



European
Reference
Network

for rare or low prevalence
complex diseases

 Network
Paediatric Cancer
(ERN PaedCan)



20th of September 2023
Andrada Turcas & Mark Gaze

Chemo-radiation resistant,
undifferentiated H&N carcinoma in a
paediatric patient

Moderation: Teresa de Rojas



Funded by the European
Union's EU4Health Programme



COI declaration

- None

6 yo girl

- No data on medical history- adopted at 3yo from the social care system

February '22- Symptoms

- Dysphagia
- Loss of appetite
- Weight loss
- Fever
- Nasal obstruction
- Palpebral ptosis (right)
- Enlarged right cervical lymph nodes (painful)



What could it be?

A

- Tonsillar abscess

B

- Lymphoma

C

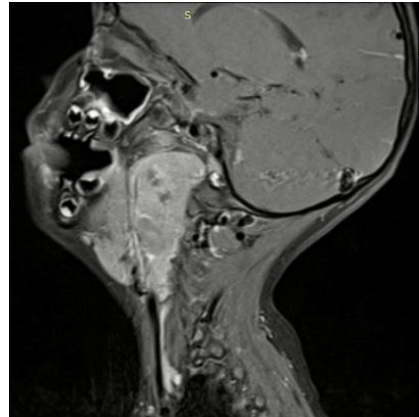
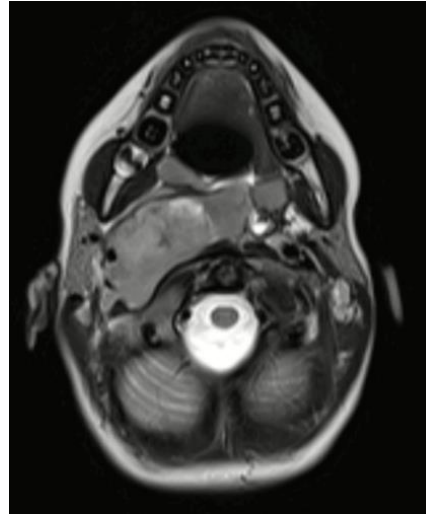
- H&N Solid tumour

D

- Acute Leukaemia

Labs

- Grade 1 anemia
- Slight left deviation on bone marrow aspirate
- Negative for viral infections (EBV, CMV, HBV, HCV, HIV)



MRI

- Right retro-and para-pharyngeal tumour (5/5/4cm), heterogenous enhancement
- Encasing the R carotid artery
- Enlarged neck nodes- 1.5cm R/ 2.4cm L

Biopsy

Undifferentiated (G3) nasopharyngeal carcinoma

– Ki67- 60%

- IHC- excludes- RMS, Lymphoma, Paraganglioma, Neuroendocrine carcinoma, Melanoma

2nd
review

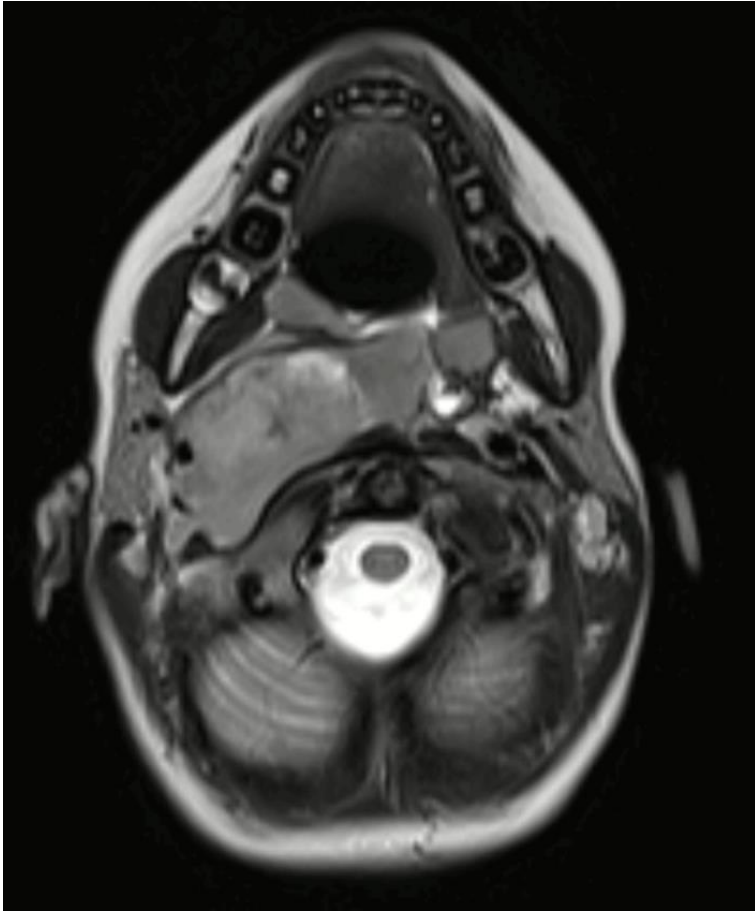
Undifferentiated (G3) carcinoma of the minor salivary glands

- Could not exclude
 - High grade **mucoepidermoid carcinoma**
 - High grade **clear cell hyalinizing carcinoma**
- Neg. EBV
- ❖ EWSR1 (22q12) rearrangement

Diagnosis

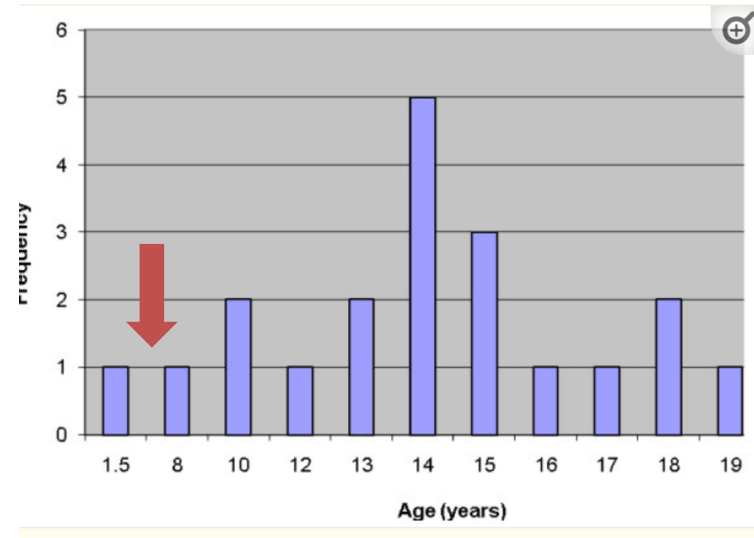
T2 N1 M0 (Stage III)

Undifferentiated (G3) **minor salivary glands** – (probable) **muco-epidermoid carcinoma**



Minor salivary glands carcinoma

- Salivary gland tumours ~ 0.5% of all malignancies in children and adolescents
- 2nd most common H&N tumour, after RMS
- <10% occur in the minor salivary glands
 - usually in the hard/soft palate (site with most glandular tissue);
 - *may arise in lymph nodes around salivary glands*
- most common **malignant** tumours are **mucoepidermoid carcinomas**
- 5-year OS~ 95%



How do you treat?

A

- Surgery

B

- Chemo+Surgery

C

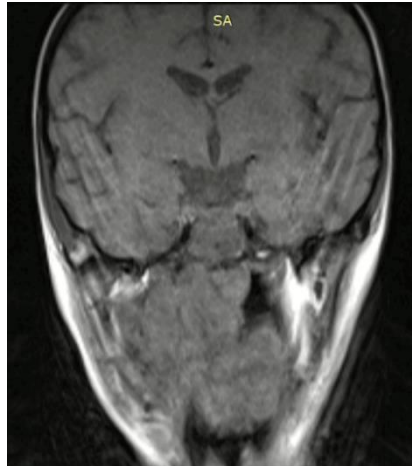
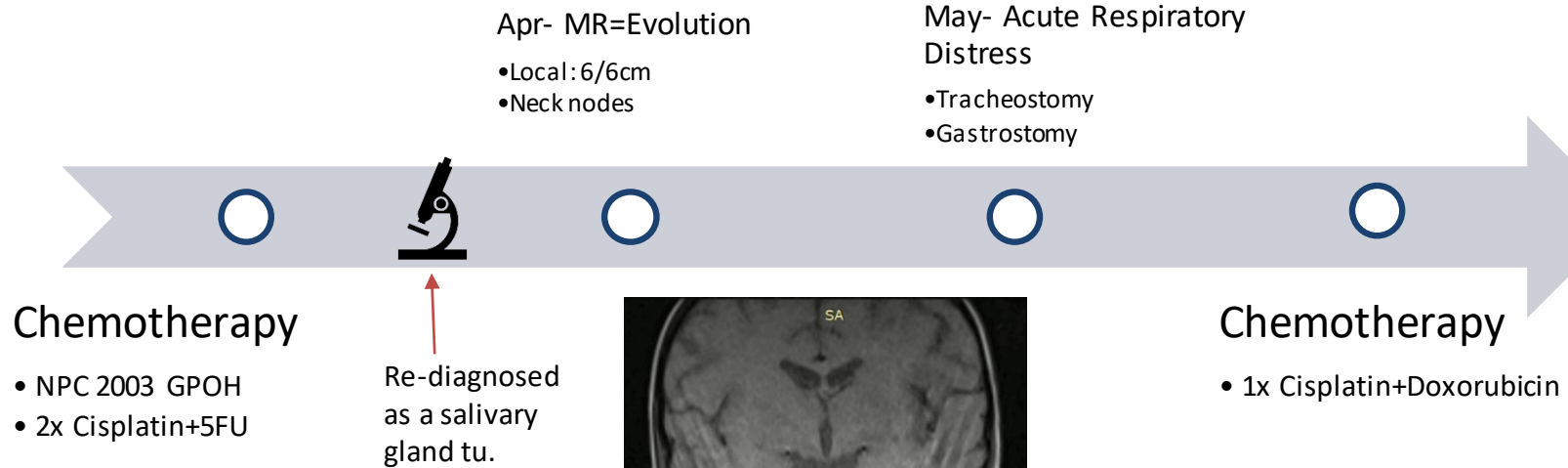
- Chemo+Radiation

D

- Chemo+Surgery+Radiation

E

- Other (targeted therapy, immunotherapy)

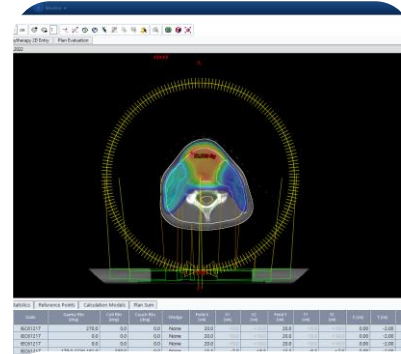


H&N Radiotherapy

Practice guidelines

ESTRO ACROP guidelines for positioning, immobilisation and position verification of head and neck patients for radiation therapists

Michelle Leach¹, Mary Coffey², Miriam Mast³, Filipe Moura⁴,
 Andreia Orstavik⁵, Danilo Posini⁶, Aude Vaandering⁷



Simulation

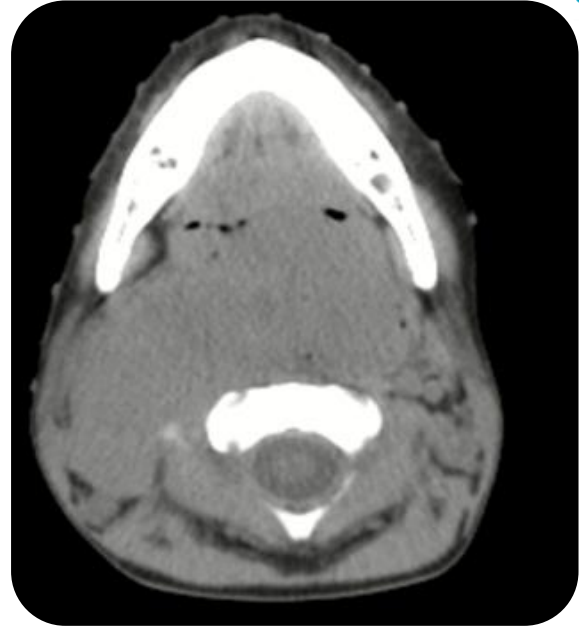
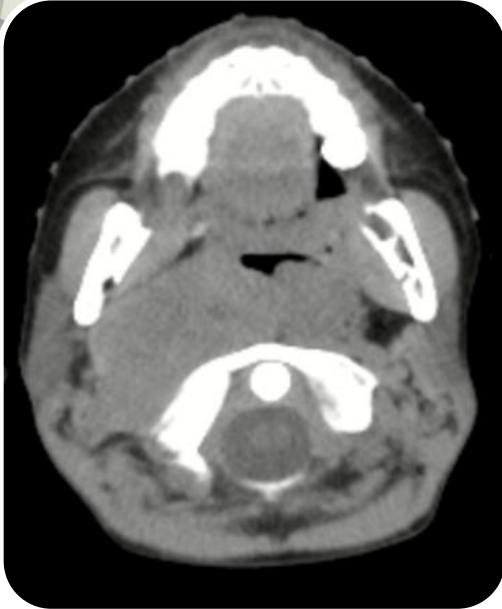
- CT scan in treatment position
- Immobilization- reduce patient movements during treatment
- Special devices- vacuum mattress, headrests, thermoplastic mask, etc.

Treatment planning

- Delineation of target volumes and Organs at Risk
- Plan development and dose calculation (Dosimetrist, Medical Physicist)

Treatment delivery

- 1 fraction (treatment session) each day (Mo-Fri), usually 1.8-2Gy/fraction
- 25-35 fractions (5-7 weeks)

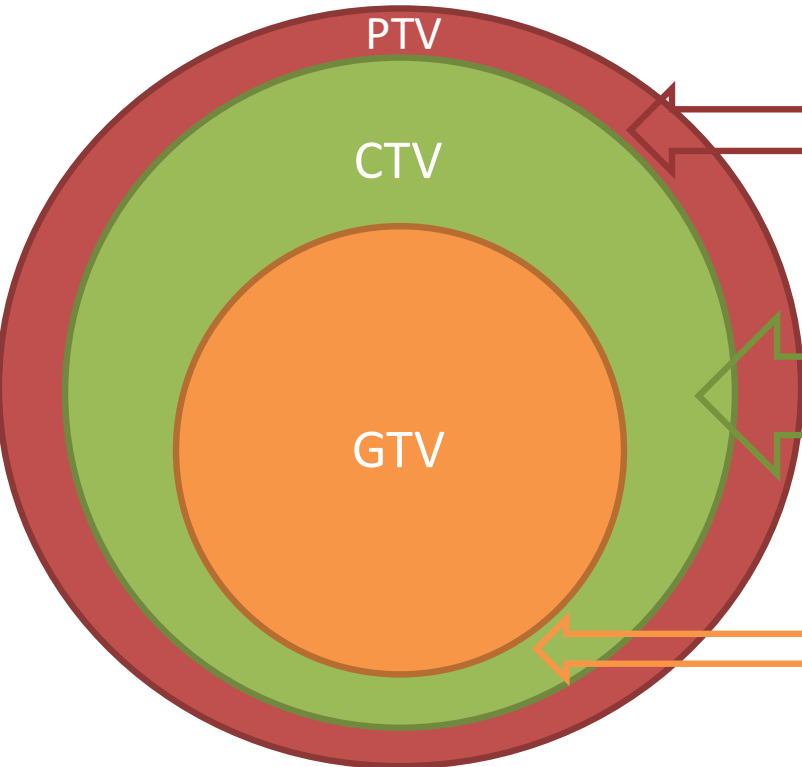


Mid-May: CT simulation

Acute obstruction of Tracheostomy tube
(severe infection)- transferred to ICU
Antibiotics

June

Contouring principles



Planning Target Volume

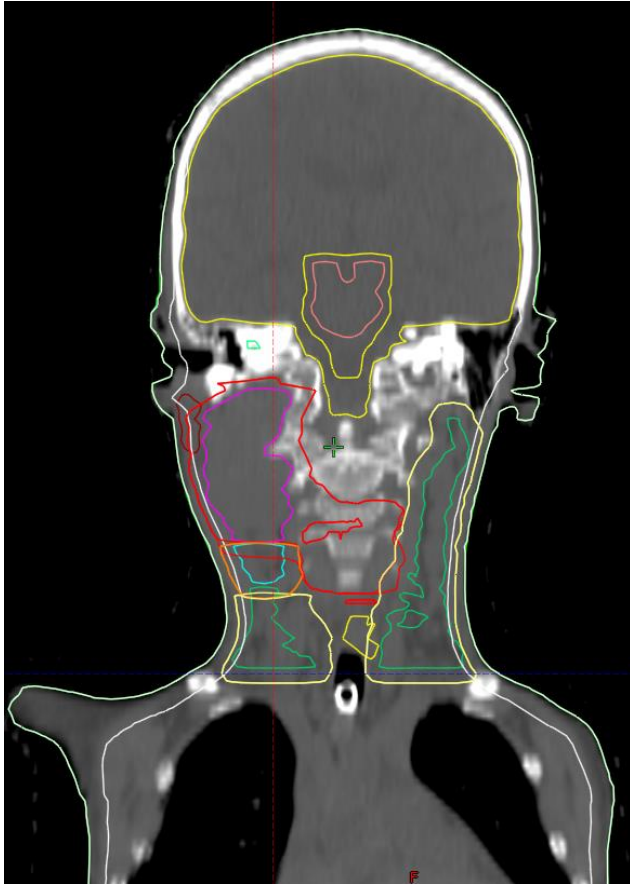
- Geometrical margin (3-5mm) added to account for positioning uncertainty and variability

Clinical Target Volume

- Subclinical microscopic disease
- Tissue that might be infiltrated with tumour cells, not visible on imaging
 - 1-3cm around the tumour
 - Regional lymph nodes- tumour drainage

Gross Tumour Volume

- Visible tumour (imaging)



GTV

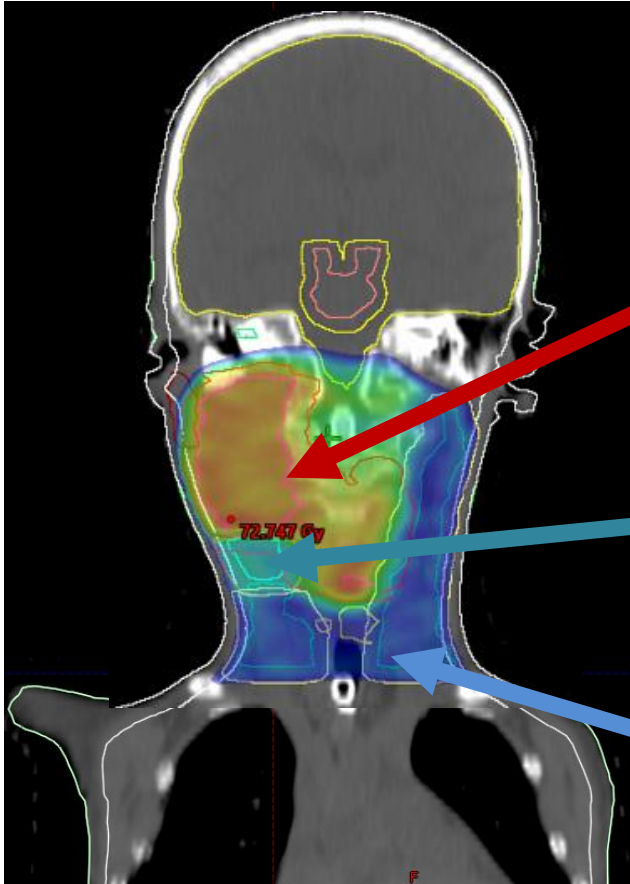
- Primary tumour
- Involved lymph nodes

CTV

- Margin around the gross (visible) tumour
- Elective- Negative lymph nodes on imaging
 - with high risk of involvement
 - with medium/low risk of involvement

PTV

- 3mm margin around each CTV



70Gy

High Risk

- Primary
- Involved lymph nodes

59.4Gy

Intermediate Risk

- Level III right (inferior half)

54Gy

Low Risk

- Level II+III left
- Level IV L+R

Organs at risk and Toxicities



Dermatitis
Moist desquamation

Hyperpigmentation,
Fibrosis



Mucositis Dysphagia

Malnutrition
Dental issues

Xerostomia



Bone necrosis
Growth impairment
Facial/spinal deformities

Review > *Lancet Oncol.* 2019 Mar20(3):e155-e166. doi: 10.1016/S1470-2045(19)30034-8.

Management of vertebral radiotherapy dose in paediatric patients with cancer: consensus recommendations from the SIOPE radiotherapy working group

Bianca A Hoeven¹, Christian Carrie², Beate Timmermann³, Henry C Mandeville⁴,

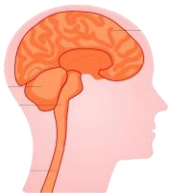
Adverse events of local treatment in long-term head and neck rhabdomyosarcoma survivors after external beam radiotherapy or AMORE treatment

Reineke A Schoot¹, Olga Slater², Cécile M Ronckers¹, Aeilko H Zwinderman³, Alfons J M Balm⁴,

Facial deformation following treatment for pediatric head and neck rhabdomyosarcoma; the difference between treatment modalities. Results of a trans-Atlantic, multicenter cross-sectional cohort study

Marinka L F Hol^{1,2,3}, Daniel J Indelicato⁴, Olga Slater⁵, Frederic Kolb⁶, Richard J Hewitt⁷, Juling Ong⁸, Alfred G Becking³, Jenny Gains⁹, Julie Bradley⁴, Eric Sandler¹⁰, Mark N Gaze⁹, Bradley Pieters¹¹, Henry Mandeville¹², Raquel Dávila Fajardo¹³, Reineke Schoot¹, Johannes H M Merks¹, Peter Hammond¹⁴, Ludwig E Smeets^{1,3}, Michael Suttie¹⁴

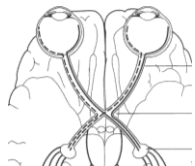
Organs at risk and Toxicities



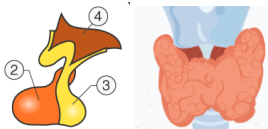
Radionecrosis → Neurocognitive decline
Myelitis



Hearing loss



Cataract, Optic neuropathy → Visual impairment
Dry eye



Endocrine dysfunction

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss

P.R. Brock, R. Maibach, M. Childs, K. Rajput, D. Roebuck, M.J. Sullivan, V. Laithier, M. Ronghe, P. Dall'igna, E. Hiyama, B. Brichard, J. Skeen, M.E. Mateos, M. Capra, A.A. Rangaswami, M. Ansari, C. Reznitzer, G.J. Veal, A. Covezzoli, L. Brugières, G. Perilongo, P. Czauderna, B. Morland, and E.A. Neuwelt

Pediatric Normal Tissue Effects in the Clinic (PENTEC): An International Collaboration to Analyse Normal Tissue Radiation Dose-Volume Response Relationships for Paediatric Cancer Patients

L S Constine¹, C M Ronckers², C-H Hua³, A Olch⁴, L C M Kremer², A Jackson⁵, S M Bentzen⁶

What can we do for a better therapeutic ratio?

A

- Prescribe a lower dose to reduce the risk of toxicities

B

- Proton therapy- to reduce the dose to the healthy tissues

C

- Carbon ion therapy- to increase the therapeutic effect on the tumour

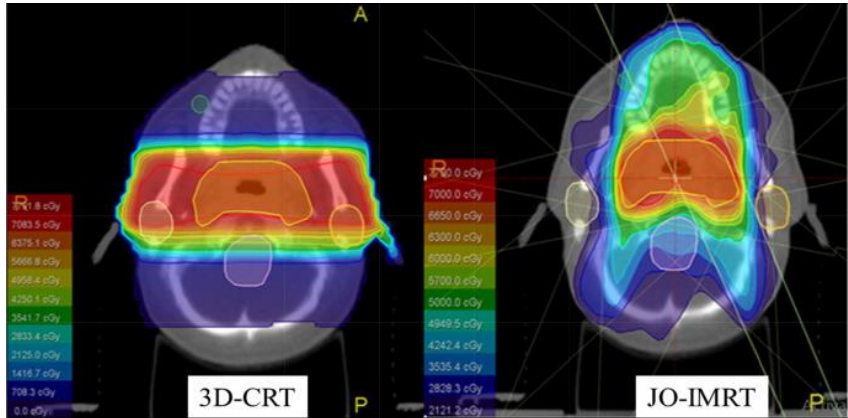
D

- Photon 3D conformal radiotherapy instead of IMRT

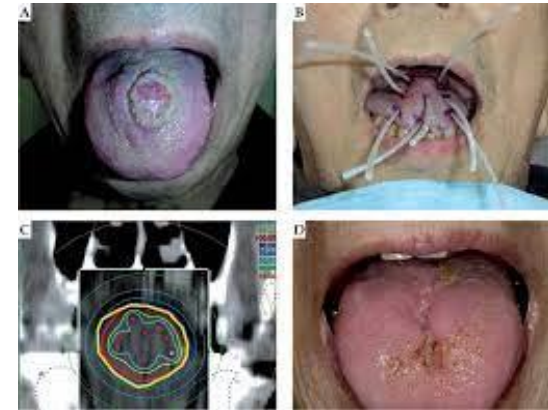
E

- Deliver the dose only locally with brachytherapy

RT Delivery



EBRT techniques



Brachytherapy

[Radiother Oncol. 2019 Feb;131:21-26. doi: 10.1016/j.radonc.2018.10.036. Epub 2018 Dec 17.](#)

AMORE treatment as salvage treatment in children and young adults with relapsed head-neck rhabdomyosarcoma

Bas Vaanwerk ¹, Marinka L F Hol ², Reineke A Schoot ³, Willemijn B Breunis ¹, Maartje M L de Win ⁴, Henrike Westerveld ⁵, Raquel Davila Fajardo ⁶, Peerooz Saeed ⁷, Michiel W van den Brekel ⁸, Bradley R Pieters ⁹, Simon D Strackee ⁹, Ludi E Smeele ⁹, Johannes H M Merks ¹⁰

A National Referral Service for Paediatric Brachytherapy: An Evolving Practice and Outcomes Over 13 Years

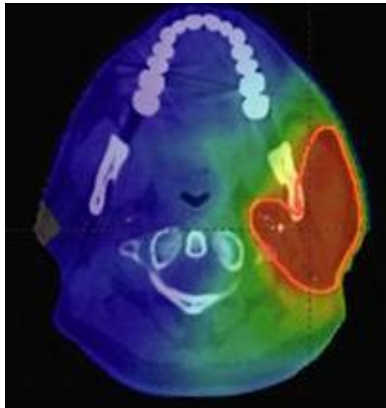
M.N. Gaze ¹, N. Smeulders ¹, R. Ackwerh ¹, C. Allen ¹, N. Bal ¹, M. Boutros ¹, A. Cho ¹, G. Eminowicz ¹, E. Gill ¹, M.W. Fittall ¹, P.D. Humphries ¹, P. Lim ¹, I. Mushtaq ¹, T. Nguyen ¹, C. Peet ¹, D. Pendse ¹, S. Polhill ¹, H. Rees ¹, G. Sands ¹, A. Shankar ¹, O. Slater ¹, T. Sullivan ¹, P.J. Hoskin ¹

¹ University College London Hospitals NHS Foundation Trust, London, UK
² Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
³ University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK

Different types of radiation

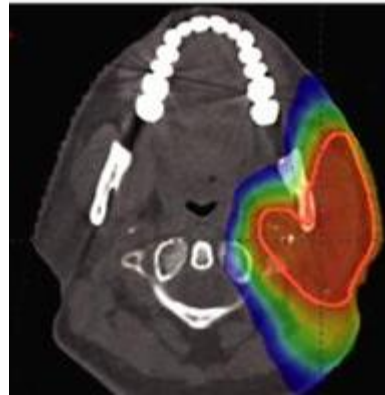
Photons

- Widely available
- Good tumour control
- Plenty of evidence



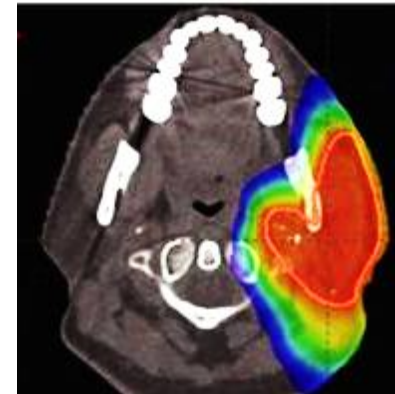
Protons

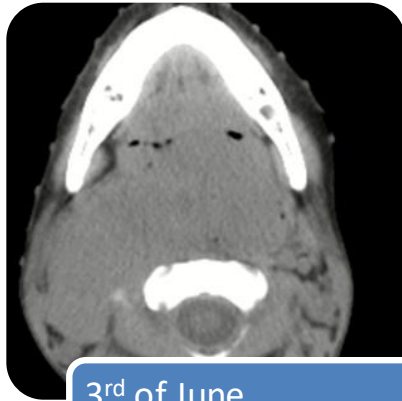
- Reduced toxicities
- Same tumour control
- Not always accessible



Carbon Ions

- (potentially) higher biological effect/tumour (High-LET radiation)
- (potentially) less toxicities
- Little → no data for paediatrics
- 4 centres/Europe





3rd of June

- 7cm lymph node
- Growing primary tumor

6th of June-27th of July



29th of July

- After RT- slight growth of primary tumor

- Trismus improved- can open her mouth and feed herself/drink
- Lymph nodes shrunken, softer and mobile
 - G2 Radio-dermatitis

Genetic testing

Panel Analysis: Solid Tumor Cancer

Comprehensive genomic next generation sequencing test that targets mutations, copy numbers, fusions, and other cancer-relevant changes in the tumors.

Analysis result: **POSITIVE**

1 Biomarker	Approved treatment	Other findings
Tumor Mutation Burden: TMB-high (60 Mutations/Megabase)	Pembrolizumab	Trials: 4 Phase 2 1 Phase 1/Phase 2
3 Variants of biological significance, Tier 3		
KMT2C: p.Y987*, Likely Pathogenic KMT2C: p.R973G, Likely Pathogenic KMT2C: p.C391*, Pathogenic		
26 Variants of uncertain significance, Tier 3		

High TMB
KMT2C mt



AVAILABLE CLINICAL TRIALS

Phase 2 clinical trials (4)

IPILIMUMAB, ATEZOLIZUMAB, NIVOLUMAB

The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy.
[NCT04591431](#)

Qualifying variant

Biomarker	Classification	Score
TMB-high	Tier 1A Pathogenic	60 Mutations/Megabase

Contact

Silvia Violetti; silvia.violetti@clinicaltrialsfmp.it; +390683977939;

ATEZOLIZUMAB

Continuous ReAssessment With Flexible Extension in Rare Malignancies - CRAFT: The NCT-PMO-1602 Phase II Trial
[NCT04551521](#)

Qualifying variant

Biomarker	Classification	Score
TMB-high	Tier 1A Pathogenic	60 Mutations/Megabase

Phase 1/Phase 2 clinical trials (1)

PEMBROLIZUMAB

A Phase I/II Study of Pembrolizumab (MK-3475) in Children With Advanced Melanoma or a PD-L1 Positive Advanced, Relapsed or Refractory Solid Tumor or Lymphoma (KEYNOTE-051)
[NCT02332688](#)

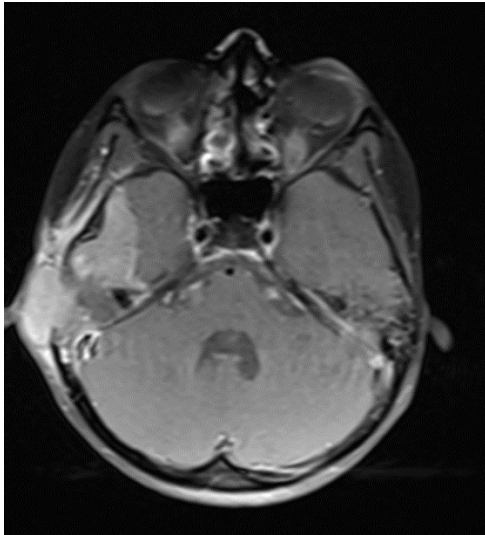
Qualifying variant

Biomarker	Classification	Score
TMB-high	Tier 1A Pathogenic	60 Mutations/Megabase

Contact

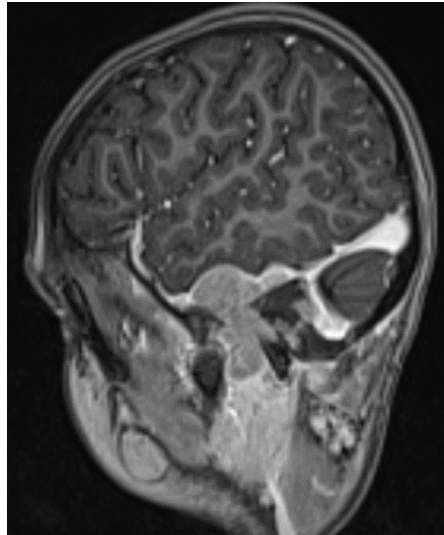
United States: CO, IN, MA, NY, TN, TX, UT, WA
 Toll Free Number: 1-888-577-8839;

September 2022



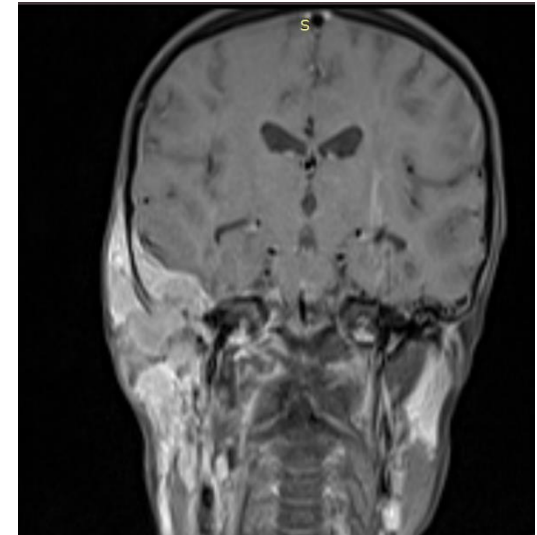
Disease progression

- Intracranial extension- temporal lobe invasion



Further chemotherapy

- metronomic Doxorubicin+Metothrexate (August-October)



Progressively deteriorated

- Died November 2022 (8 months from diagnosis)



Discussion

Take home messages

Minor salivary glands malignancies

- rare, challenging diagnosis and treatment

Importance of peer/centralized review of pathology

- to avoid giving the wrong treatment or delays

Genetic testing

- Ideally undertaken early, to know all treatment options available and plan accordingly

Radiotherapy

- is efficient for most H&N tumours, but some tumours carry intrinsic radioresistance;
- *nonetheless, in this case radiation still offered quick symptom relief
- consider potential toxicities and take into account that combined treatment modalities can cause more severe effects – explore other available techniques (protons, brachytherapy, etc.)