HITRI plus
Heavy Ion Therapy Research Integration

Case Study on Salivary Gland in Heavy Ion Therapy

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CNAO National Center for Oncological Hadrontherapy

CNAO
Centro Nazionale di Adroterapia Oncologica

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

Case 1

Italian, female, 44 years old.

No comorbidities.

Allergies: contrast intolerance of both CT an MRI.

Smoker (2 packages per week).

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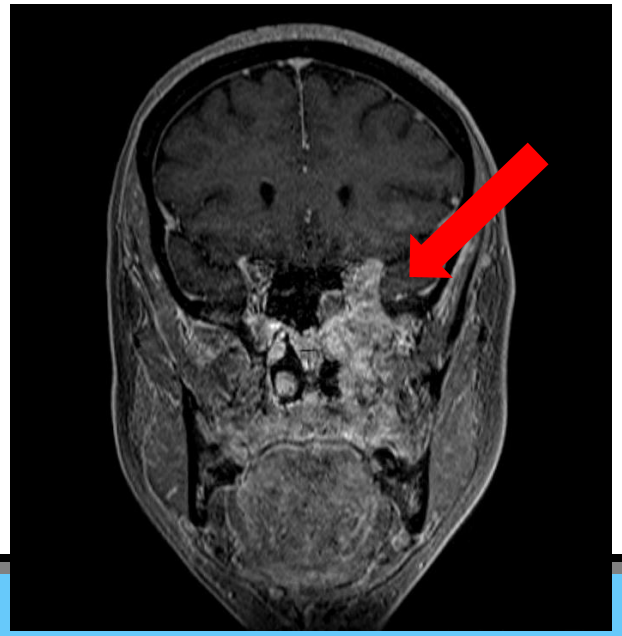
Oncological history

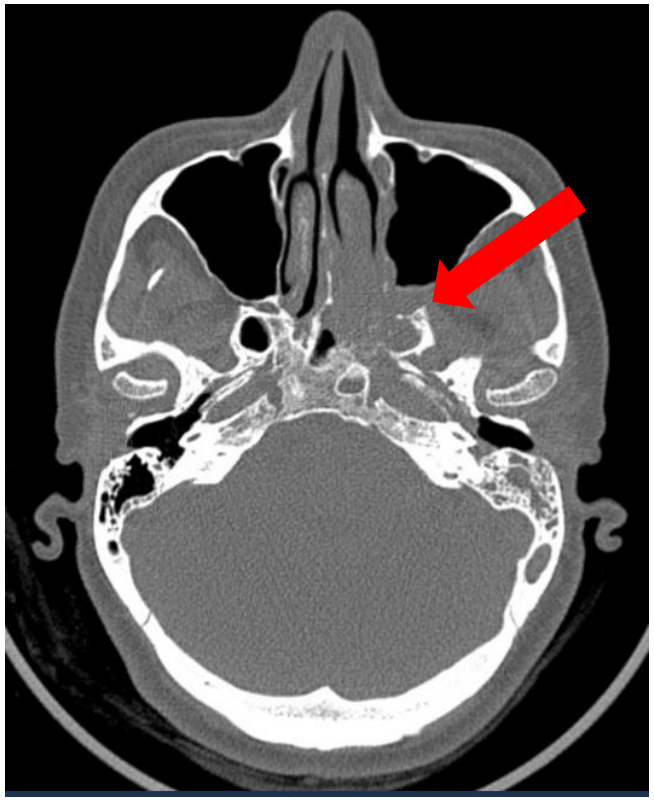
January - June 2017: under treatment for sinusitis and turbinate hypertrophy.

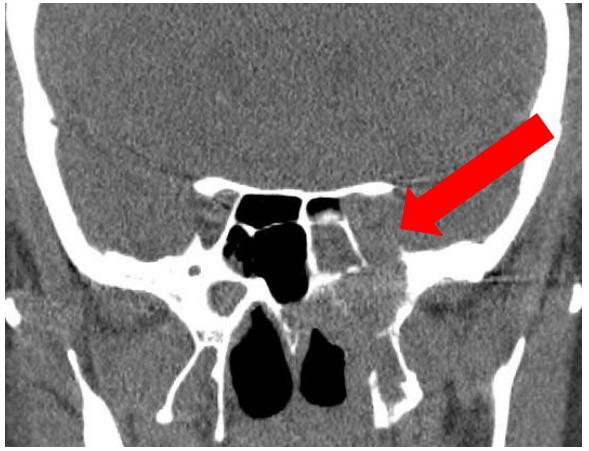
Jule 2017: **diplopia** → eye examination: ophthalmologist prescribed a head CE-MRI.

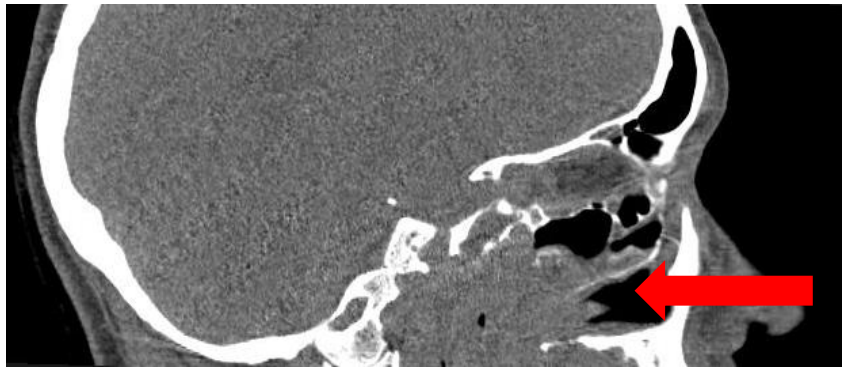
08/2017 head CE-MRI: **nasopharyngeal heteroplastic lesion** with "plaque" development along the posterior and left lateral walls and little vegetative component. Marginal infiltration of parapharyngeal space, the tumor extends to the pterygopalatine fossa and to the buccal space. It extends to the inferior orbital fissure, with **perineural diffusion** and **permeative infiltration** of the posterior third of the orbital floor and lamina papyracea.



08/2018 cranial CT: **dilatation and partial erosion of the bone walls,** adjacent to the vidian canal and foramen rotundum, the infraorbital canal and of the greater and lesser palatine foramen **due to perineural infiltration**. The left pterygo-palatine fossa and laterally the pterygo-maxillary fissure widened due to infiltrative-erosive phenomena and due to the **extension towards the infratemporal fossa**. The lesion invaded the left nasal cavities posteriorly with bone resorption of the left middle and inferior nasal turbinates. The tumour also erodes part of the orbital floor posteriorly, **widening and infiltrating both the inferior and superior orbital fissures**.







09/2018 Left posterior nasopharynx biopsy: fragments of nasopharyngeal mucosa, including salivary gland-type lobules, bony trabeculae and muscle tissue, with infiltration from **adenoid-cystic carcinoma**, with **solid** and **cribriform** growth pattern.

10/2018 Total Body CE-CT scan**: no distant metastasis**.

Stage (TNM 8° edition) **cT4b cN0 M0**

CNAO

Multidisciplinary evaluation

- No surgical indication.
- No chemotherapy.
- Yes radiotherapy → valuation for **hadrontherapy.**

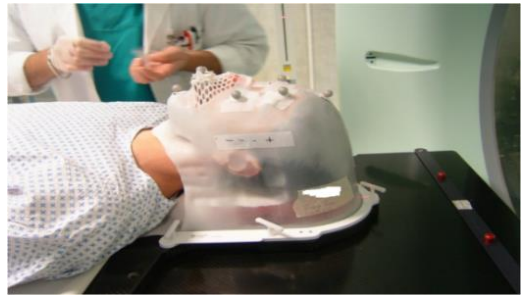
November 2018, clinical evaluation in CNAO: KPS 100, non-subjective reduction in visual acuity. Hypoesthesia (left V2-V3 region), tinnitus on the left side, normosmia, no dysphagia, no dysgeusia. Pain quantification (NRS 0-10 scale): 2/10 left cheekbone and frontal sinus. → **Clinical indication for carbon ion radiotherapy.**

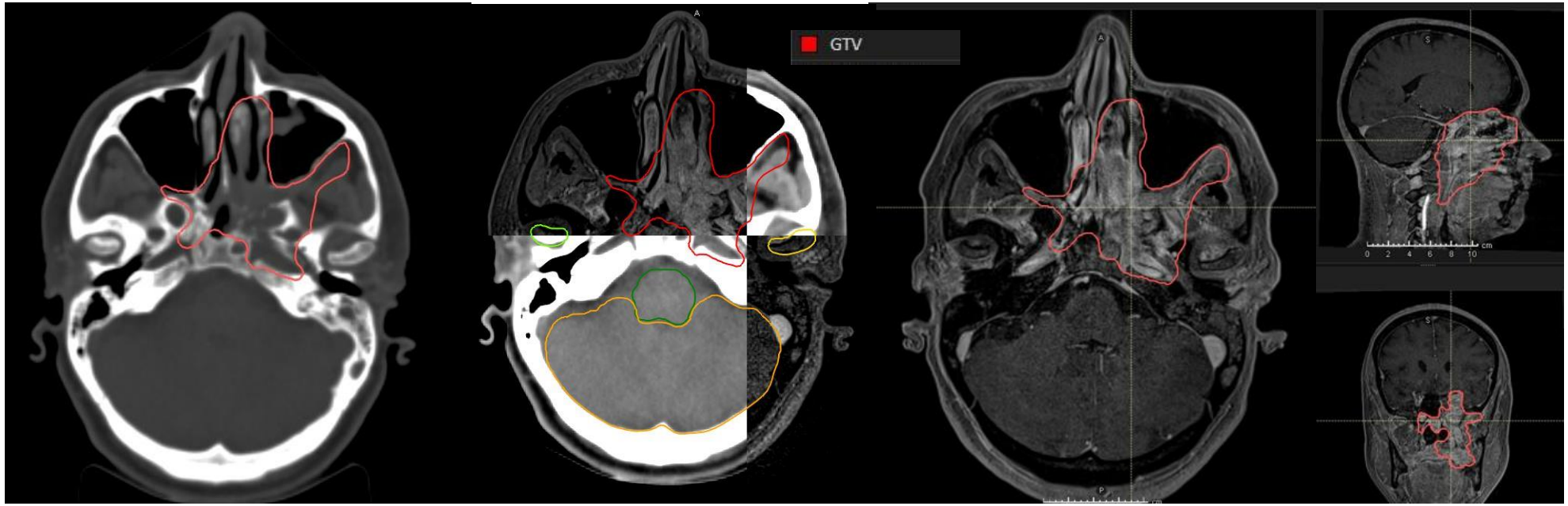
Baseline exams:

- 11/2018 Eye examination: 10/10 visual acuity bilaterally with no limitation in motility.
- 11/2018 Hypothalamic-pituitary function tests: within limits.
- 11/2018 Audiometry: bilateral hearing loss, greater on the left.
- 11/2018 Echocolordoppler TSA: within limits.
- 12/2018 Oral cavity cleaning.

SIMULATION: CT and CE-MRI

In preparation for the treatment, the patient was immobilized with a thermoplastic device in a supine position. A set of 2-mm-thick computed tomographic (CT) and contrastenhanced MR images was acquired for treatment planning, using the same immobilization device and rigidly registered each other in order to better outline target volumes and organs at risk.





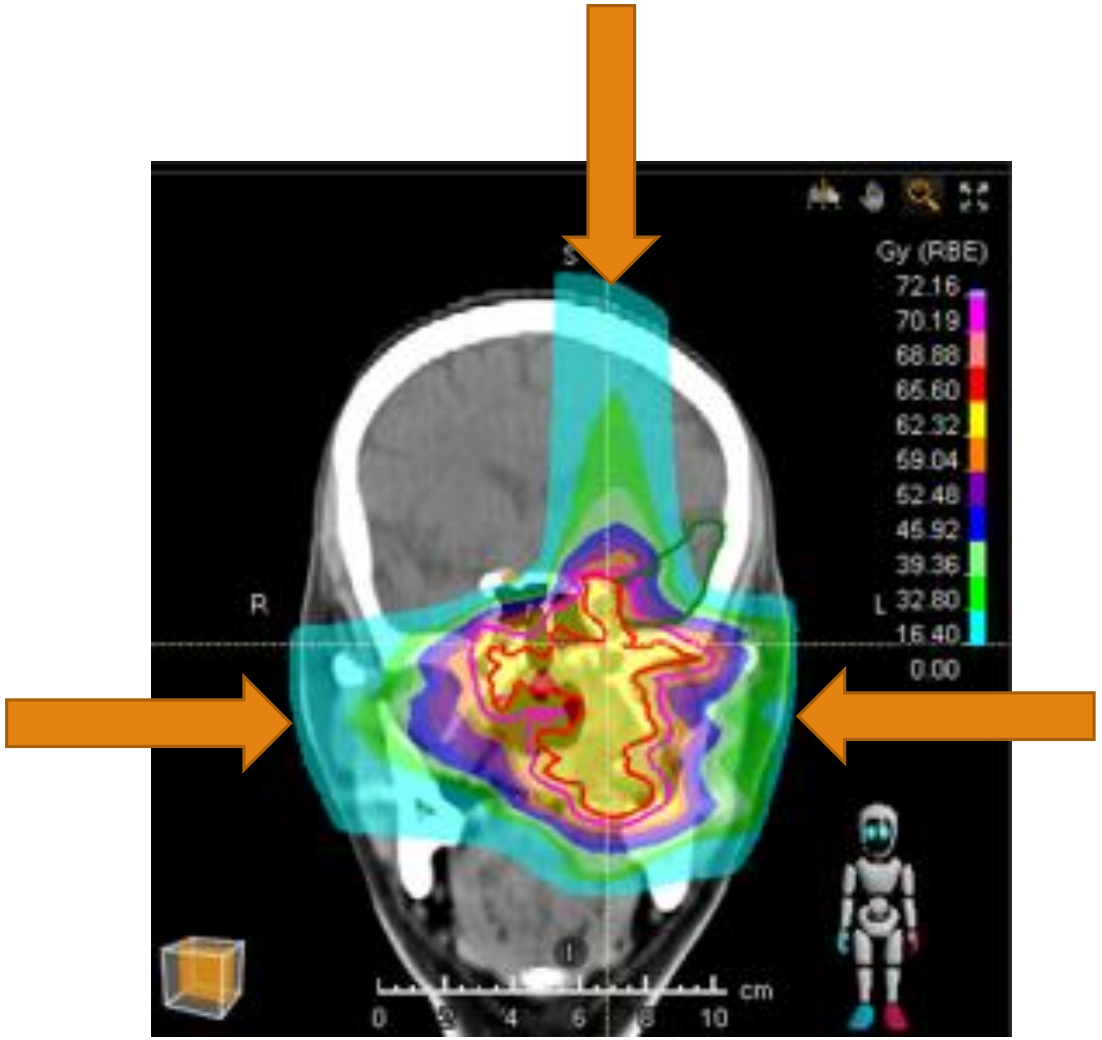
Simulation CT (without CE) *CT-MRI fusion* *Simulation CE-MRI*

PLANNING

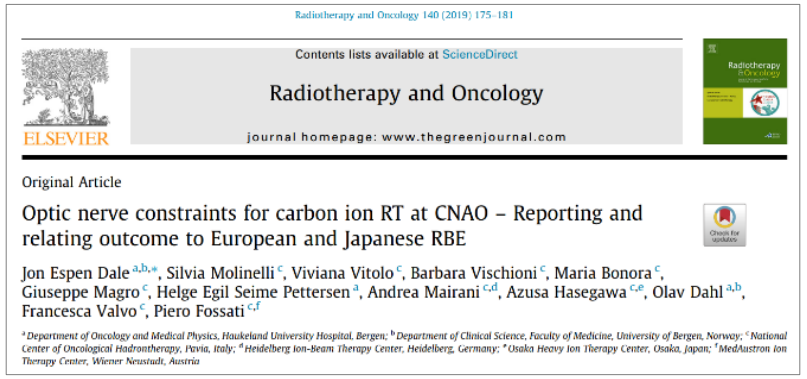
Treatment was planned with synchrotron-based scanning **carbon ion beams** (pencil beam scanning and spill-by-spill active energy variation). The dose prescribed was **65.6 Gy (relative biological effectiveness, RBE) in 16 fractions, 4.1 Gy (RBE) per fraction** (4 fractions per week). LR-CTV: 41 Gy(RBE) in 10 fr, 4.1 Gy(RBE)/fr. HR-CTV (boost): 24.6 Gy(RBE) in 6 fr, 4.1 Gy(RBE)/fr.

LR-CTV and HR-CTV: D95% ≥ 95%, D98% ≥ 90%.

HR-CTV: D2% ≤ 103%.



PLANNING - Optic pathways and Brainstem



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Original Article

Optic nerve constraints for carbon ion RT at CNAO – Reporting and relating outcome to European and Japanese RBE

Jon Espen Dale [a,b,*], Silvia Molinelli [c], Viviana Vitolo [c], Barbara Vischioni [c], Maria Bonora [c], Giuseppe Magro [c], Helge Egil Seime Pettersen [a], Andrea Mairani [c,d], Azusa Hasegawa [c,e], Olav Dahl [a,b], Francesca Valvo [c], Piero Fossati [c,f]

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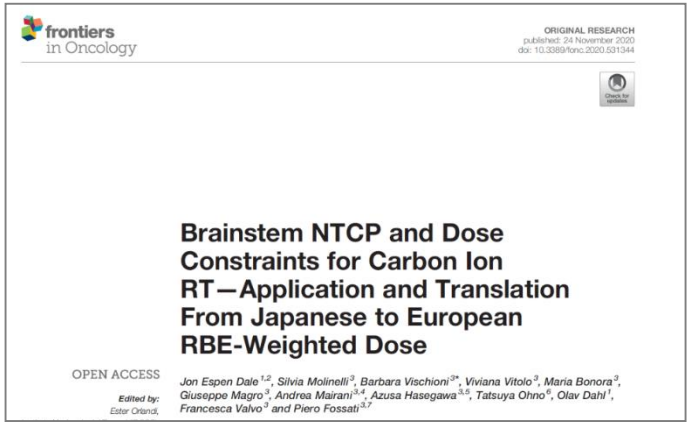


frontiers in Oncology

ORIGINAL RESEARCH

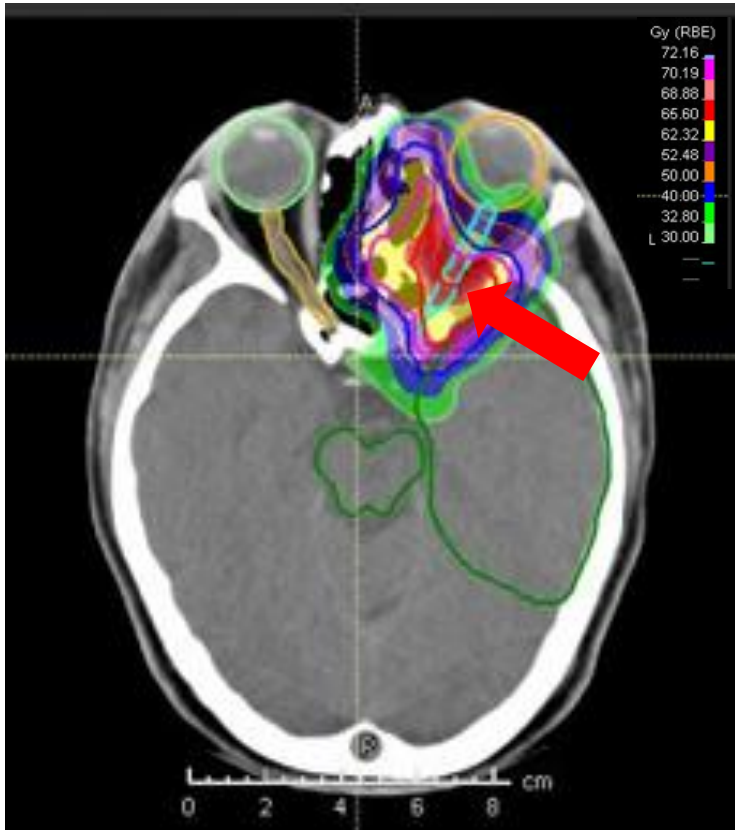
Brainstem NTCP and Dose Constraints for Carbon Ion RT—Application and Translation From Japanese to European RBE-Weighted Dose

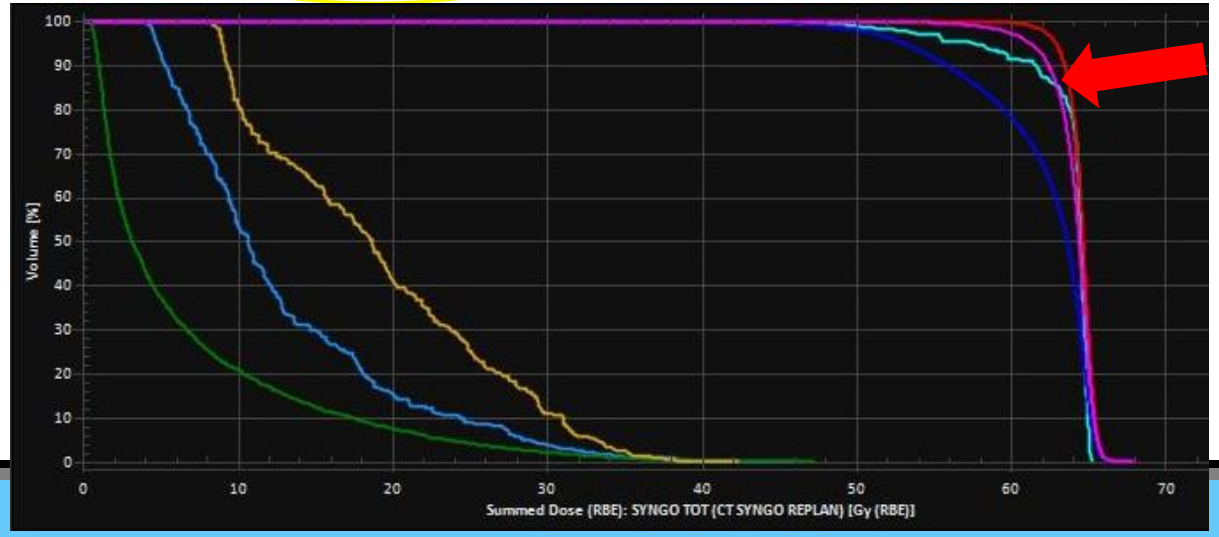
OPEN ACCESS

Jon Espen Dale [1,2], Silvia Molinelli [3], Barbara Vischioni [3*], Viviana Vitolo [3], Maria Bonora [3], Giuseppe Magro [3], Andrea Mairani [3,4], Azusa Hasegawa [3,5], Tatsuya Ohno [6], Olav Dahl [1], Francesca Valvo [3] and Piero Fossati [3,7]

- $D_{1\%} \leq 45$ Gy (RBE)
- $D_{20\%} \leq 37$ Gy (RBE)

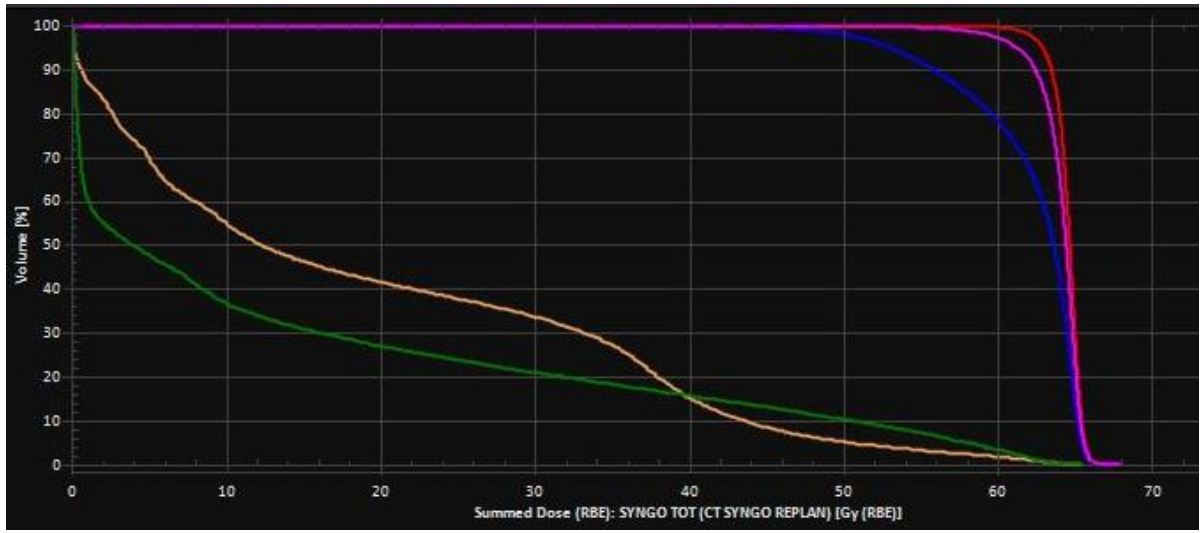
$D_{1\%} \leq 40$ Gy (RBE)





ROI	ROI vol. [cm³]	Dose [Gy (RBE)] D99	D98	D95	Average	D50	D2	D1
Brainstem	21.29	0.58	0.65	0.82	6.44	3.16	30.70	34.13
GTV	94.20	61.14	62.01	62.88	64.52	64.68	65.90	66.09
HR-CTV	182.28	57.36	59.20	61.20	64.05	64.43	65.84	66.02
LR-CTV	301.41	47.45	49.92	53.01	61.97	63.64	65.71	65.90
OpticChiasm	1.20	4.27	4.45	4.78	12.83	10.66	32.38	35.02
OpticNrv_L	0.99	49.40	52.35	57.50	63.59	64.54	65.13	65.21
OpticNrv_R	1.16	8.45	8.83	8.98	19.03	18.73	35.19	36.74

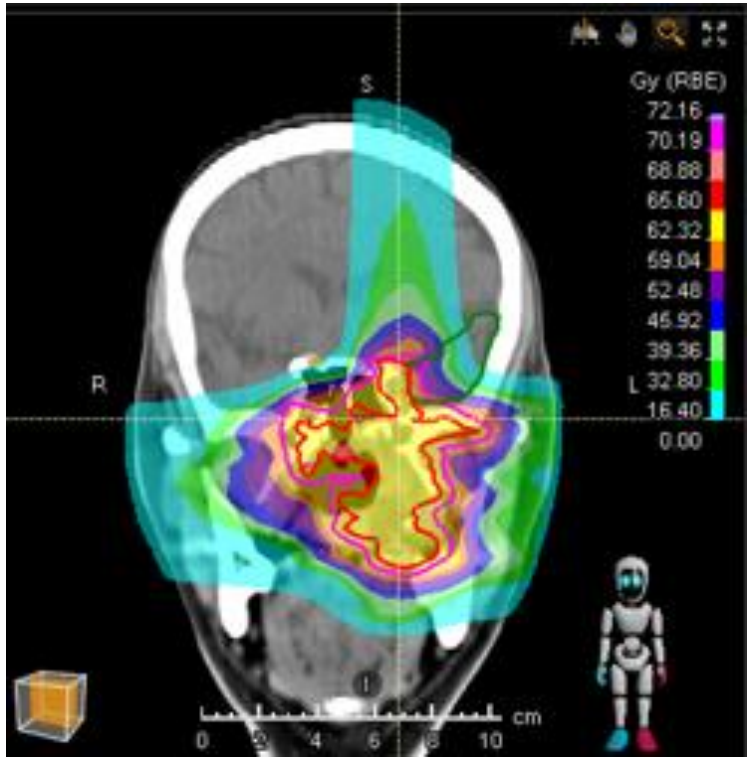
PLANNING - Brain parenchyma



Frontal lobe: D1cc = 63.3 Gy(RBE)
D2cc = 62.35 Gy(RBE)
D5cc = 58.4 Gy(RBE)

Left Temporal lobe: D1cc = 62.17 Gy(RBE)
D2cc = 60 Gy(RBE)
D5cc = 54 Gy(RBE)

$D_{2CC} \leq 54$ Gy (RBE)



Carbon Ion Dose Constraints in the Head and Neck and Skull Base: Review of MedAustron Institutional Protocols

Piero Fossati, MD[1]; Ana Perpar, MD[2]; Markus Stock, PhD[1]; Petra Georg, MD[1]; Antonio Carlino, PhD[1]; Joanna Gora, PhD[1]; Giovanna Martino, MSc[1]; Eugen B. Hug, MD[1]

Table 6. Dose constraints for brain parenchyma at MedAustron Ion Therapy Center (Wiener Neustadt, Austria).

Fractionation	Safe constraint, Gy RBE (LEM)	Low-to-medium risk, Gy RBE (LEM)
Japanese	$D_{1cm^3} < 54$	$D_{1cm^3} < 64$
	$D_{5cm^3} < 50$	$D_{5cm^3} < 60$
German	$D_{1cm^3} < 56.7$ equivalent to $NTD_{\alpha/\beta=2Gy} = 65$	$D_{1cm^3} < 59$ equivalent to $NTD_{\alpha/\beta=2Gy} = 69$

Abbreviations: Gy RBE, Gy relative biological effectiveness; LEM, local effect model; *D*, dose; NTD, normalized total dose.

TREATMENT

From 21/01/2019 to 19/02/2019 the patient was treated with **carbon ion radiotherapy: 65.6 Gy (RBE) in 16 fractions, 4.1 Gy (RBE)** per fraction (4 fractions per week). LR-CTV: 41 Gy(RBE) in 10 fr, 4.1 Gy(RBE)/fr. HR-CTV (boost): 24.6 Gy(RBE) in 6 fr, 4.1 Gy(RBE)/fr.

Treatment was well tolerated and no interruption was needed.

No acute grade ≥ G3

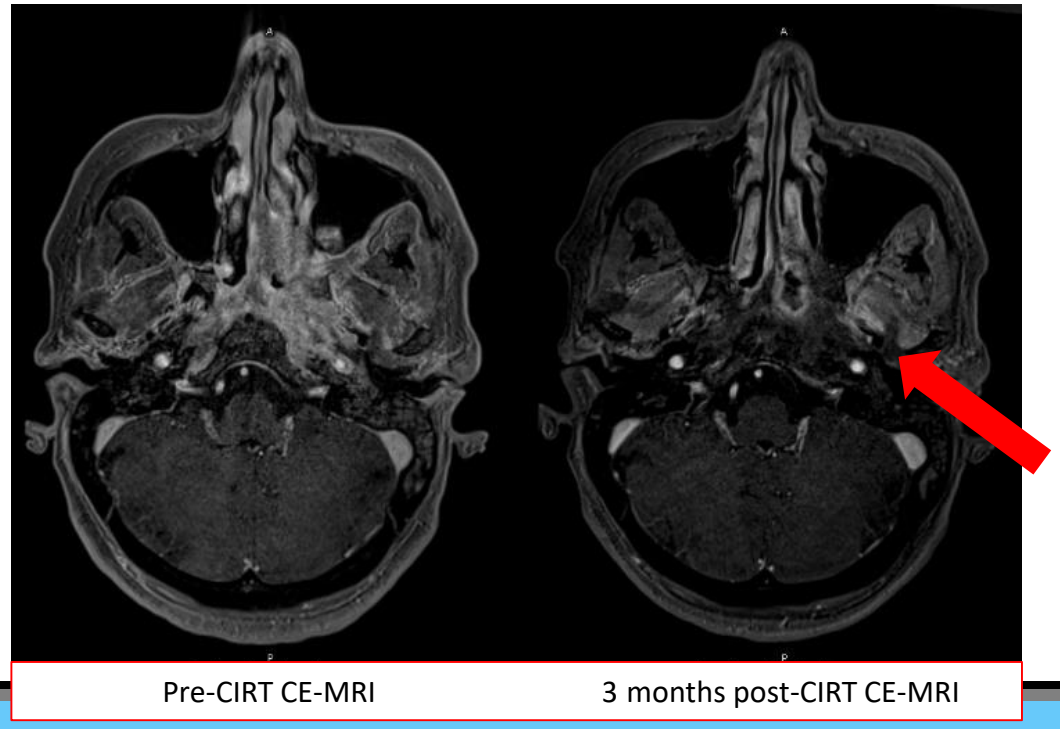
Acute toxicity (according to CTCAE V 5.0):

During CIRT: G2 mucositis, G1 edema, G2 neuropathic pain, G2 erythema, G1 alopecia, G1 eye (conjunctivitis).

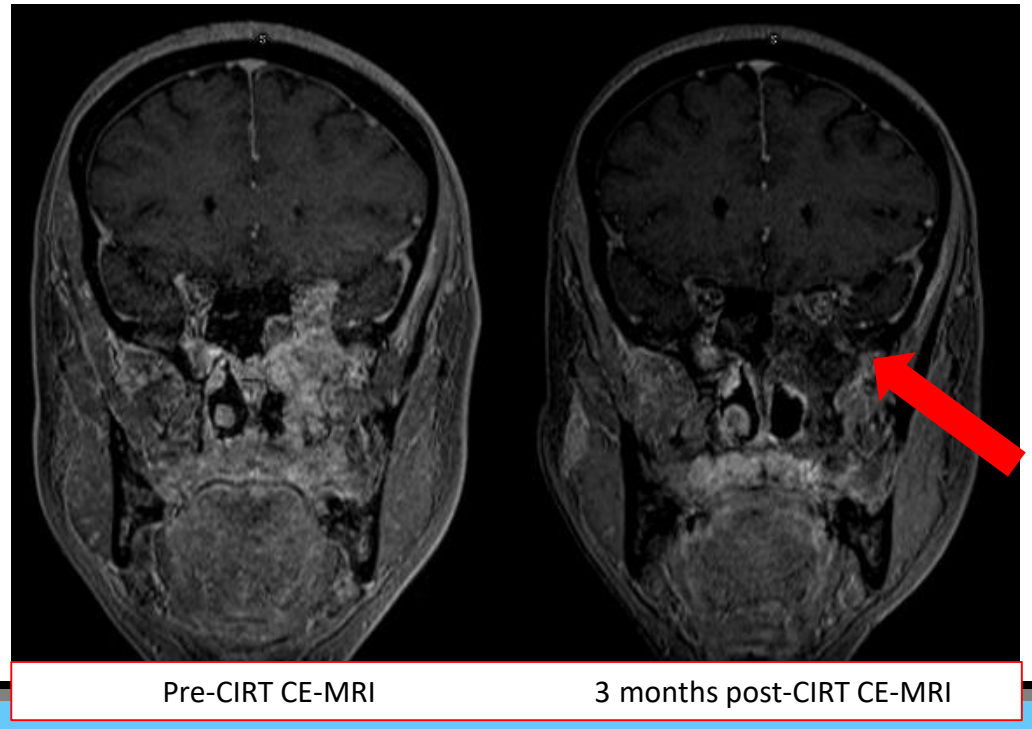
At the end of CIRT: G2 erythema, G2 mucositis, G1 alopecia, G1 eye (conjunctivitis), G1 neuropathic pain.

FOLLOW-UP: 3 months

<u>04/2019 H/N CE-MRI</u>: treated pathological tissue, centered in correspondence with the vault and wall left side of the nasopharynx, **has a drastic reduction in vascularity and absence of signal restriction in DWI. It is difficult to parameterise and appears reduced in size** especially due to the disappearance of some of its exophytic components at the level of the maxillary sinus and in left nasal cavity. In the endocranial site, the tissue willing to surround the intrapetrous segment of the carotid siphon, cavernous sinus and left inferior orbital fissure is also **completely devascularized.**

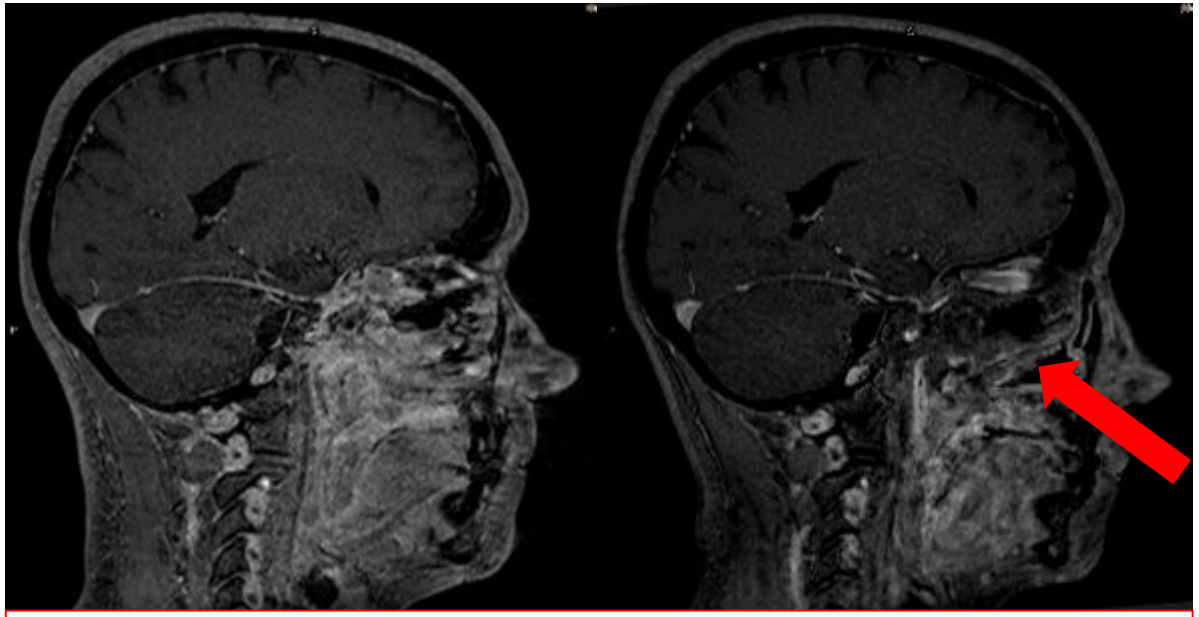


Pre-CIRT CE-MRI | 3 months post-CIRT CE-MRI

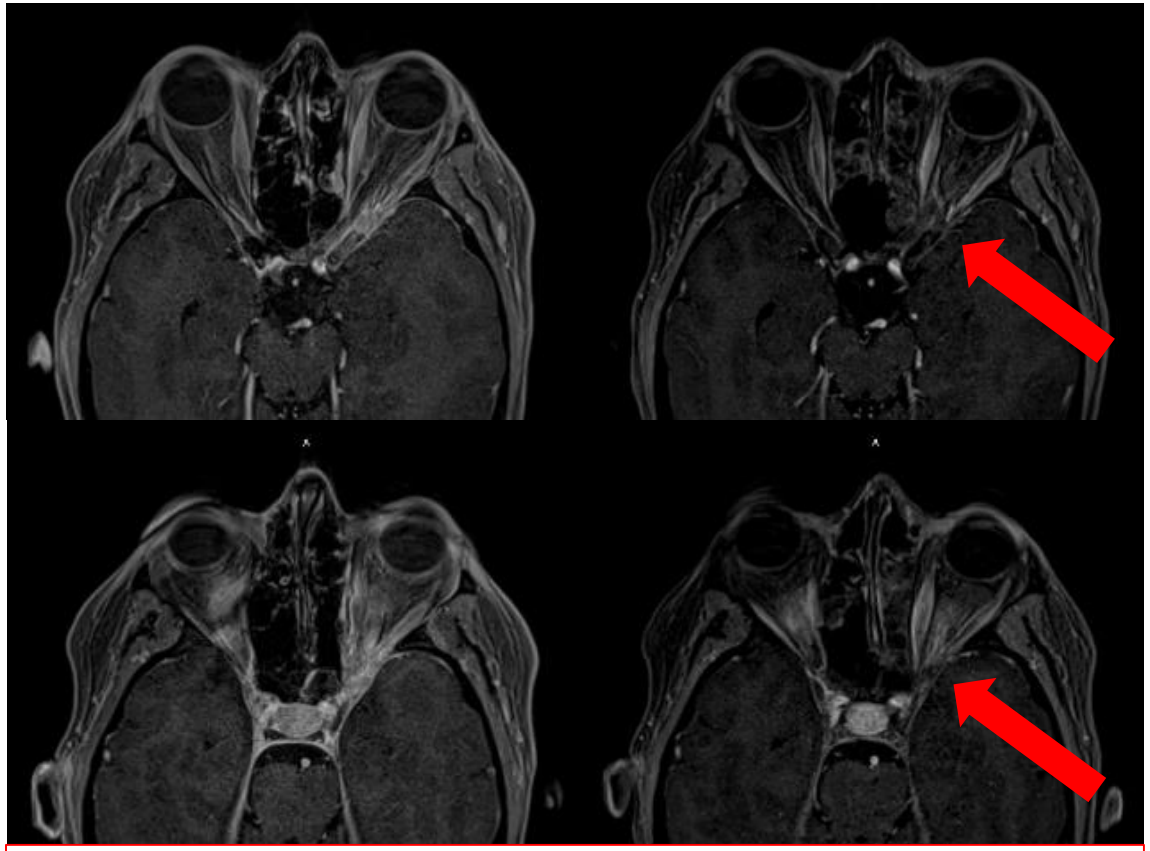


Pre-CIRT CE-MRI | 3 months post-CIRT CE-MRI

FOLLOW-UP: 3 months



Pre-CIRT MRI | 3 months post-CIRT MRI



Pre-CIRT MRI | 3 months post-CIRT MRI

Acute toxicity at 3 months (CTCAE V 5.0): G1 dry mouth, G1 dysgeusia, G1 alopecia (frontal region and eyelashes of the left eye), G1 watering left eye, G1 left suborbital edema, G1 mucositis.

FOLLOW-UP

6 months:

07/2019 H/N CE-MRI **:** stable disease.

Subacute toxicity at 6 months (CTCAE V 5.0): G1 dry mouth, G2 watering eyes.

9 months:

09/2019 ENT examination: in fibroscopy presence of abundant sero-mucous crusts in the left nasal cavity e nasopharynx. **No evidence of suspicious lesions**.

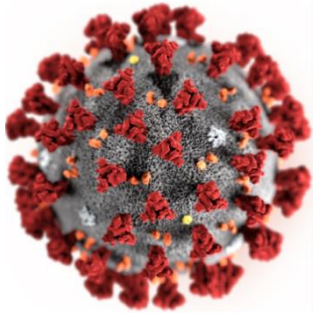
09/2019 Eye examination: 10/10 visual acuity bilaterally.

11/2019 CE-CT chest abdomen-pelvis: negative.

11/2019 H/N CE-MRI**:** stable disease.

Late toxicity at 9 months (CTCAE V 5.0): G1 dry mouth, G1 watering eyes, G1 neuropathy (V2 paresthesia).

FOLLOW-UP



2020: due to the SARS-CoV-2 pandemic, the patient did not carry out regular follow-ups.

07/2020 ENT examination: in fibroscopy presence of seromucous crusts adherent to the nasopharynx. No evidence of suspicious lesions.

09/2020 Eye examination: 10/10 visual acuity bilaterally.

09/2020 H/N CE-MRI: stable radiological findings. The treated tissue centered at the vault and left side wall of the nasopharynx remains stable at dimensions and characteristics of signal, free of pathological CE and signal restriction in diffusion sequences, as from non-oncological tissue active as a result of radiation treatment. No brain complications. Lack of latero-cervical and jugulo-digastric lymph glandular swellings.

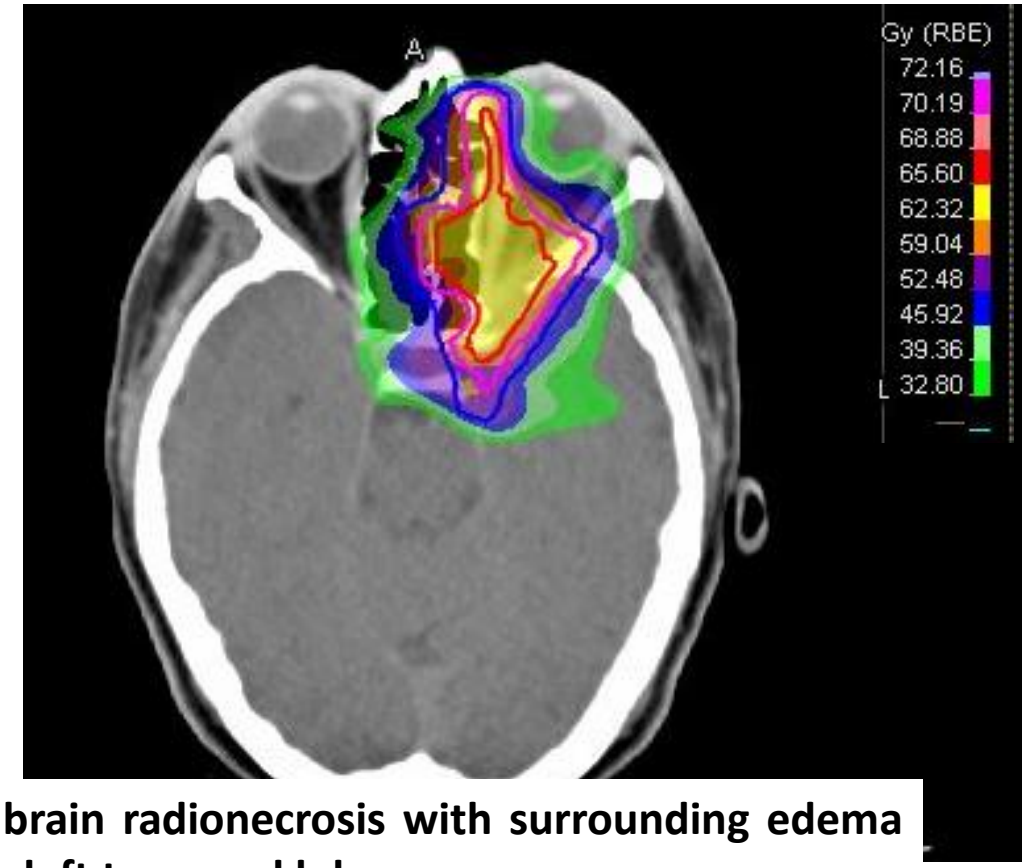
02/2021 H/N CE-MRI: stable. Increased reactive/inflammatory material in the ethmoidal cells, in the left otomastoid site, in the paranasal sinus cavities, especially on the left.

03/2021 CE-CT chest abdomen-pelvis: negative.

06/2022 H/N CE-MRI: **intracranial spread of disease in the left temporal lobe.**

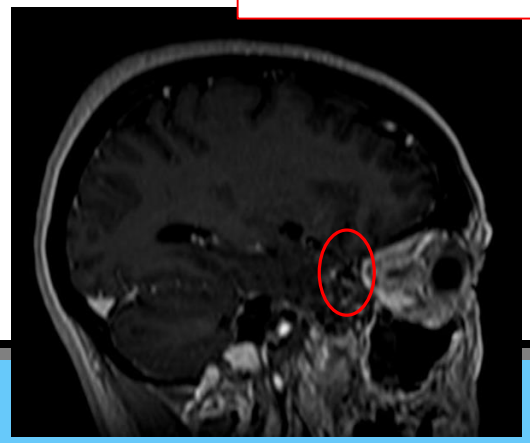
?

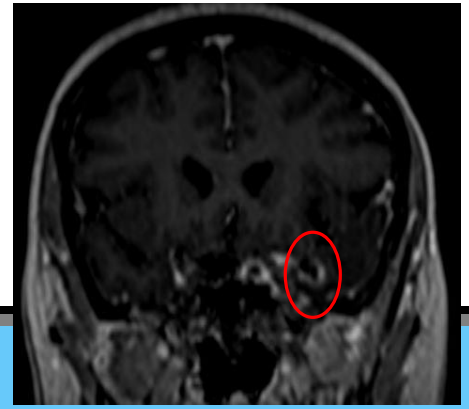
FOLLOW-UP – 3 years and 5 months

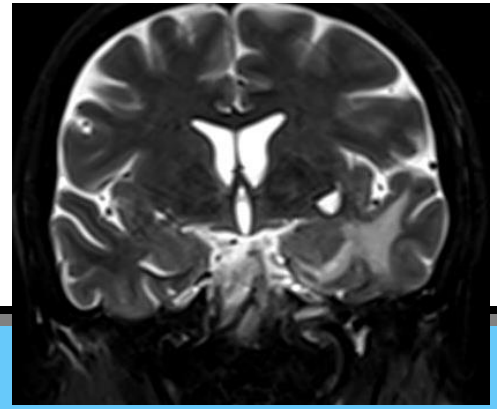


06/06/2022 CE-MRI

Probable foci of brain radionecrosis with surrounding edema at the level of the left temporal lobe.





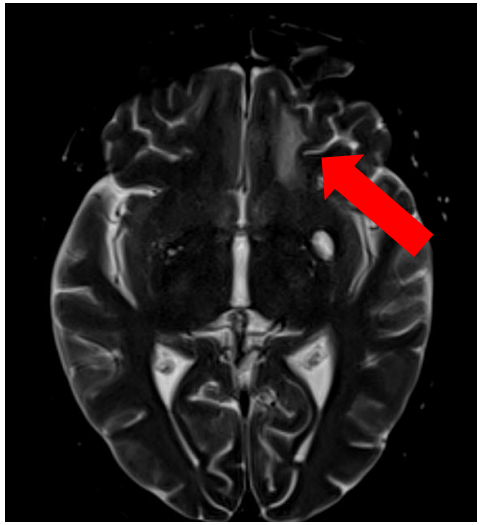


FOLLOW-UP

07/2022 ENT examination: left maxillary and ethmoid chronic rhinosinusitis. **No evidence of suspicious lesions**.

09/2022 neurological examination: **no neurological signs**. Prescribed therapy with steroid and antiepileptic medications (the patient refused to take the medications). EEG required.

10/2022 H/N CE-MRI: **stable disease**. At the level of the **temporal lobe morphological CEs pseudocercinata** and contiguous vasogenic **edema are stable** which by site are likely to have a post-actinic radionecrotic nature**; more evident currently similar foci of radionecrosis also at the level of the ipsilateral rectus and orbital gyruses, with a slight increase in the contextual edema.**



November 2022, clinical state (3 years and 9 months):

KPS 90. Events of mild short-term memory impairment. G1 dry mouth, G1 watering eyes, G2 dysgeusia, anosmia (G1), G2 neuropathy (trigeminal paresthesia, V2). No medications.

FOLLOW-UP – 4 years and 3 months

In February 2023 the patient contacted us reporting **a sudden drop in vision on the left eye** that started two weeks before.

01/2023 eye examination: total amaurosis of the left eye, miosis deficit, normal fundus. Optical Projection Tomography was normal.

02/2023 H/N CE-MRI : stable radiological findings.

02/2023 neurological examination: left amaurosis, hypoesthesia tactile pain in the trigeminal area on the left. EEG required. Prescribed therapy with steroid and antiepileptic medications.

05/2023 H/N CE-MRI: the **treated tissue** appears **stable**. **Brain radionecrosis areas are stable with slight increase in surrounding edema.**

Late toxicity at 4 years and 3 months (CTCAE V 5.0):

G1 dry mouth, G1 watering eyes, G2 dysgeusia, anosmia(G1), G2 brain RN, G2 neuropathy (V2 paresthesia), **G4** left visual impairment.

Medications: levetiracetam 500 mg once a day.

Local-regional control at 4 years and 3 months

G4 left visual impairment → ***Follow-up***

Case 2

Italian, female, 34 years old.

Comorbidities: in 2005 thyroidectomy for multinodular goiter, treated with hormone replacement therapy (levothyroxine).

No allergies.

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

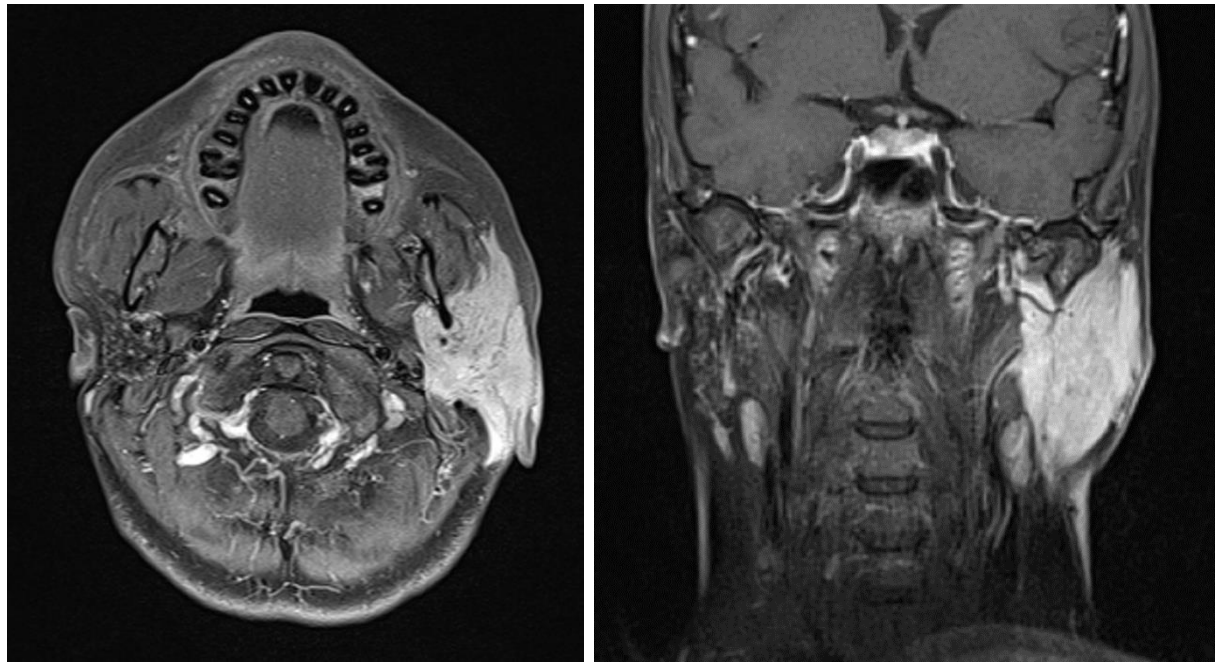
Oncological history

2013: left parotid swelling.

06/2017: dimensional increase, tenderness and pain of the left parotid swelling.

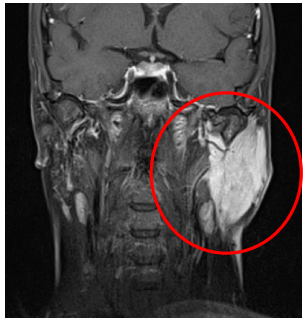
09/2017: left facial paralysis (cn VII) Grade II (House-Brackmann facial nerve grading system).

09/2017 head CE-MRI: **pathological tissue** with infiltrative characteristics that **completely replaces the left parotid gland** of 67x35 mm and cranio-caudal extension of about 74 mm. The lesion superficially infiltrates the subcutaneous tissue where also the infiltration of the cutaneous plane cannot be excluded. Deeply the tissue creeps into the stylomastoid foramen with **thickening and c.e. of the intra-mastoid tract of the VII cranial nerve by perineural diffusion**. There is infiltration of the left masseter muscle.



01/2018 tru-cut core biopsy: **Adenoid-cystic carcinoma.**

Stage (TNM 8° edition) **cT4a cN0 M0**



03/2018 CE-CT chest abdomen-pelvis: negative for metastasis.

03/2018 surgical evaluation: total parotidectomy with facial sacrifice, left mandibulectomy + free-flap reconstruction and laterocervical emptying (left I-IV and Va)→ evaluated as a **possible non-radical surgery**.

The patient refused demolitive surgery.

CNAO

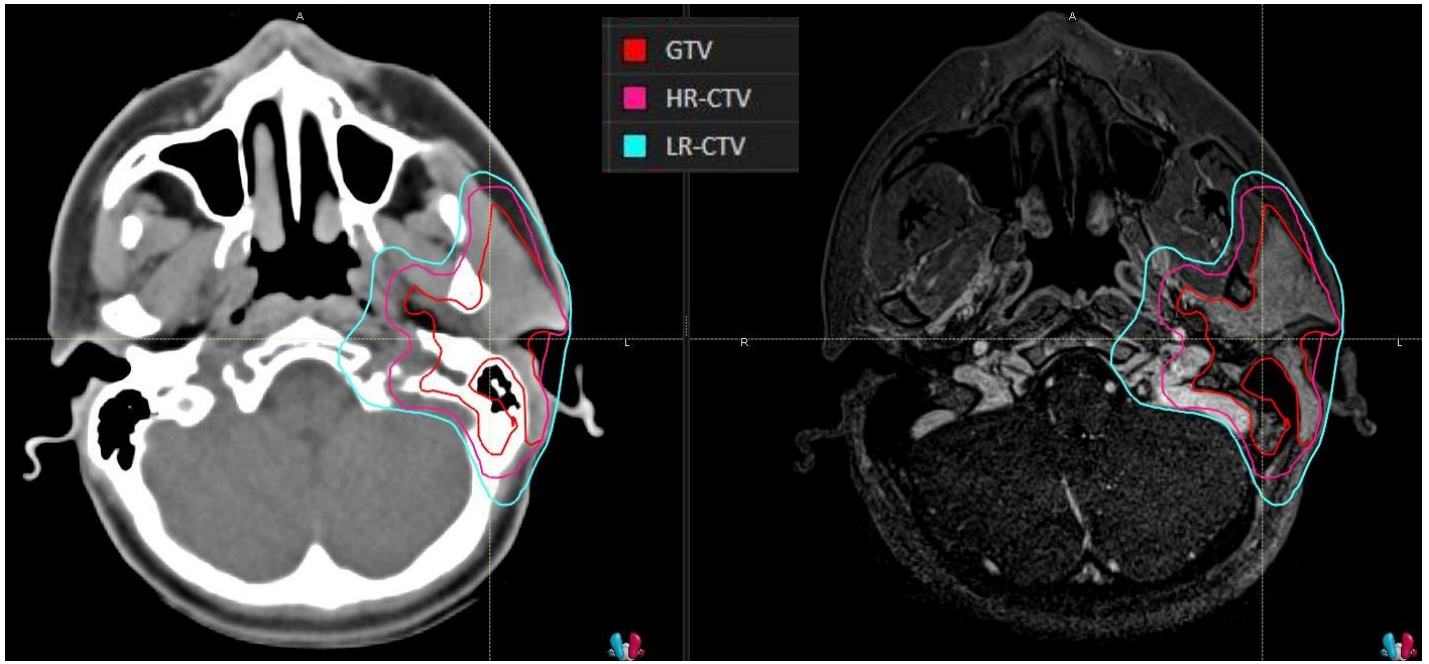
03/2018 clinical evaluation in CNAO: KPS 100. Slight deviation of the left labial fissure. Pain on palpation of left parotid swelling especially retroauricular region. She does not take pain medications. No hearing or eye problems. → **Clinical indication for carbon ion radiotherapy.**

Baseline exams:

- 03/2018 Audiometry: normal.
- 03/2018 Echocolordoppler TSA: within limits.
- 03/2018 Oral cavity cleaning.

SIMULATION: CT and CE-MRI

In preparation for the treatment, the patient was immobilized with a thermoplastic device in a supine position. A set of 2-mm-thick computed tomographic (CT) and contrastenhanced MR images was acquired for treatment planning, using the same immobilization device and rigidly registered each other in order to better outline target volumes and organs at risk.

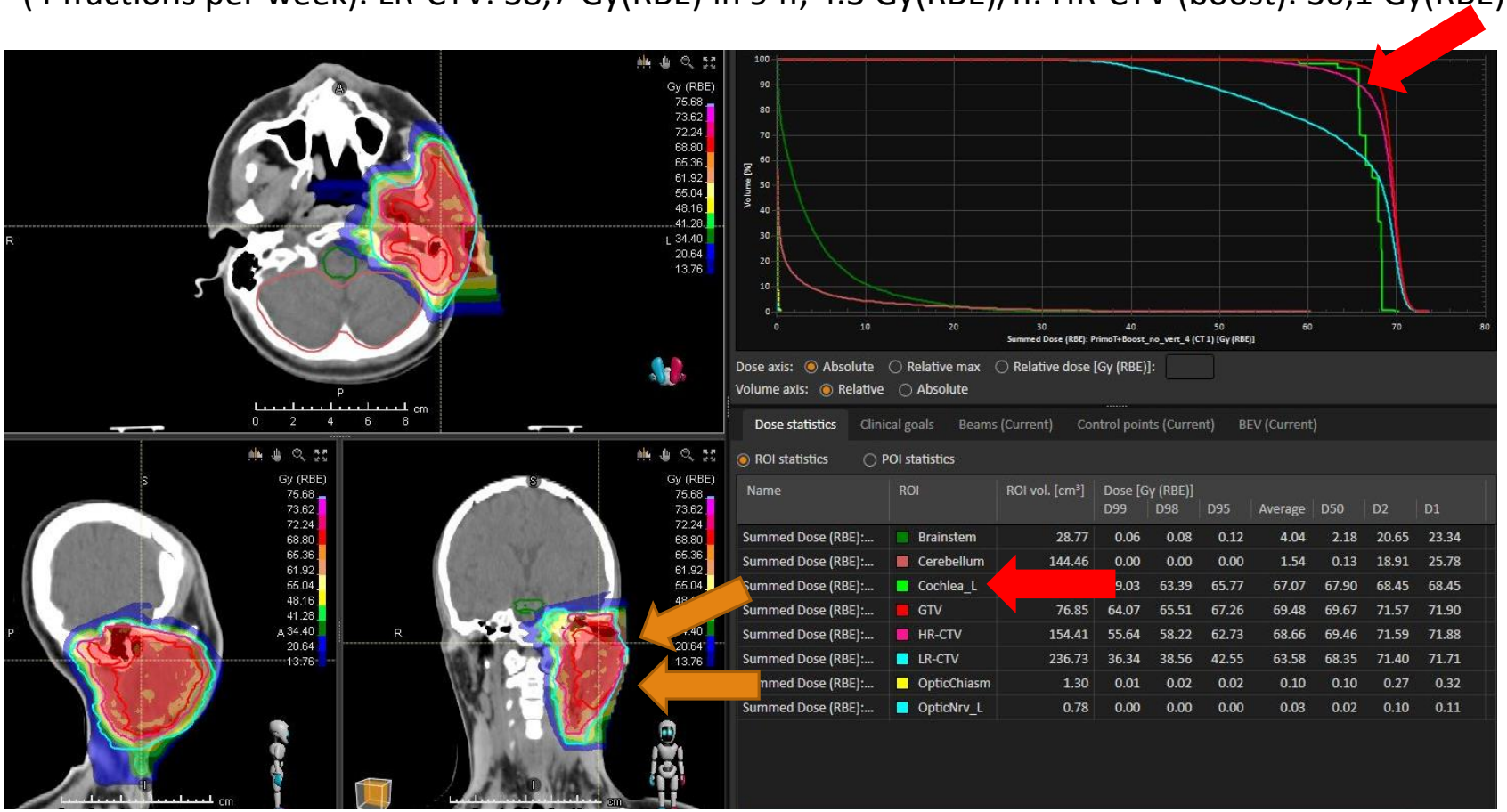


Simulation CT (without CE) *Simulation CE-MRI*

GTV = 76.84 cc

PLANNING & TREATMENT

From 03/04/2018 to 29/04/2018 the patient was treated with synchrotron-based scanning **carbon ion radiotherapy** (pencil beam scanning and spill-by-spill active energy variation). The dose prescribed was **68.8 Gy (RBE) in 16 fractions, 4.3 Gy (RBE)** per fraction (4 fractions per week). LR-CTV: 38,7 Gy(RBE) in 9 fr, 4.3 Gy(RBE)/fr. HR-CTV (boost): 30,1 Gy(RBE) in 7 fr, 4.3 Gy(RBE)/fr.



Treatment was well tolerated and no interruption was needed.

Acute toxicity (CTCAE V 5.0):

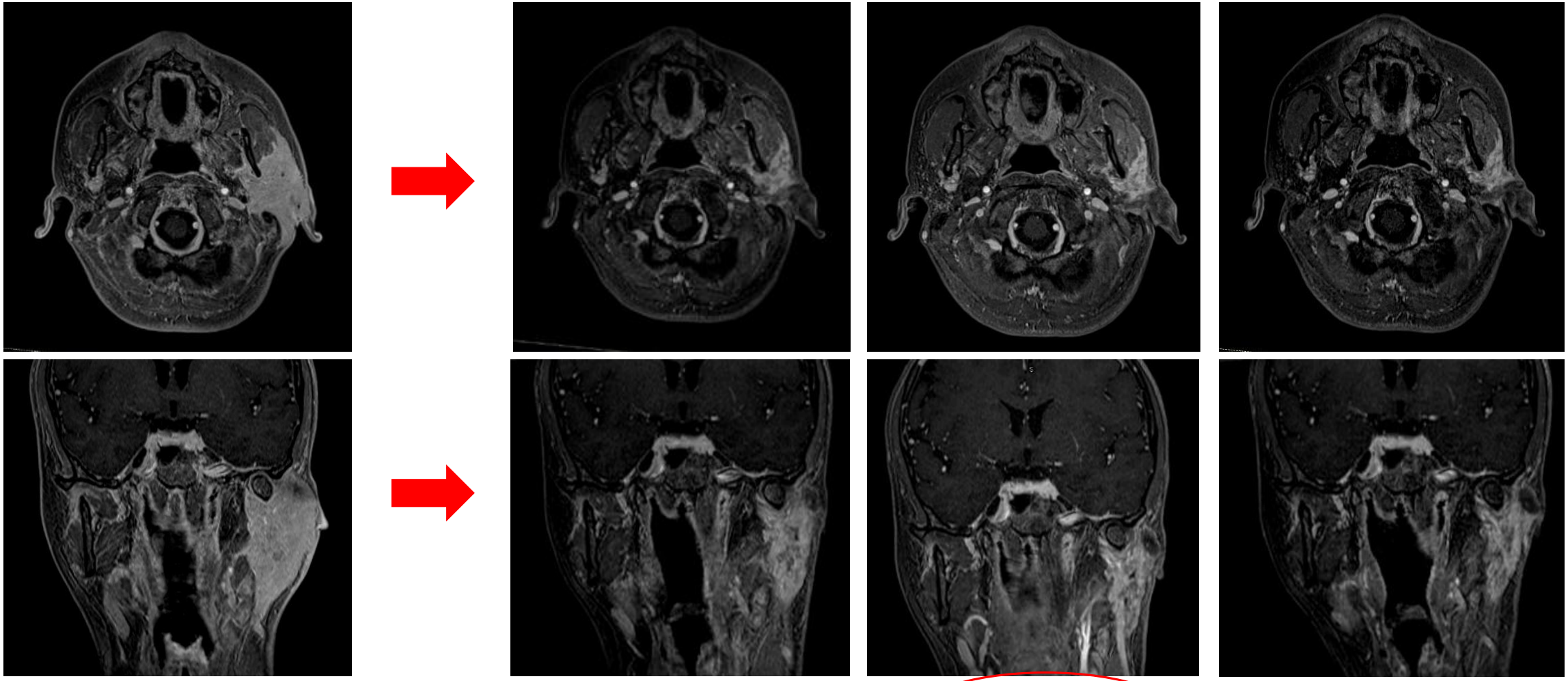
During CIRT: G1 erythema, G1 mucositis, G1 left middle ear inflammation.

At the end of CIRT: G1 erythema, G1 mucositis, G1 left middle ear inflammation.

FOLLOW-UP

GTV = 76.84 cc → 17.33 cc

↓ 78%



March 2018
(pre-CIRT CE-MRI)

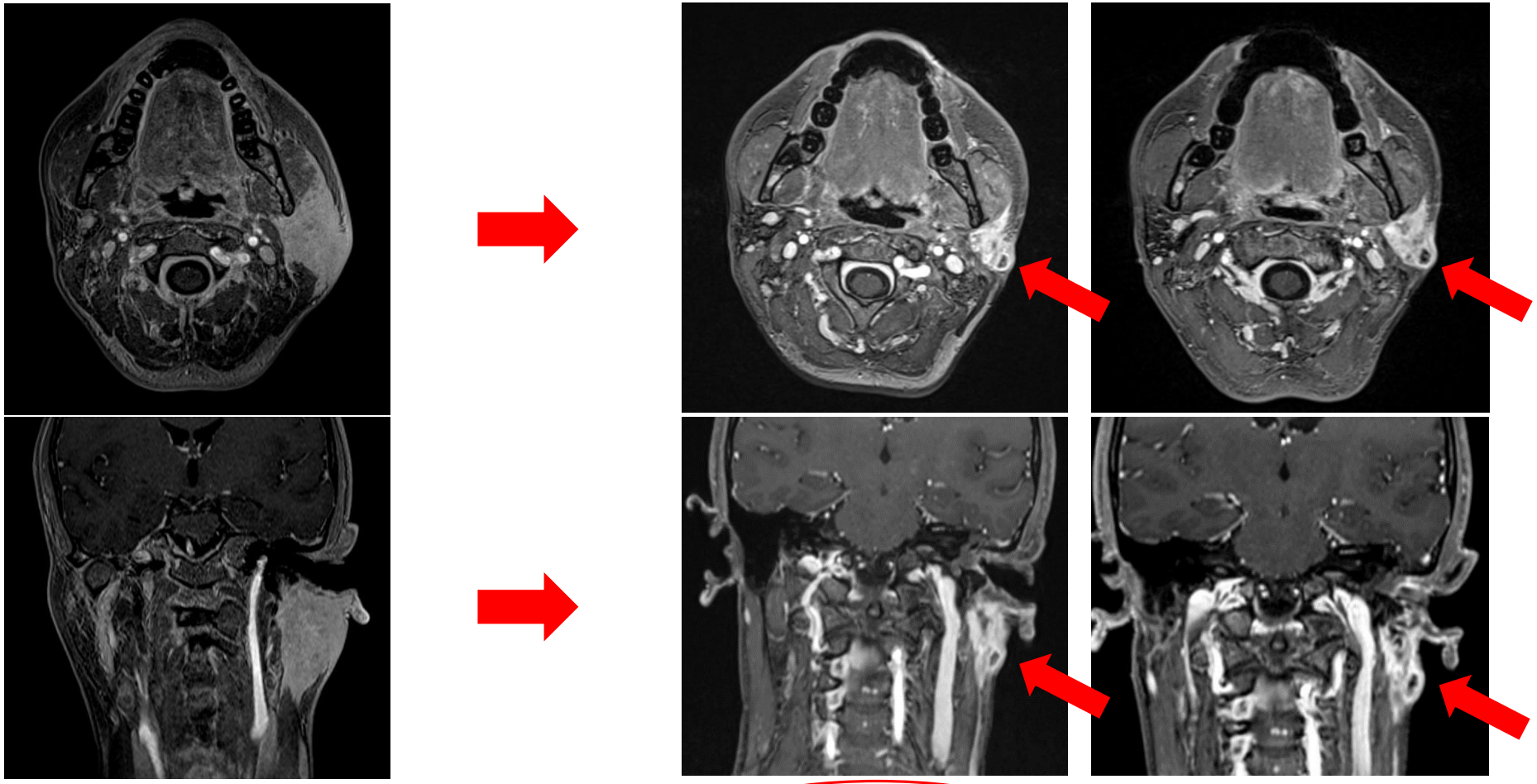
Jule 2018
(FUP 3 months)

November 2018
(FUP 6 months)

March 2019
(FUP 12 months)

Maximum late toxicity (CTCAE V 5.0) during FUP: G2 left otitis and mastoiditis. No longer visible left facial paralysis.

FOLLOW-UP



March 2018
(pre-CIRT CE-MRI)

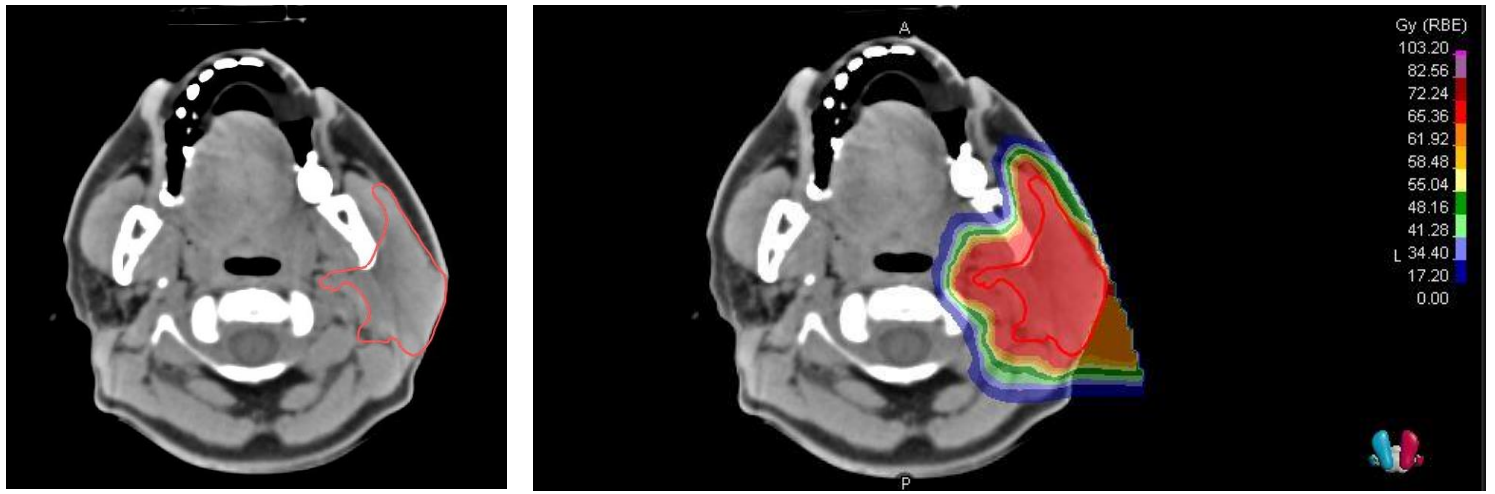
July 2020
(FUP 2 yrs and 3 mos)

March 2021
(FUP 3 yrs)

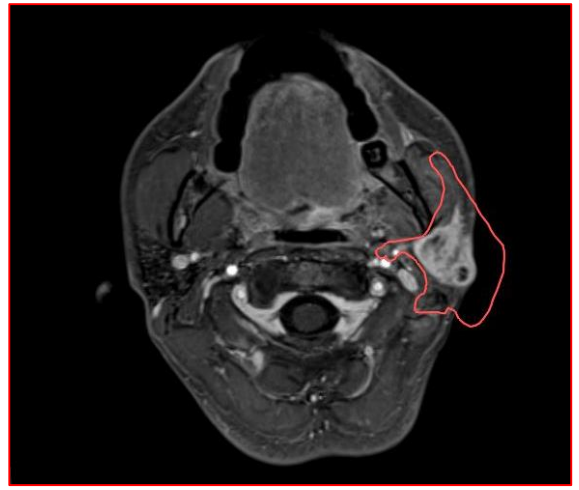
Late toxicity FUP 3 yrs (CTCAE V5.0) : G1 left hearing loss.

FOLLOW-UP

05/2021 Left parotid fine-needle aspiration cytology: **Category V** (Suspicious for Malignancy, Milan System for Reporting Salivary Gland Cytopathology). **The morphological finding suggests an adenoid-cystic carcinoma**, to be confirmed by histological examination.



CIRT March-April 2018



CE-MRI March 2021

02/2021 CE-CT chest abdomen-pelvis: negative.

Multidisciplinary evaluation

- Surgery?
- Re-RT?
- FOLLOW-UP?

FOLLOW-UP

May 2021 (FUP 3 years and 2 months):

G1 left hearing loss, G1 lockjaw, **left facial deficit and periauricular hypoesthesia**. → **CIRT toxicity or local disease recurrence**?

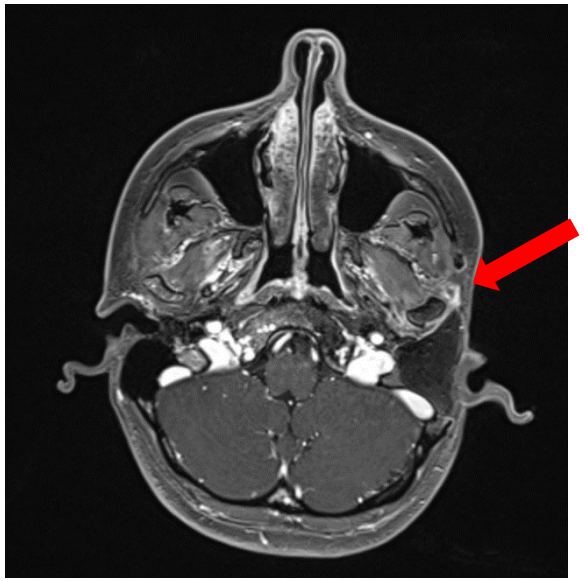
08/2021 Left radical parotidectomy with sacrifice of the VII CN up to the geniculate ganglion + exeresis of the CUE, tragus and tympanic membrane + mastoidectomy + removal of the ossicular chain + obliteration of the auditory tube + reconstruction with free thigh flap + tracheotomy + SND (left levels II and III): Macroscopically described nodule corresponds to localization of **adenoid cystic carcinoma with tubular and cribriform architecture**, in the absence of areas of solid growth/dedifferentiated areas (**grade II**). Present widespread phenomena of **perineural infiltration**; no evidence of vascular invasion. The neoplasm infiltrates the dermis, hypodermis and focally the underlying striated muscle tissue. **The deep and circumferential margins of surgical resection were positive** for carcinoma.

Stage (TNM 8° edition): **rpT2 pN0(0/17) R1 M0**

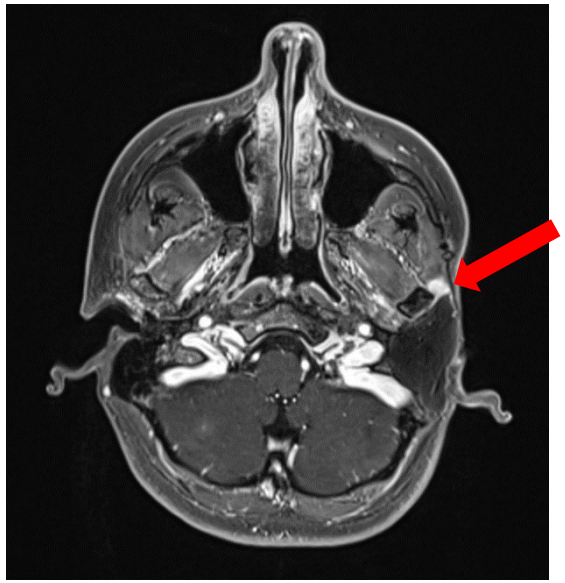
Multidisciplinary evaluation

- Surgery?
- Re-RT?
- FOLLOW-UP?

FOLLOW-UP – 4 years and 9 months



November 2021
Postoperative CE-MRI

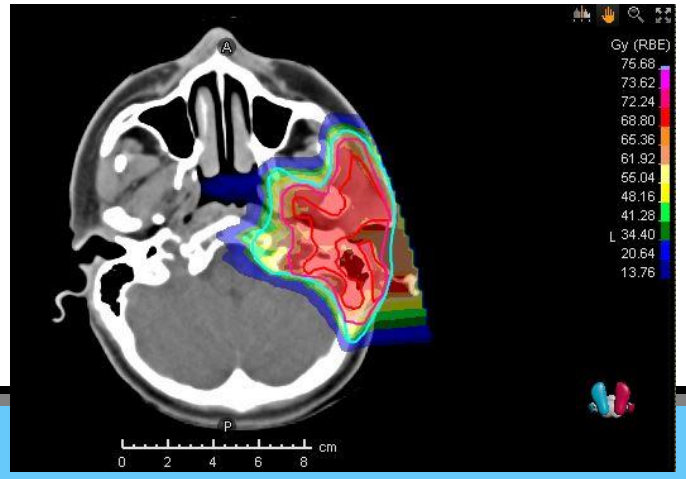


February 2022
(FUP 3 yrs and 10 mos)

January 2023
(FUP 4 yrs and 9 mos)

<u>01/2023 CE-CT chest abdomen-pelvis</u>: negative.

<u>01/2023 clinical state:</u> total paralysis of left VII c.n., slight tenderness at the level of the surgical scar, hypoesthesia of the left auricle.



Follow-up

THANK YOU

HITRI
Heavy Ion Therapy Research Integration

CNAO
Centro Nazionale di Adroterapia Oncologica

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