

Prof. Damien C. Weber :: Centre for Proton Therapy :: Paul Scherrer Institute :: UniBE

# Proton therapy plus management of cancer patients: can we make the math's work for

November 16<sup>th</sup> 2022, Inselspital, Bern

AYAs?



Goals of this talk

- Definition of AYAs/TYAs (Many!)
- Recognize that there are an increasing number of survivors of AYA cancers
- Recognize that survivors of AYA cancers have unique health issues long after cancer care
- Review the results of AYAs treated with proton at PSI (H&N, sarcoma, UM and skull base tumors
- Conclusions





Whats an AYA?

#### **Adolescent and Young adult**



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- Typically patients aged 13-39 years, with exact age ranges varying by countries/publications or programs
- NCCN defines as <u>15-39 years of age</u>
- ✤U. Iowa (UIHC) AYAs defined as 13-31 years
- ✤15-29 (Netherlands)
- ♦ NHS 15-25 years

Holland-Frei Cancer Medicine. 6th editi

Cancer Medicine: Definition of Older adolescent and Young Adult: 15 to 29 years of age (<u>https://www.ncbi.nlm.nih.gov/books/NBK13167/</u>)

Adolescence (10-19 years) and young (or emerging) adults (20-24 years)

https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(18)30079-8/fulltext



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#### Unique group of patients

- -Start of adult life
- -Beginning of career development
- -Psychosocial and financial implications
- Unique ethical ecosystem surrounding autonomy and medical decision making
- -Under-studied population with specific needs
- Modest/no improvement of survival in high-income countries (EUROCARE-5)



#### Differences in AYA cancers

- Main Cancer types in this group:
  - Leukemia
  - Lymphoma
  - Bone and tissue tumors
  - CNS
  - Germ Cell
  - Thyroid cancers



Hudson Presentation. Need of Adolescent and Young Adults with Cancer. Report from IOM. 2013



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Side effects of Cancer Therapies

- Therapy is almost always multi-modal
  - Chemotherapy
  - o Radiation
  - Surgery

## Each of these has its own set of sequelae

- When more than one is used, the risks are often greater than additive
- Each therapy will have different doses and different systems affected, so there is no one-size-fits-all approach





#### Late effects of Surgery

| Surgical Site   | Effect  |
|-----------------|---|
| Abdominal       | Adhesions   |
| Retroperitoneal | Adrenal insufficiency<br>Solitary kidney<br>Hypertension  |
| Musculoskeletal | Amputation effects (phantom pain,<br>mobility issues, infection)<br>Skin strictures<br>Weakness |
| Thoracic        | Lung scarring   |
| CNS             | Learning disabilities<br>Ataxia<br>Speech   |



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# Late effects pf Chemotherapy

| Class           | Agents  | Effects   |
|-----------------|---|---|
| Alkylators      | Busulfan, Carboplatin,<br>carmustine, Cisplatin,<br>Cyclophosphamide,<br>Ifosfamide, Lomustine,<br>Melphalan, Thiotepa,<br>temozolomide | Secondary MDS/AML<br>Gonadal dysfunction/infertility<br>Pulmonary Fibrosis<br>Urinary tract abnormalities<br>Renal dysfunction<br>Ototoxicity<br>Dyslipidemia |
| Anthracyclines  | Daunorubicin, Doxorubicin,<br>Epirubicin, Idarubicin  | LV dysfunction<br>Cardiomyopathy  |
| Corticosteroids | Dexamethasone, Prednisone   | Reduced bone density<br>Osteonecrosis<br>Cataracts  |

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#### Late effects pf Chemotherapy

| Class               | Agents                      | Effects   |
|---------------------|-----------------------------|---|
| Vinca Alkaloids     | Vincristine,<br>Vinblastine | Peripheral sensory and motor neuropathy   |
| Anti-metabolites    | Methotrexate                | Neurocognitive impairment<br>Leukoencephalopathy<br>Liver dysfunction<br>Renal toxicity<br>Decreased bone density |
| Epipodophyllotoxins | Etoposide                   | AML   |



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#### Late effects of radiation therapy

| System Exposed to RT | Effects   |
|----------------------|---|
| CVS                  | Cardiomyopathy<br>Carotid artery disease<br>Conduction disorders<br>Pericardial fibrosis/pericarditis                             |
| CNS                  | Neurocognitive deficits<br>Cerebrovascular disease (stroke,<br>moyamoya)<br>Clinical leukoencephalopathy<br>Neurosensory deficits |
| Endocrine            | Pituitary dysfunction/altered puberty<br>Thyroid dysfunction<br>Diabetes  |
| GI                   | Esophageal strictures<br>Chronic enterocolitis<br>Bowel Obstruction   |



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## Late effects of radiation therapy (Ctnd)

| System Exposed to RT       | Effects   |
|----------------------------|---|
| Female Reproductive System | Uterine vascular insufficiency→ SAB, LBW infants, prematurity Ovarian dysfunction                     |
| Male Reproductive System   | Leydig cell dysfunction→ delayed/arrested<br>puberty<br>Sertoli dysfunction→ oligospermia/infertility |
| Pulmonary                  | Pulmonary fibrosis<br>Interstitial pneumonitis<br>Restrictive/obstructive lung disease                |
| Urinary Tract              | Bladder fibrosis<br>Vesicoureteral reflux<br>Hydronephrosis<br>Hypertension                           |
| Any System                 | Secondary neoplasms (basal cell carcinoma,<br>breast, thyroid, brain cancer)                          |

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Risk of developping CHF after TX with Anthracyclines, Radiation or Both

Time Since Diagnosis (years)

25

30

20

15

35

40

NCI Publications-Late Effects of Treatment for Childhood Cancers (PDQ). https://www.cancer.gov/types/childhood-cancers/late-effects-hp-pdg#section/ 1360



#### AYAs & survivorship

5-Year Survival Rate, Age 0-19



Source: Surveillance, Epidemiology, and End Results (SEER) Program (seer.cancer.gov)

SEER 9 area. Based on follow-up of patients into 2012







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Robison, et al. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nature Reviews-Cancer. 14, 61-70 (2014).

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#### • AYAs & survivorship (Estimated Numbers of Cancer Survivors)

Estimated and projected number cancer survivors in the United States from 1977-2022 by years since diagnosis



de Moor JS, Mariotto AB, Parry C, Alfano CM, Padgett L, Kent EE, Forsythe L, Scoppa S, Hachey M, and Rowland JH. Cancer Survivors in the United States: Prevalence across the Survivorship Trajectory and Implications for Care. Cancer Epidemiol Biomarkers Prev. 2013 Apr;22(4):561-70. doi: 10.1158/1055-9965.EPI-12-1356. Epub 2013 Mar 27.





(2015)

CEBP 24(4):653-63

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et

Phillips

#### Estimates of Prevalence of Compromised Health in Survivors AYA Cancers

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#### Modeled IQ scores after EBRT Cranial Radiation (by age at which RT was delivered)





Merchant T. et al. JCO 27;3691-97 (2009)

# Pencil beam scanning Proton Therapy





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# SB Ch/Chsa in AYAs: PSI experience : Methods

- Aims of study:
  - Clinical Outcome and Late Toxicity
  - Prognostic Factors
  - Employment status
- October 1998 to July 2017
- Median Age 30 years (Range, 15-39)
- 108 Skull Base Chordomas (n=58) / Chondrosarcomas (n=50)
- All AYAs treated with PBS-PT
- Dose:
  - High risk areas: 74Gy (RBE) Ch; 70Gy (RBE) ChSa
  - Low risk areas: 54Gy

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#### SB Ch/Chsa in AYAs: Characteristics

| Characteristics             | N                                | 108         |
|-----------------------------|----------------------------------|-------------|
| Gender                      | Female                           | 61 (56.5%)  |
|                             | Male                             | 47 (43.5%)  |
| Age at PT                   | <24                              | 25 (23.1%)  |
|                             | >=24                             | 83 (76.9%)  |
| Timing of PT                | Primary diagnosis                | 86 (79.6%)  |
|                             | Recurrence / Progressive disease | 22 (20.4%)  |
| Resection Status            | GTR / Microscopic disease        | 7 (6.5%)    |
|                             | Macroscopic Subtotal resection   | 101 (93.5%) |
| Optic apparatus compession  | None                             | 66 (62.3%)  |
| at Diagnosis <i>(n=106)</i> | Abutment                         | 18 (17%)    |
|                             | Compression                      | 22 (20.8%)  |
| Optic apparatus compression | None                             | 76 (70.4%)  |
| at PT                       | Abutment                         | 21 (19.4%)  |
|                             | Compression                      | 11 (10.2%)  |
| Brainstem compression at    | None                             | 40 (37.7%)  |
| Diagnosis <i>(n=106)</i>    | Abutment                         | 18 (17%)    |
|                             | Compression                      | 48 (45.3%)  |
| Brainstem compression at PT | None                             | 75 (69.4%)  |
|                             | Abutment                         | 19 (17.6%)  |
|                             | Compression                      | 14 (13%)    |

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#### SB Ch/Chsa in AYAs: Survival Outcomes



Median follow up 86 months (range, 12-236)



#### SB Ch/Chsa in AYAs: Prognostic factors



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#### SB Ch/Chsa in AYAs: Prognostic factors



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# SB Ch/Chsa in AYAs: Late Toxicity

- 7-yr  $\geq$  G3 Late Toxicity Free Survival 85.3%
  - $\circ$  N=16 patients (15%) ≥ G3 Late Toxicity
    - n=1 G5
      - ➤ 35 year old treated for clival chordoma.
      - Stroke at 88 months post PT. Fatal brainstem haemorrhage 99 months post PT. Evolving changes brainstem unclear if stroke / radionecrosis).
      - No recurrence
    - n=15 G3

> 10 ototoxicity, 2 CSF leaks, 1 Optic Neuropathy, 1 Epiphoria, 1 Fatigue

 $\circ$  No significant factors influencing high grade toxicity on univariate analysis

- Number of surgeries, optic apparatus or brainstem compression
- Neuro moderate G2 tox (n=9; 9%):
  - 1 Neurocognition deficit, 4 Memory impairment, 4 CNS Necrosis, 2 Seizures
- No secondary malignancy



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# SB Ch/Chsa in AYAs: Employment Hx

|                           | Employment at | Employment at time of  |
|---------------------------|---------------|------------------------|
|                           | time of PT    | last follow up         |
| Available data            | 60            | 42                     |
|                           | 00            | (32 with initial data) |
| Unemployed                | <u>5 (8%)</u> | 13 (31%)               |
| Employed, at work         | 30 (50%)      | 25 (60%)               |
| Employed, 100% sick leave | 8 (13%)       | 0 (0%)                 |
| In education              | 17 (28%)      | 4 (9.5%)               |

 ≥ G3 late tox was significantly higher in unemployed group (33%) vs employed / in education (7%); p=0.05



#### SARCOMA (non RMS) and AYAs

| Table 1 Patient characteristics a | nd tumor entities (n=67)   | n (%)        |
|-----------------------------------|----------------------------|--------------|
| Age at diagnosis (range) [years]  | Median (range)             | 22 (11 – 39) |
| Age at PT (range) [years]         | Median (range)             | 24 (15 – 39) |
| Sex                               | female                     | 36 (53.7)    |
|                                   | male                       | 31 (46.3)    |
| NM Status at diagnosis            | N+ at diagnosis            | 4 (6.0)      |
|                                   | M+ at diagnosis            | 7 (10.4)     |
| Tumor site                        | CNS/skullbase              | 7 (10.4)     |
|                                   | Head and Neck              | 16 (23.9)    |
|                                   | Thorax/Abdomen             | 6 (9.0)      |
|                                   | Spine/paraspinal           | 17 (25.4)    |
|                                   | sacral/pelvic bones        | 11 (16.4)    |
|                                   | extremities                | 5 (7.5)      |
|                                   | several sites              | 5 (7.5)      |
| Malignant bone tumors             | Ewing Sarcoma              | 15 (22.4)    |
|                                   | Osteosarcoma               | 9 (13.4)     |
| Soft tissue sarcoma               | alveolar Rhabdomyosarcoma  | 7 (10.4)     |
|                                   | embryonal Rhabdomyosarcoma | 6 (9.0)      |
|                                   | Hemangiopericytoma         | 4 (6.0)      |
|                                   | Synovial sarcoma           | 3 (4.5)      |
|                                   | Leiomyosarcoma             | 2 (3.0)      |
|                                   | other STS                  | 12 (17.9)    |
| Bening tumors                     | Desmoid tumor              | 4 (6.0)      |
|                                   | other benign               | 5 (7.5)      |
| Total                             |                            | 67 (100.0)   |

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#### SARCOMA and AYAs







#### SARCOMA and AYAs

| Туре           | Time to toxicity | Tumor entity       | Tumor site             | PT dose  |
|----------------|------------------|--------------------|------------------------|----------|
|                | (months)         |                    |                        | (Gy RBE) |
| Cataract (n=3) | 20               | Embryonal RMS      | CNS                    | 46.8     |
|                | 39               | Ewing sarcoma      | Epipharynx/nasopharynx | 59.4     |
|                | 41               | Osteosarcoma       | Epipharynx/nasopharynx | 70.0     |
| Mastoiditis    | 52               | STS                | Skullbase              | 76.0     |
| (n=1)          |                  |                    |                        |          |
| Osteonecrosis  | 63               | Embryonal RMS      | Mandibula              | 74.0     |
| (n=1)          |                  |                    |                        |          |
| Paraplegia     | 12               | Hemangioperizytoma | Spinal                 | 64.0     |
| (n=1)          |                  |                    |                        |          |





# Proton therapy for uveal melanoma in adolescents/young adults (AYAs) and adults: a matched cohort analysis

Variables used in matching

```
cvar <- c(
    "Country",
    "Sex",
    "Familial_melanoma",
    "year_treated",
    "Reduced_safety_margin",
    "LTD",
    "MTD",
    "Thickness",
    "Exteriorisation",
    "Ant_margin",
    "iris_origin",
    "other_known_tumors",
    "T_cat"
}</pre>
```



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|------|-----------|-----|----|-------|
|      | Ţ         |     |    |       |



|                               | Stratified by AY | A              |        |
|-------------------------------|------------------|----------------|--------|
|                               | 0                | 1              | SMD    |
| n                             | 270              | 270            |        |
| Country (%)                   |                  |                | 0.009  |
| СН                            | 59 (21.9)        | 58 (21.5)      |        |
| border                        | 138 ( 51.1)      | 139 ( 51.5)    |        |
| other                         | 73 ( 27.0)       | 73 ( 27.0)     |        |
| sex = Male (%)                | 104 (38.5)       | 111 ( 41.1)    | 0.053  |
| Familial_melanoma = TRUE (%)  | 8 ( 3.0)         | 6 ( 2.2)       | 0.047  |
| year_treated (mean (SD))      | 2001.59 (3.17)   | 2001.47 (3.21) | 0.035  |
| Reduced_safety_margin = FALSE | (%) 270 (100.0)  | 270 (100.0)    | <0.001 |
| LTD (mean (SD))               | 16.38 (4.35)     | 16.18 (4.18)   | 0.047  |
| MTD (mean (SD))               | 13.94 (3.88)     | 13.88 (3.72)   | 0.016  |
| Thickness (mean (SD))         | 6.20 (2.89)      | 6.07 (2.76)    | 0.047  |
| Exteriorisation = TRUE (%)    | 13 ( 4.8)        | 9 ( 3.3)       | 0.075  |
| Ant_margin (%)                |                  |                | 0.048  |
| anterior choroid              | 61 ( 22.6)       | 58 ( 21.5)     |        |
| ciliary body                  | 67 (24.8)        | 66 ( 24.4)     |        |
| iris                          | 33 (12.2)        | 31 (11.5)      |        |
| posterior choroid             | 109 (40.4)       | 115 ( 42.6)    |        |
| iris_origin (%)               |                  |                | 0.051  |
| no                            | 241 ( 89.3)      | 245 ( 90.7)    |        |
| unlikely                      | 18 ( 6.7)        | 16 ( 5.9)      |        |
| yes                           | 11 ( 4.1)        | 9 ( 3.3)       |        |
| Other_known_tumors = TRUE (%) | 8 ( 3.0)         | 10 ( 3.7)      | 0.041  |
| T_cat (%)                     |                  |                | 0.059  |
| 1                             | 19 ( 7.0)        | 21 ( 7.8)      |        |
| 2                             | 78 ( 28.9)       | 82 (30.4)      |        |
| 3                             | 78 (28.9)        | 79 (29.3)      |        |
| 4                             | 95 (35.2)        | 88 (32.6)      |        |



### Survival (Kaplan-Meyer)





# **Provisional conclusions**

- No significant differences in OS ans local recurrences between AYAs and ADULTS
- No significant difference between DMFS









# Demographic data



| Demographic data |                |  |  |
|------------------|----------------|--|--|
| Sex male         | 53.5% (38)     |  |  |
| Age              | 8.9 (0.3-37.9) |  |  |
| ≥ 18 yo          | 19.7% (14)     |  |  |
| Anesthesia       | 40.8% (29)     |  |  |
| QoL              | 43.1% (31)     |  |  |









- Ewing's Sarcoma
- Osteosarcoma
- Chondrosarcoma
- Fibrosarcoma





#### **Tumor characteristics**

| Rhabdomyosarcoma (n= 51) |              |       |            |  |
|--------------------------|--------------|-------|------------|--|
| Ma                       | le sex       | 52.9% | 27         |  |
| Age                      | 2            | 8.2   | (0.3-35.9) |  |
| Adι                      | ılt          | 13.7% | 7          |  |
| Sub                      | Subtype      |       |            |  |
| •                        | Emrbyonal    | 62.7% | 32         |  |
| •                        | Alveolar     | 31.4% | 16         |  |
| •                        | Spindle cell | 5.9%  | 3          |  |
| Stage                    |              |       |            |  |
| •                        | IIA          | 7.8%  | 4          |  |
| •                        | ш            | 82.4% | 42         |  |
| •                        | IV           | 9.8%  | 5          |  |

#### FOXO3-PAX1 status avaliable in 60% of RMS



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| Soft tissue sarcomas (n= 54) |       |    |  |
|------------------------------|-------|----|--|
| Orbit                        | 31.2% | 17 |  |
| Nasal cavity/Nasopharynx     | 27.8% | 15 |  |
| Infratemporal fossa          | 11.1% | 5  |  |
| Oral cavity/Oropharynx       | 9.3%  | 5  |  |
| Pterygoid fossa              | 5.6%  | 3  |  |
| Retroauricular/Middle ear    | 5.6%  | 3  |  |
| Paranasal Sinus              | 3.7%  | 2  |  |
| Parapharyngeal space         | 3.7%  | 2  |  |
| Submandibular                | 1.9%  | 1  |  |

| Bone sarcomas (n= 17) |       |   |
|-----------------------|-------|---|
| Ethmoid               | 35.3% | 6 |
| Maxilar               | 23.5% | 4 |
| Mandible              | 11.8% | 2 |
| Frontal               | 5.9%  | 1 |
| Cygomatic             | 5.9%  | 1 |
| Nasal                 | 5.9%  | 1 |
| Middle ear            | 5.9%  | 1 |
| Orbit                 | 5.9%  | 1 |



#### **Treatment characteristics: Protocol**

#### 82% were treated inside or according to a protocol







#### Treatment characteristics: Surgery

#### Most of the patients did not undergo surgery

| Surgery             |         |       |    |
|---------------------|---------|-------|----|
| Surgery             | Surgery | 43.7% | 31 |
|                     | Biopsy  | 56.3% | 40 |
| Number of surgeries | 0       | 56.3% | 40 |
|                     | 1       | 35.2% | 25 |
|                     | 2       | 7%    | 5  |
|                     | 3       | 1.4%  | 1  |
| Margin last surgery | Biopsy  | 56.3% | 40 |
|                     | RO      | 9.9%  | 7  |
|                     | R1      | 14.1% | 10 |
|                     | R2      | 29.7% | 14 |





#### Treatment characteristics: Chemotherapy

#### 93% received chemotherppy as part of the treatment

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|----------------------------|--|
|                            |  |

| Chemotherapy      |                     |       |    |
|-------------------|---------------------|-------|----|
| ChT at            | Yes                 | 93%   | 66 |
| any time<br>of Tx | No                  | 7%    | 5  |
| Timing            | ChT-prePRT          | 90.1% | 64 |
|                   | ChT-<br>concomitant | 76.1% | 54 |
|                   | ChT-postPRT         | 60.6% | 43 |





#### Treatment characteristics: Proton therapy



|                | Gy (RBE)                              |
|----------------|---------------------------------------|
| Total dose     | 54 (36 – 73.8)                        |
| Dose per Fr    | 1.8 (1.8 - 2.2)                       |
| Boost dose     | 9 (3.6 – 19.8)                        |
|                |                                       |
|                | Size (cc)                             |
| GTV            | Size (cc)<br>32.9 ± 37                |
| GTV<br>CTV_Low | Size (cc)<br>32.9 ± 37<br>139.5 ± 122 |

- All patients were treated with SFO
- PRT to a metastasis in the H&N area of 1 patient (1.4%)
- Lymph node irradiation in 21.1 %
- Vertebrae irradiation in 8.5%



#### All patients presented acute toxicity



| Acute toxicity |       |    |  |
|----------------|-------|----|--|
| Only Grade 1   | 26.8% | 19 |  |
| Grade 2        | 54.9% | 39 |  |
| Grade 3        | 18.3% | 13 |  |





*46)* 

#### 63.9% of all patients presented late toxicity (n=



| Late toxicity |       |    |
|---------------|-------|----|
| No toxicity   | 35.2% | 25 |
| Only Grade 1  | 40.8% | 29 |
| Grade 2       | 18.3% | 13 |
| Grade 3       | 5.6%  | 4  |





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# Follow-up and events

Median follow-up: 37 months (3.5 – 220)

- 12 Deaths (16.9%) of which 11 were due to disease
- 13 Local failures (18.3%)
  - 12 in-field local failures
  - 1 marginal
- 12 Distant failures 16.9%

| Distant Failures |                   |  |
|------------------|-------------------|--|
| HNSa-11          | Peritoneal, Liver |  |
| HNSa-12          | Leptomeningeal    |  |
| HNSa-16          | Leptomeningeal    |  |
| HNSa-17          | Soft tissue       |  |
| HNSa-22          | Lymph nodes       |  |
| HNSa-31          | Brain             |  |
| HNSa-37          | Brain             |  |
| HNSa-40          | Paquimeningeal    |  |
| HNSa-43          | Lungs             |  |
| HNSa-50          | Soft tissue       |  |
| HNSa-65          | Lungs             |  |
| HNSa-74          | Brain             |  |



**Provisional data** (6 patients pending for an update of the follow-up)

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**Overall** survival

#### Local Failure Free Survival

#### Distant progression free survival





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#### Take home messages

- Definition of AYAs varies
- PSI treats a fair amount of AYAs with proton therapy
- PT offers good toxicity profile with high RT doses
- Clinical outcome of AYA patients identical to adults (skull base tumors)
- Decompression of Optical structures and Brainstem at RT -> Value of surgery
- Outcome of adults and AYAs with Ums seems to be identical
- OS@3yo of sarcoma (non-RMS and RMS) 69-85%



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# Thank you for your attention

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