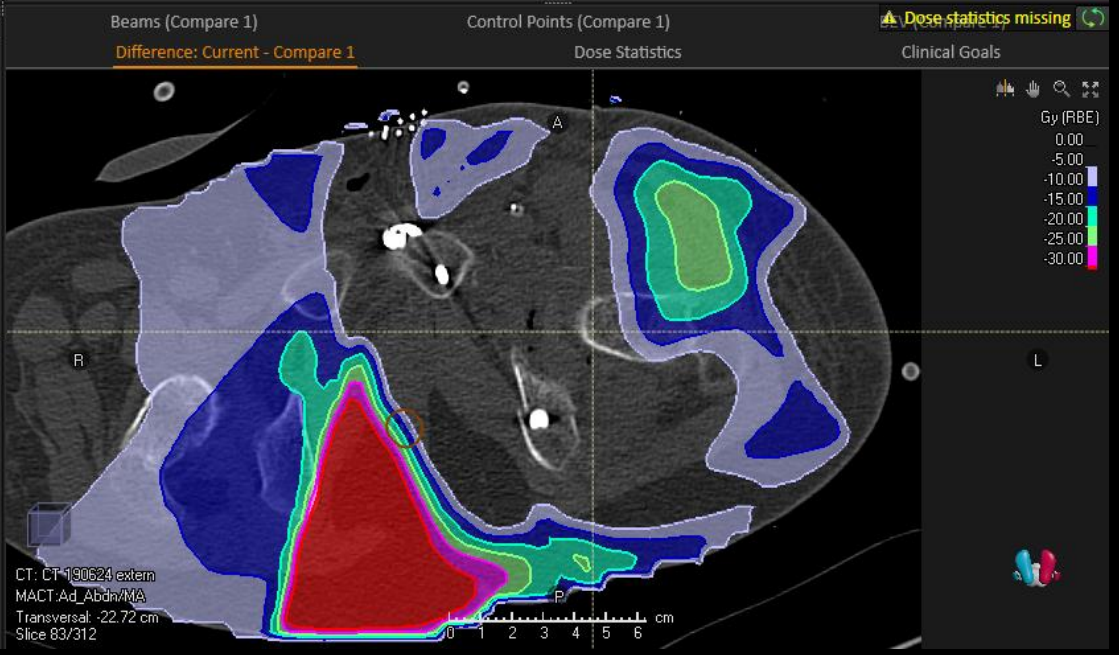

protons
Gy (RBE)
59.40
56.70
51.30
48.60
45.00
40.00
35.00
30.00
25.00
20.00
10.00
0.00
Plan dose (RBE): Plan2CT...
Plan dose: 1:BeckenLi,B...
DVH
Volume [%]
Dose [Gy (RBE)], Gy]
Solid protons
Dashed photons
Dose axis: Absolute Relative max Relative dose [Gy (RBE), Gy]:
Volume axis: Relative Absolute
Compare 1
Select dose
Plan dose: 1:BeckenLi,B (CT 190624 extern)
Beams (Compare 1)
Control Points (Compare 1)
Dose statistics missing
Difference: Current - Compare 1
Dose Statistics
Clinical Goals
photons
Gy
Gy (RBE)
0.00
-5.00
-10.00
-15.00
-20.00
-25.00
-30.00
CT: CT-190624 extern
MACT:Ad_Abdn/MA
Transversal: -19.57 cm
Slice 128/312

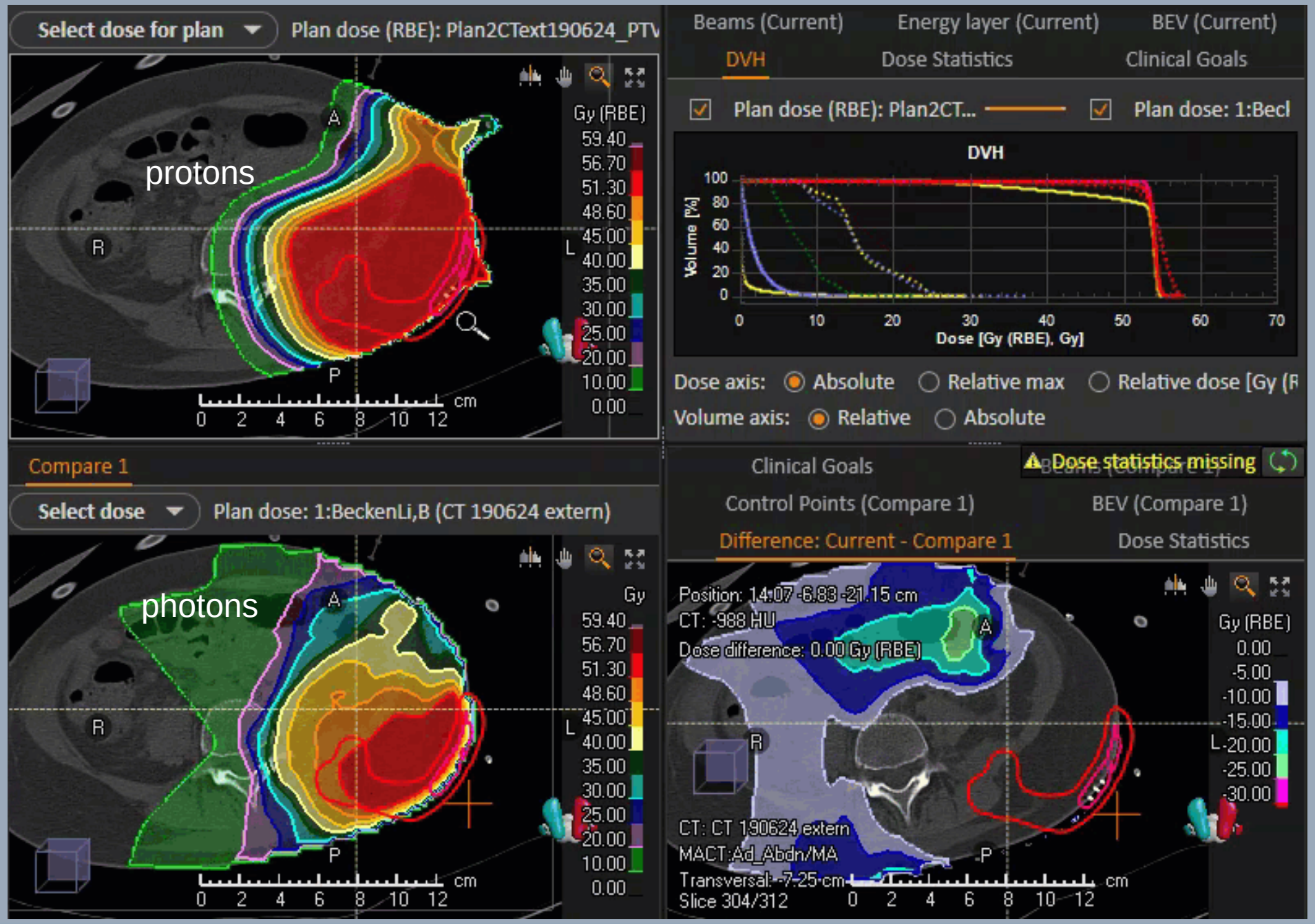
ANUS


protons
Gy (RBE)
59.40
56.70
51.30
48.60
45.00
40.00
35.00
30.00
25.00
20.00
10.00
0.00
A
P
cm
0 1 2 3 4 5 6


Plan dose (RBE): Plan2CT...
Plan dose: 1:BeckenLi,B...
DVH
Volume [%]
Dose [Gy (RBE)], Gy]
Solid protons
Dashed photons
Dose axis: Absolute Relative max Relative dose [Gy (RBE), Gy]:
Volume axis: Relative Absolute


dose
Plan dose: 1:BeckenLi,B (CT 190624 extern)
photons
Gy
59.40
56.70
51.30
48.60
45.00
40.00
35.00
30.00
25.00
20.00
10.00
0.00
A
P
cm
0 1 2 3 4 5 6


Beams (Compare 1)
Control Points (Compare 1)
Dose statistics missing
Difference: Current - Compare 1
Dose Statistics
Clinical Goals
Gy (RBE)
0.00
-5.00
-10.00
-15.00
-20.00
-25.00
-30.00
A
R
L
P
cm
0 1 2 3 4 5 6
CT: CT 190624 extern
MACT:Ad_Abdn/MA
Transversal: -22.72 cm
Slice 83/312

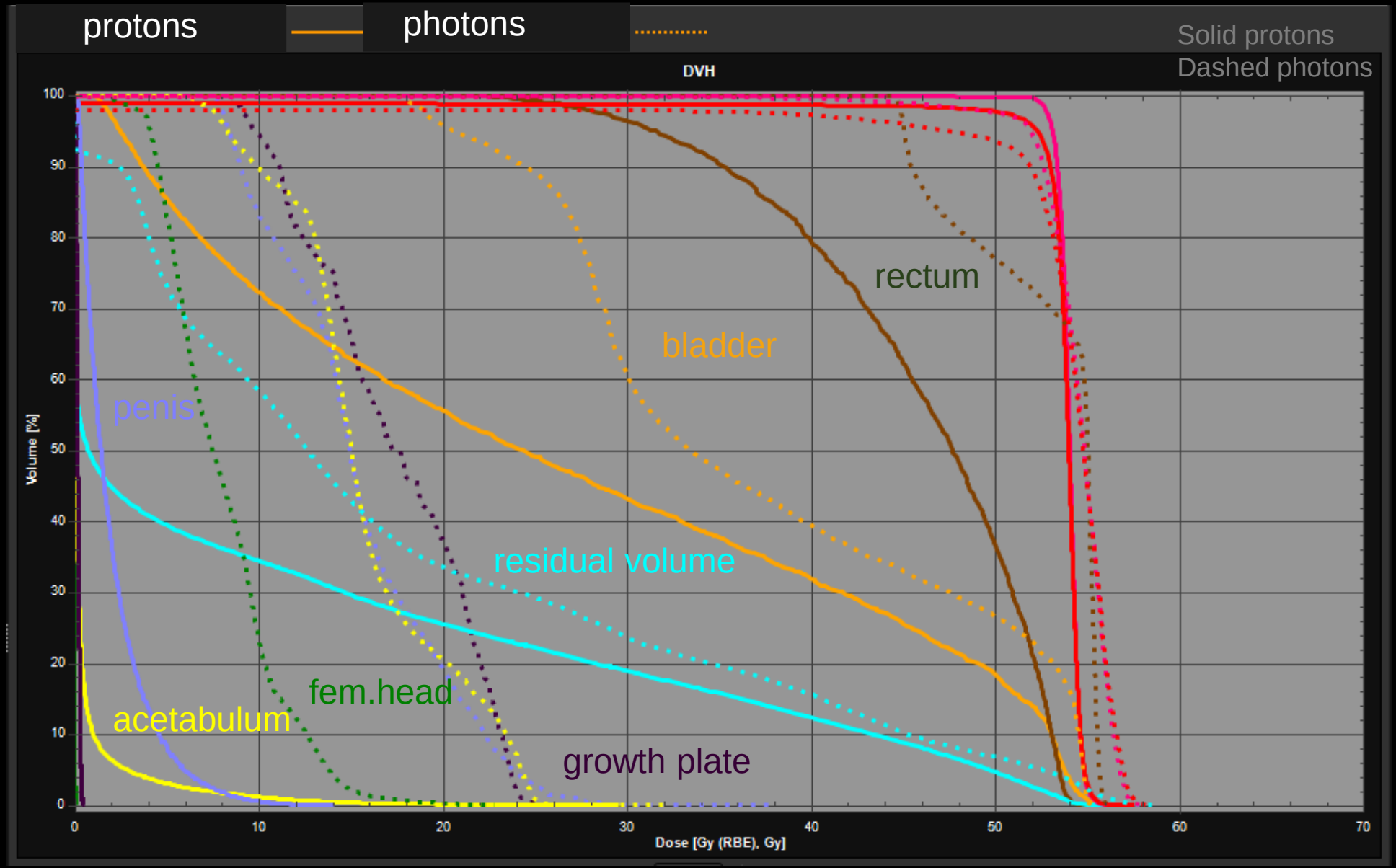


rectum
fem.head
bladder
acetabulum
penis
growth plate

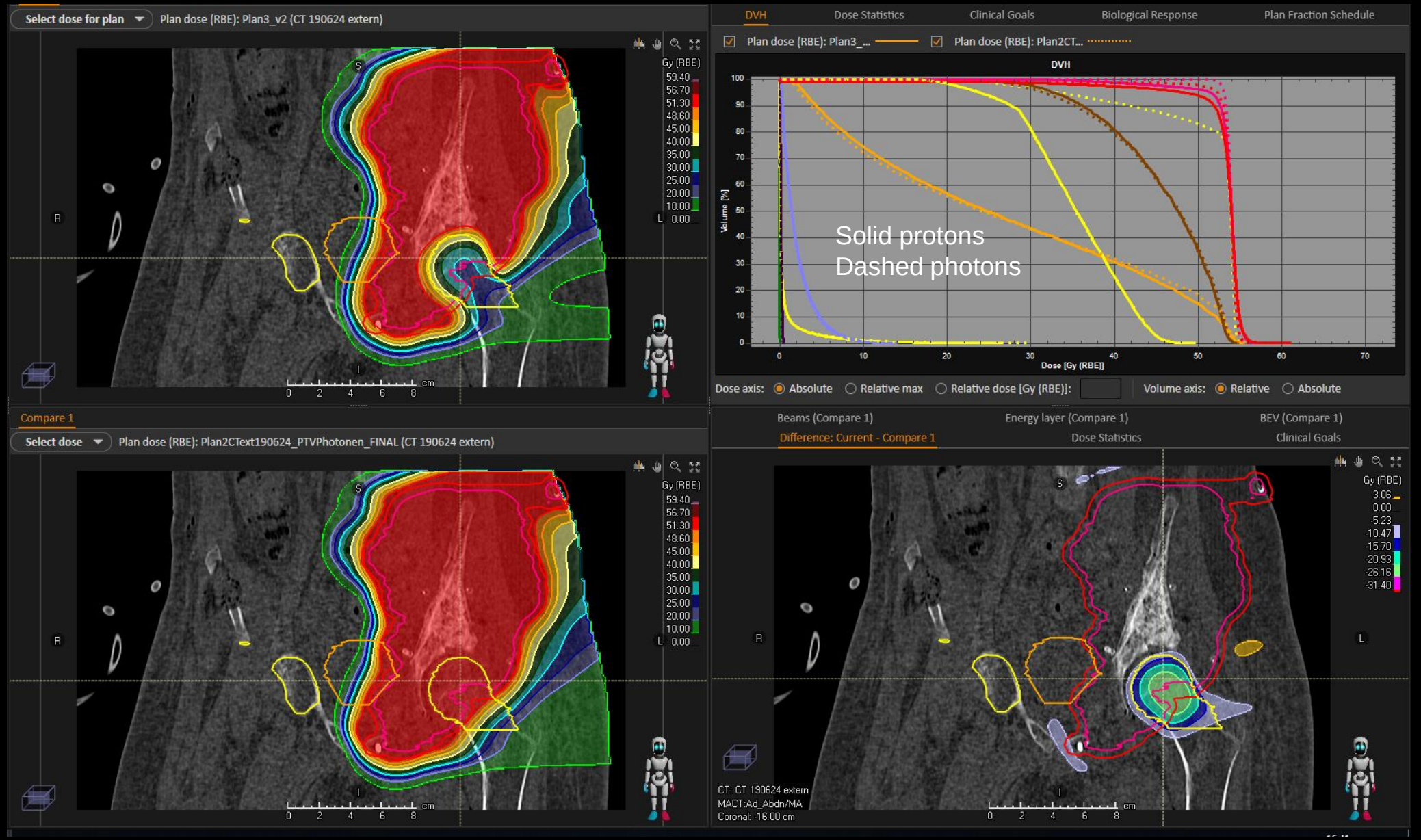
Video

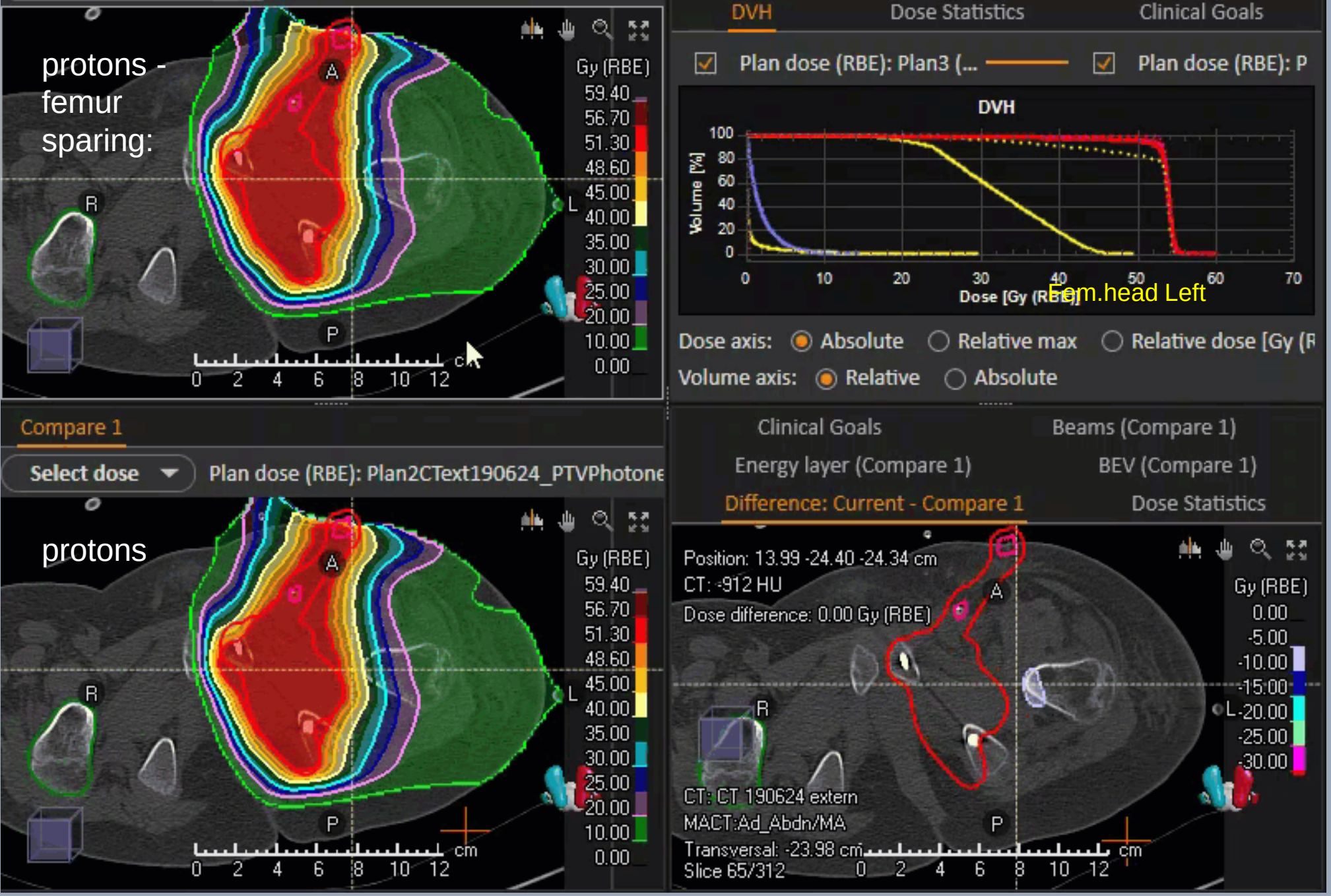
Note: Runs automatically in presentation mode

Summed plans: Protons vs. Photons *DVH*



FEMUR SPARING

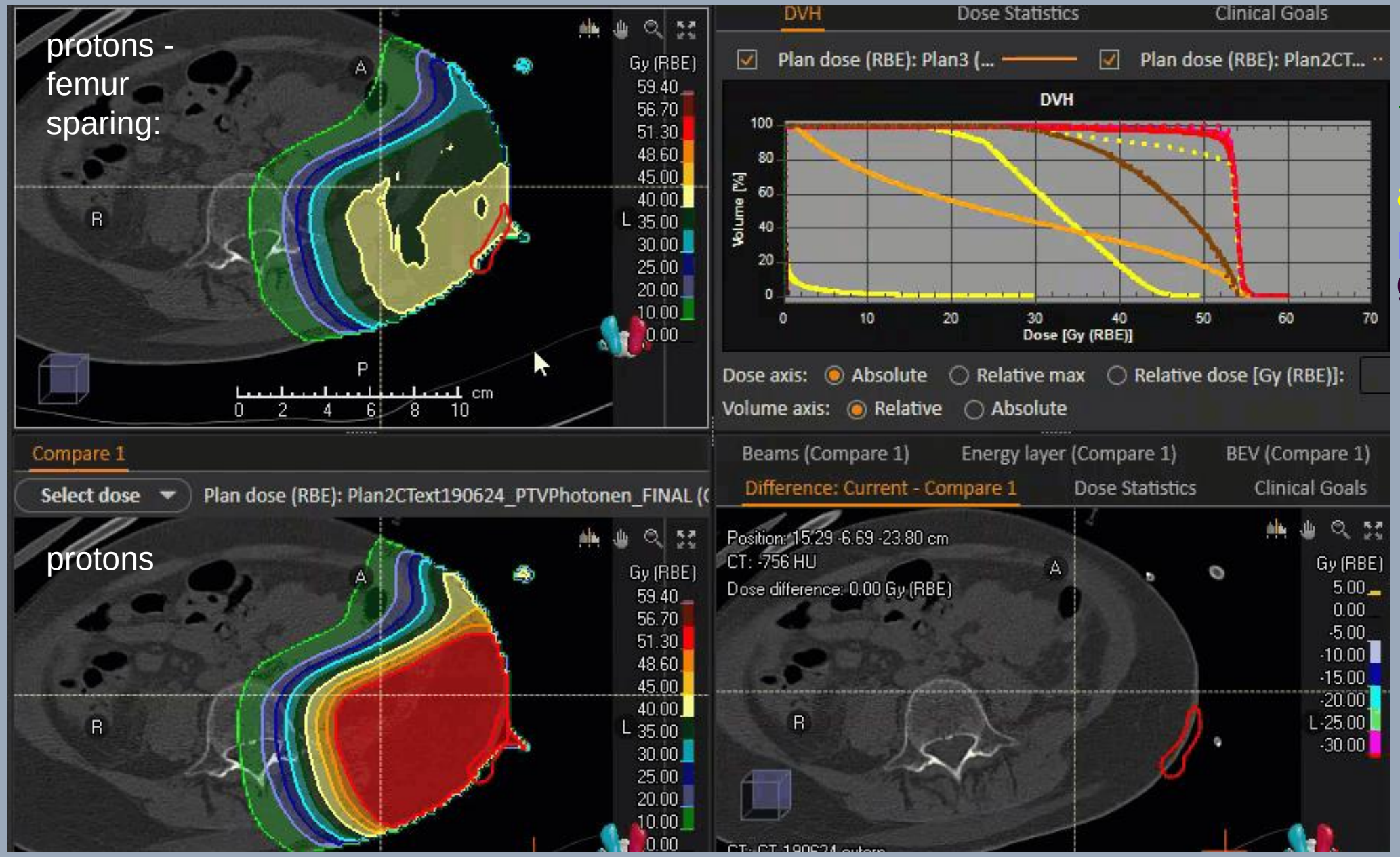




rectum
fem.head
bladder
acetabulum
penis
growth plate

Video FEMUR SPARING short (i.e. only femur region)

Note: Runs automatically in presentation mode



rectum
fem.head
bladder
acetabulum
penis
growth plate

Video FEMUR SPARING

Note: Runs automatically in presentation mode.

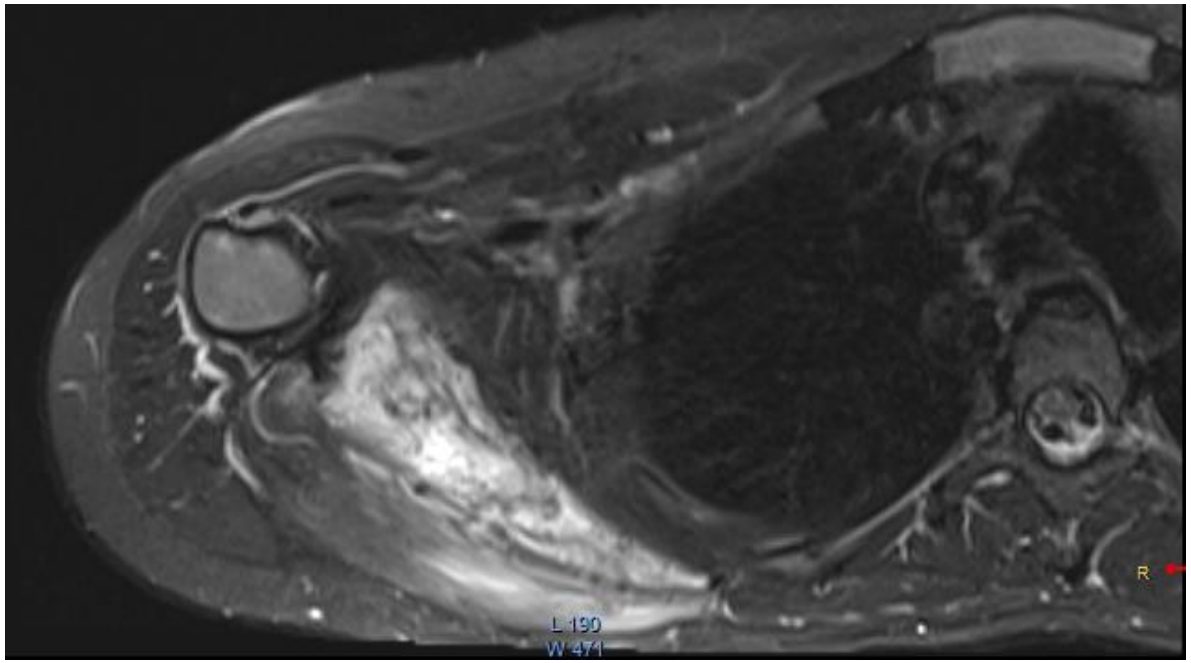
CASE HISTORY

female, 14 years

Dx 01/2019

Ewing Sarcoma scapula

- St.p. neoadjuvant chemotherapy acc. to COG AEWS0031
- St.p. resection of the scapula and axillary lymphadenectomy - minimal bone margins
- St.p. adjuvant CHT
- Indication for adjuvant local treatment with PBT



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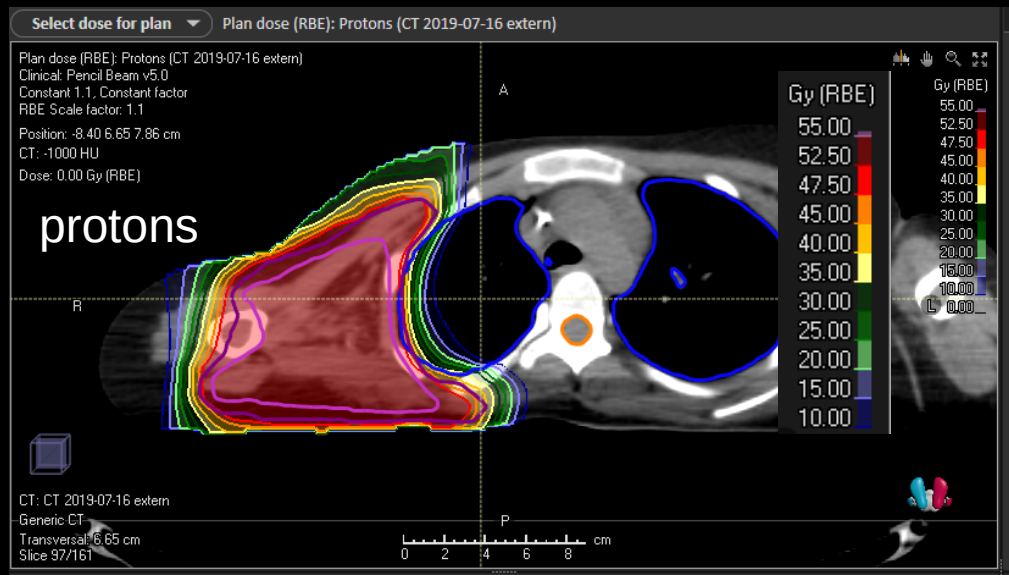
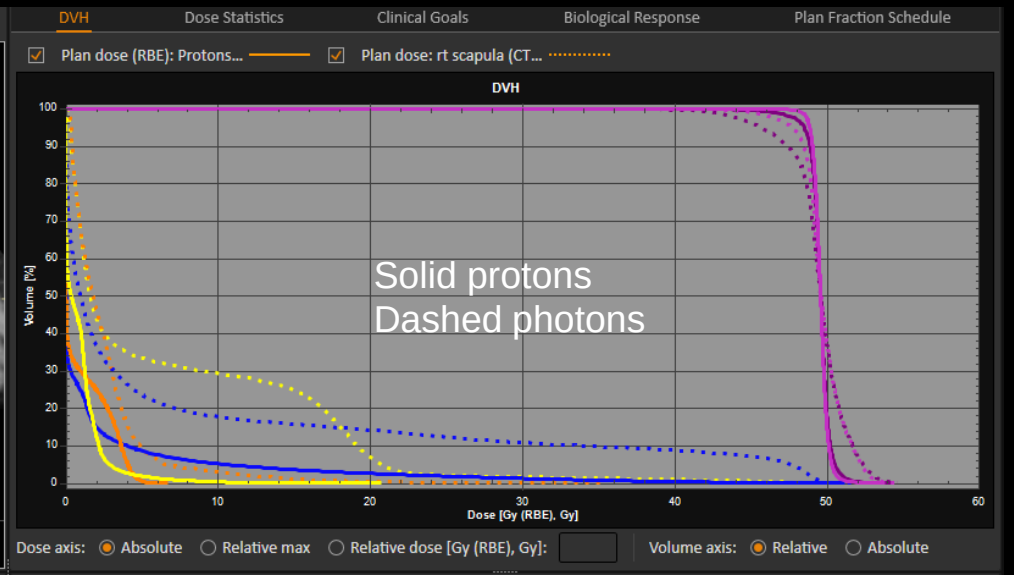
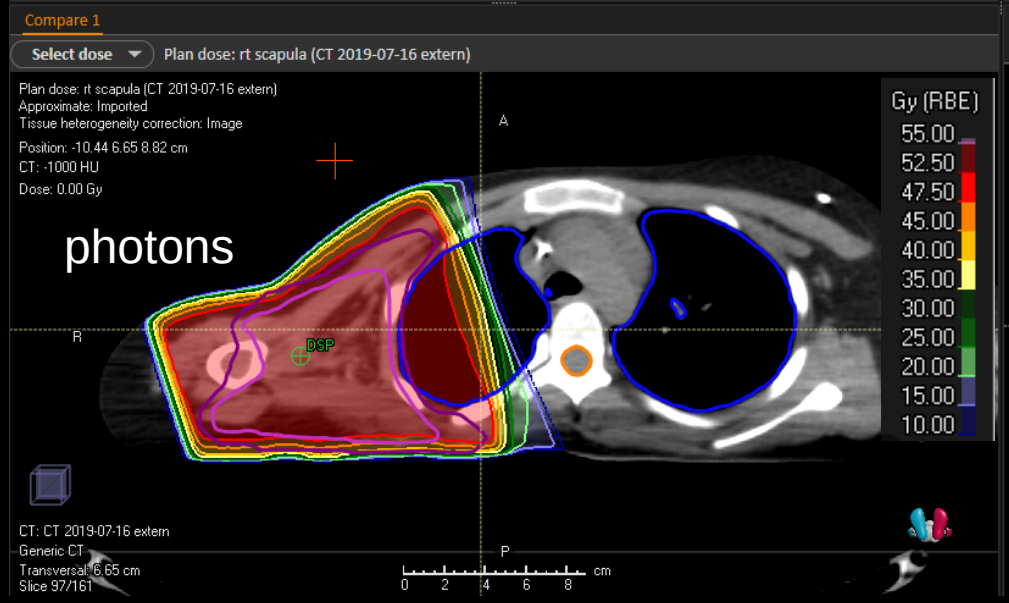
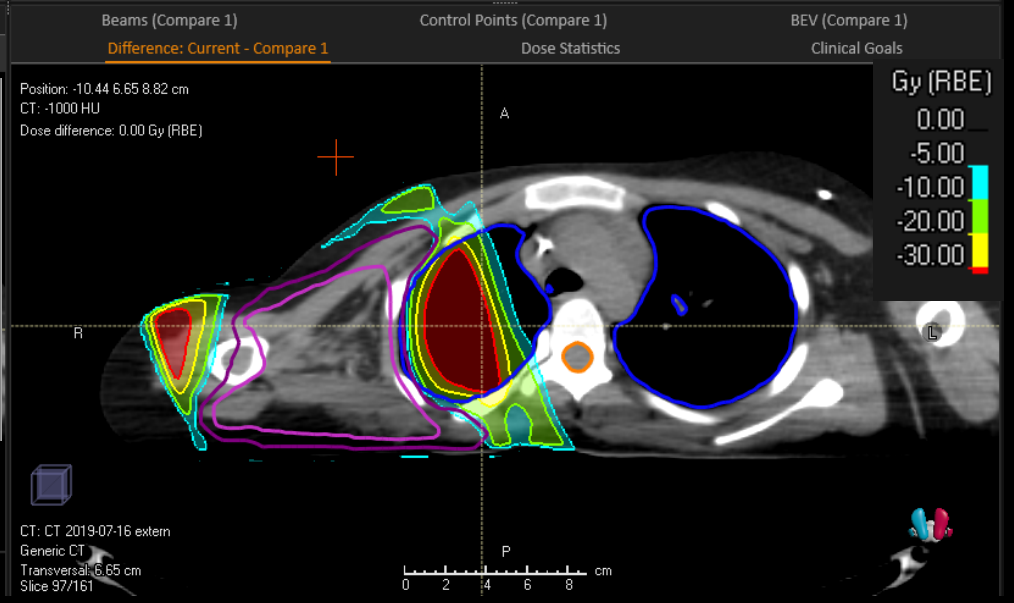






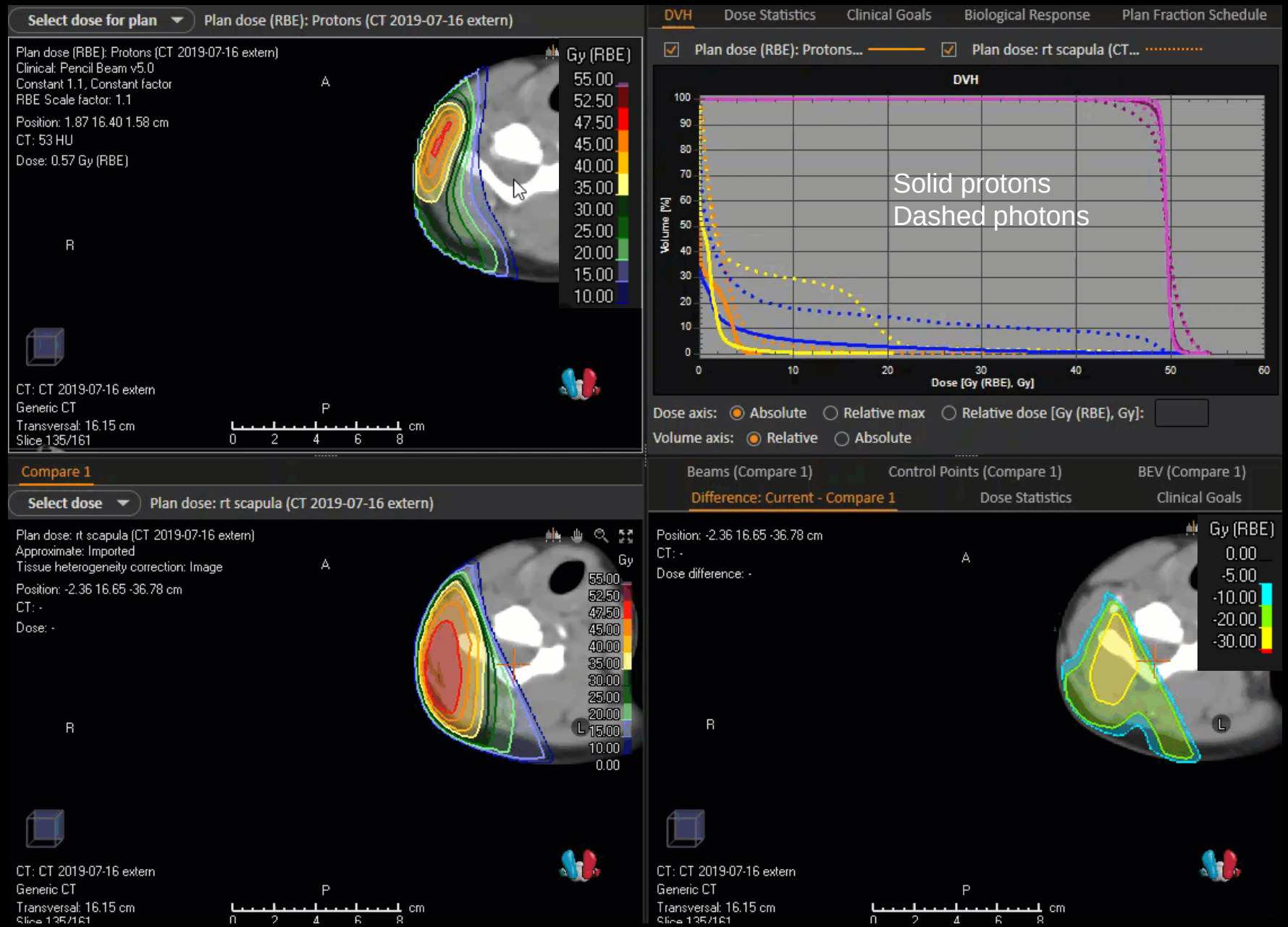


extern_CTV
extern_rt breast
extern_cord
extern_lung
extern_PTV

SIB PTV1+PTV2
PTV3 sequential to SIB

GHD 55.2Gy

PTV1 43.2Gy_1.8Gy
PTV2 48.0Gy_2.0Gy
PTV3 7.2Gy_1.8Gy



Video

Note: Runs automatically in presentation mod

- extern_CTV
- extern_rt breast
- extern_cord
- extern_lung
- extern_PTV

SIB PTV1+PTV2
PTV3 sequential to SIB

GHD 55.2Gy

PTV1 43.2Gy_1.8Gy
PTV2 48.0Gy_2.0Gy
PTV3 7.2Gy_1.8Gy

summary

RMS and Ewing Sarcomas are pediatric bone and soft tissue sarcomas which

Have good overall prognosis

Show good response to chemotherapy and radiotherapy

→ RMS and Ewing are NO standard indication for CIRT

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548