UNIVERSITY OF KRAGUJEVAC,
FACULTY OF MEDICAL SCIENCES

RADIOTHERAPY OF CENTRAL NERVOUS SYSTEM TUMORS

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CA CANCER J CLIN 2018;68:394–424

Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries

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- Primary tumors of the central nervous system in adults account for 1.6% of all malignancies
- The incidence of the CNS tumors is 3.5 per 100,000 inhabitants
- During 2018, 296 851 patients were affected
- The incidence of the disease in men is 3.9, while in women it is 3.1 per 100,000

Indications for radiotherapy of CNS tumors

- High and low grade gliomas
- Residual disease
- Recurrent disease
- Benign tumors
- Metastases

Radiotherapy of benign tumors

- Meningiomas
- Pituitary tumors
- Craniopharyngiomas
- Arteriovenous malformations
- Hemangioblastomas and Hemangiopericytomas
- Glomus Jugular Tumor
- Pineocytomas
- Chordomas
- Vestibular schwannomas
- Gangliogliomas
- Central neurocytomas

Specifics of CNS tumor classification

- The TNM classification was not used
- Tumor localization, histological and molecular characteristics are more important parameters than the size of the tumor itself
- WHO classifies tumors of the CNS according to the type of cells from which they arise and the biological characteristics of the tumor, from the least aggressive (benign) to the most aggressive forms of malignant tumors.
- The WHO classification revised in 2016 also integrated molecular parameters to define many tumor entities
- The WHO classification revised in 2021 includes new onesmolecular subtypes and a new grading system

Neuro-Oncology

23(8), 1231–1251, 2021 | doi:10.1093/neuonc/noab106 | Advance Access date 29 June 2021

The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

David N. Louis, Arie Perry, Pieter Wesseling, Daniel J. Brat, Ian A. Cree, Dominique Figarella-Branger, Cynthia Hawkins, H. K. Ng, Stefan M. Pfister, Guido Reifenberger, Riccardo Soffietti, Andreas von Deimling, and David W. Ellison

Table 7 Newly Recognized Tumor Types in the 2021 WHO Classification of Tumors of the Central Nervous System

Newly Recognized Tumor Types
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
High-grade astrocytoma with piloid features
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (provisional type)
Myxoid glioneuronal tumor
Multinodular and vacuolating neuronal tumor
Supratentorial ependymoma, *YAP1* fusion-positive
Posterior fossa ependymoma, group PFA
Posterior fossa ependymoma, group PFB
Spinal ependymoma, *MYCN*-amplified
Cribriform neuroepithelial tumor (provisional type)
CNS neuroblastoma, *FOXR2*-activated
CNS tumor with *BCOR* internal tandem duplication
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant
Intracranial mesenchymal tumor, FET-CREB fusion positive (provisional type)
CIC-rearranged sarcoma
Primary intracranial sarcoma, *DICER1*-mutant
Pituitary blastoma

Table 8 Tumor Types With Revised Nomenclature or Revised Placement in the 2021 WHO Classification of Tumors of the Central Nervous System

Tumor Types With Revised Nomenclature or Revised Placement
Astrocytoma, IDH-mutant (covers grades 2-4; eliminates the term "Glioblastoma, IDH-mutant")
Diffuse midline glioma, H3 K27-altered (changes "mutant" to "altered" given multiple mechanisms)
Chordoid glioma (removes site designation)
Astroblastoma, *MN1*-altered (adds genetic modifier)
Supratentorial ependymoma, *ZFTA* fusion-positive (reflects changes in fusion partner and gene nomenclature; see text)
Embryonal tumor with multilayered rosettes (removes genetic modifier to allow for genetic subtypes)
Malignant melanotic nerve sheath tumor (conforms to terminology in soft tissue pathology literature)
Solitary fibrous tumor (removes the term "hemangiopericytoma" to conform fully with soft tissue pathology nomenclature)
Mesenchymal chondrosarcoma (formerly a subtype)
Adamantinomatous craniopharyngioma (formerly a subtype)
Papillary craniopharyngioma (formerly a subtype)
Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma (grouped rather than separate)
Pituitary adenoma/PitNET (adds the term "PitNET")

Radiotherapy of CNS tumors

- Curative (radical, postoperative) or palliative
- External beam radiotherapy (EBRT) or brachytherapy (BT)

Contents lists available at ScienceDirect

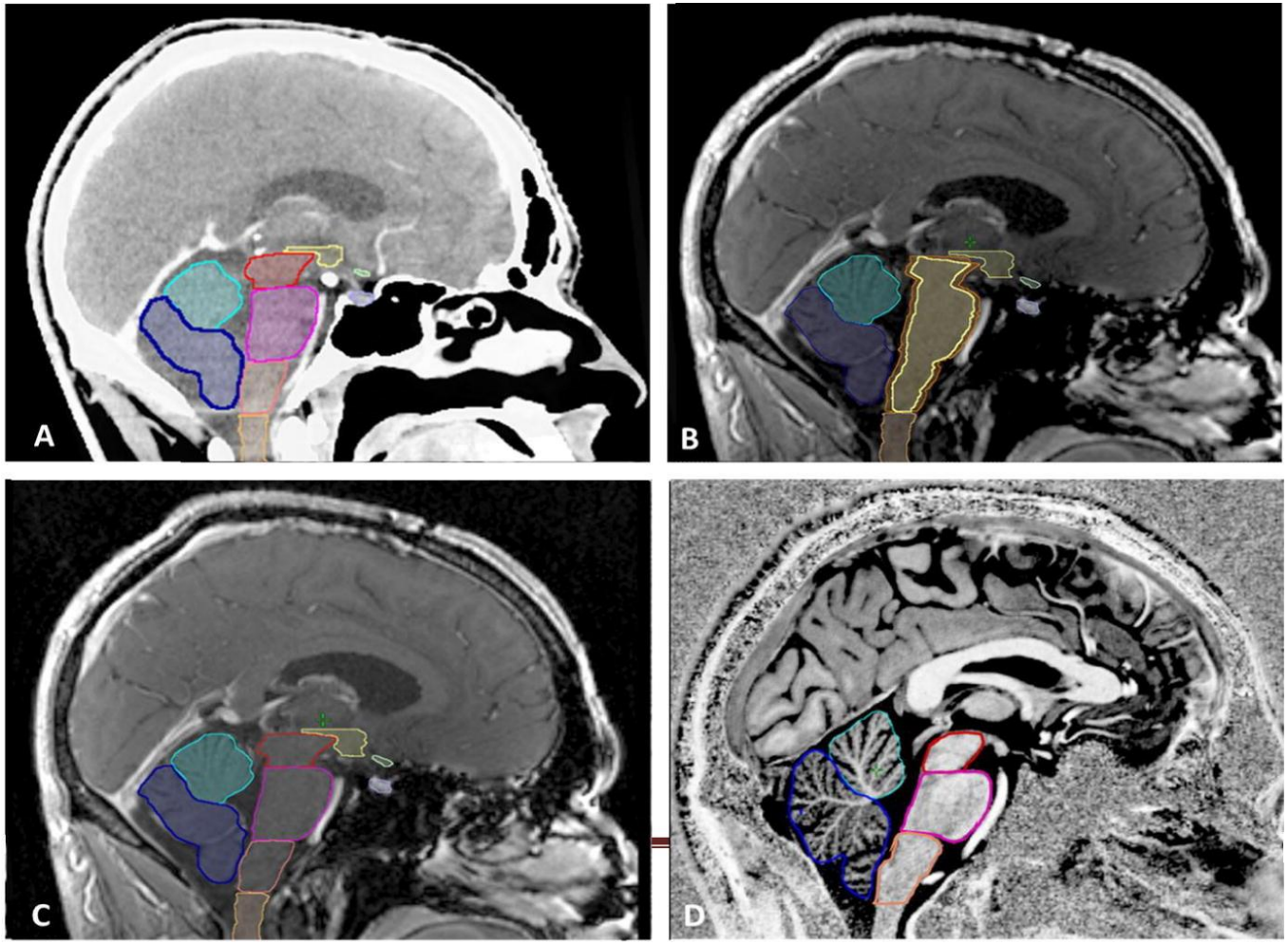
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

EPTN consensus

The EPTN consensus-based atlas for CT- and MR-based contouring in neuro-oncology

Daniëlle BP Eekers [a,b,*], Lieke in 't Ven [a], Erik Roelofs [a,c], Alida Postma [d], Claire Alapetite [e], Neil G. Burnet [f], Valentin Calugaru [g,h], Inge Compter [a], Ida E.M. Coremans [i,j], Morton Høyer [k], Maarten Lambrecht [l], Petra Witt Nyström [w,x], Alejandra Méndez Romero [j,m], Frank Paulsen [n], Ana Perpar [o], Dirk de Ruysscher [a,l], Laurette Renard [p], Beate Timmermann [y,z,aa], Pavel Vitek [q], Damien C. Weber [r], Hiske L. van der Weide [s], Gillian A. Whitfield [t,u], Ruud Wiggenraad [j,v], Esther G.C. Troost [ab,ac,ad,ae,af], on behalf of the taskforce "European Particle Therapy Network" of ESTRO



EBRT

- LINAC
- X-rays (energy 4 to 10 MV)
- The target volume (primary tumor or tumor bed) is irradiated with a total therapeutic dose of 50 to 60 Gy, which is applied in daily fractions of 1.6 to 2 Gy

Local radiotherapy in one phase

- Benign tumors, minor high-grade malignant tumors and tumors without infiltrative growth
- Continuously in one phase
- Fusion with multiple imaging modalities (CT, MR or PET)
- Macroscopically visible tumor or tumor bed, with a zone of microscopic infiltration of the surrounding tissue by cells

Local radiotherapy in two phases

- High-grade tumors, with pronounced infiltrative growth and peritumoral edema
- Cone Down mode
- Phase I - dose is applied to the target volume up to the OAR radiotolerance threshold
- Phase II (boost) dose to target volume

Whole beam radiotherapy – WBRT

- As part of the implementation of the first phase of RT at CSI
- Prophylactic in the presence of other extracranial tumors
- Presence of intracranial metastases (with or without SRS/SRT)

Craniospinal radiotherapy - CSI

- Tumors that have a tendency to metastasize through the cerebrospinal fluid (medulloblastoma, ependymoma, choroid plexus tumors, anaplastic tumors of the pineal region, germinomas)

Craniospinal radiotherapy of medulloblastoma

- CSI is one of the most complex RT techniques applied in the oncology department
- Patient position and immobilization
- Most often, pronation with a head mask, although supination with immobilization of the body is also possible
- CTV must integrate:
- Intracranial and spinal meninges extend inferiorly to the lower border of the thecal sac
- Cribriform plates
- Temporal lobe
- Base of skull

Craniospinal radiotherapy

Arrangement of radiotherapy fields

- Lateral opposite cranial fields, with one or more spinal fields closely matching the lower edge of the cranial field
- Fields can be centered on the outer edge of the canthus to minimize divergence into the contralateral lens
- Protection of the face, jaw, nasal structures and lenses is carried out
- A "moving junction" technique can be applied between spinal fields to minimize the risk of overdosing or underdosing

Craniospinal radiotherapy

Dosimetry

Cranial fields: lateral opposite fields with protection are used. A CT image is always used to define the actual dose distribution and midplane dose

Spinal fields: direct posterior megavoltage field up to 6 MeV. The very shape of the spine means that the dose to the medulla in different positions will be different, mostly due to the different distance from the beam. If the dose distribution varies by more than 10% a compensator must be used to equalize the dose along the medulla

Craniospinal radiotherapy

Dose prescription

Cranial fields: dose specification at the mid-point of the central axis

Spinal fields: the dose is specified on the front edge of the spinal cord (back edge of the vertebral body). The goal is to achieve a dose range of −5% to +7%. In order to achieve this level of homogeneity it is sometimes necessary to compensate by adding "top-up fields"

TD 23.4Gy in 13 fractions, 1.8Gy per day for "standard risk" medulloblastoma

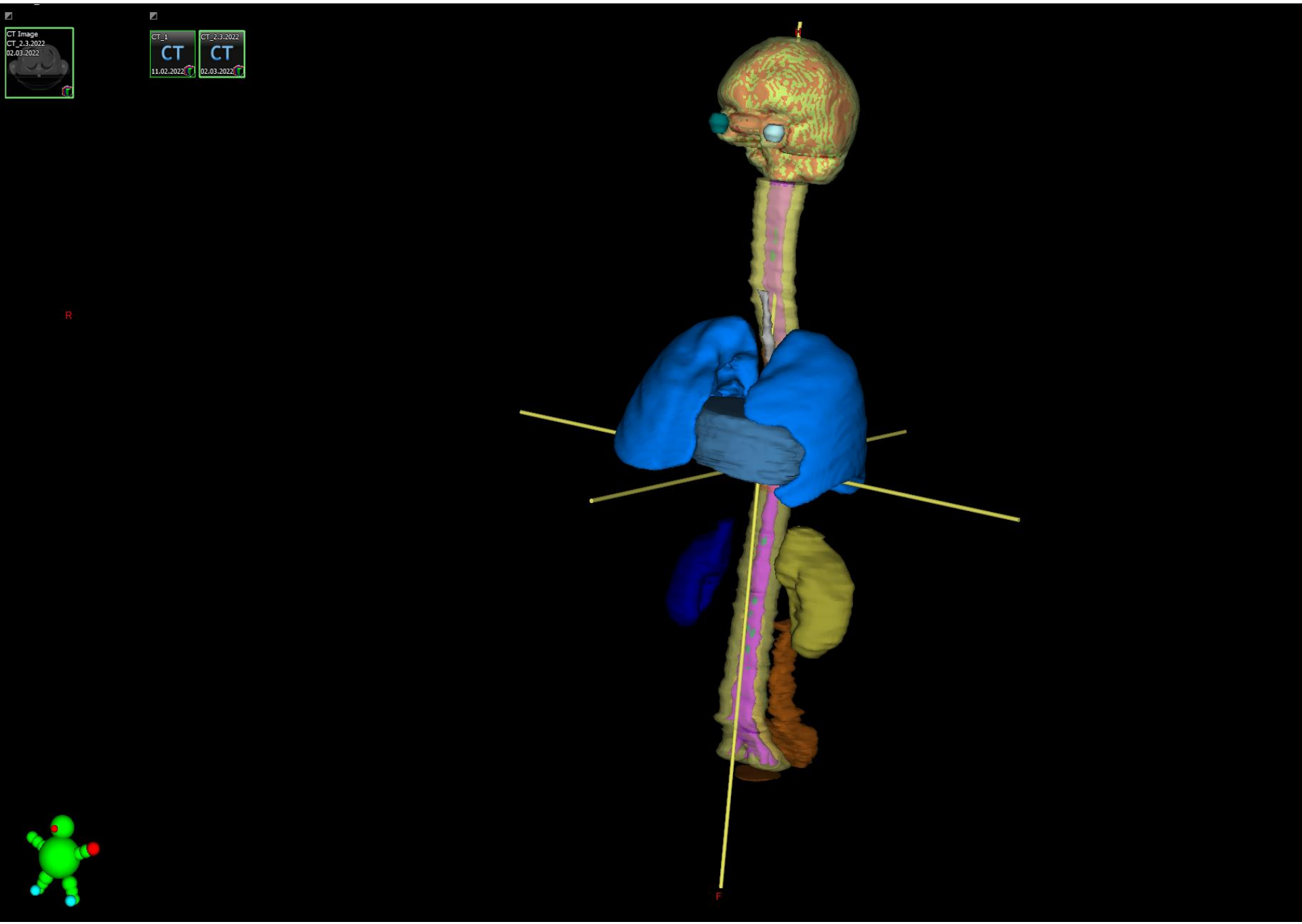
Depending on the clinical findings, other RT regimens are possible

Craniospinal radiotherapy

- The lower border of the spinal field is at the lower edge of the second sacral vertebra
- The lower border of the thecal sac varies and therefore it is recommended that the lower border of the spinal field be determined on MRI
- The spinal field should be wide enough to cover the meningeal extension along the nerve roots and intervertebral foramina in the lumbar region
- The spinal field is typically 5-7cm wide

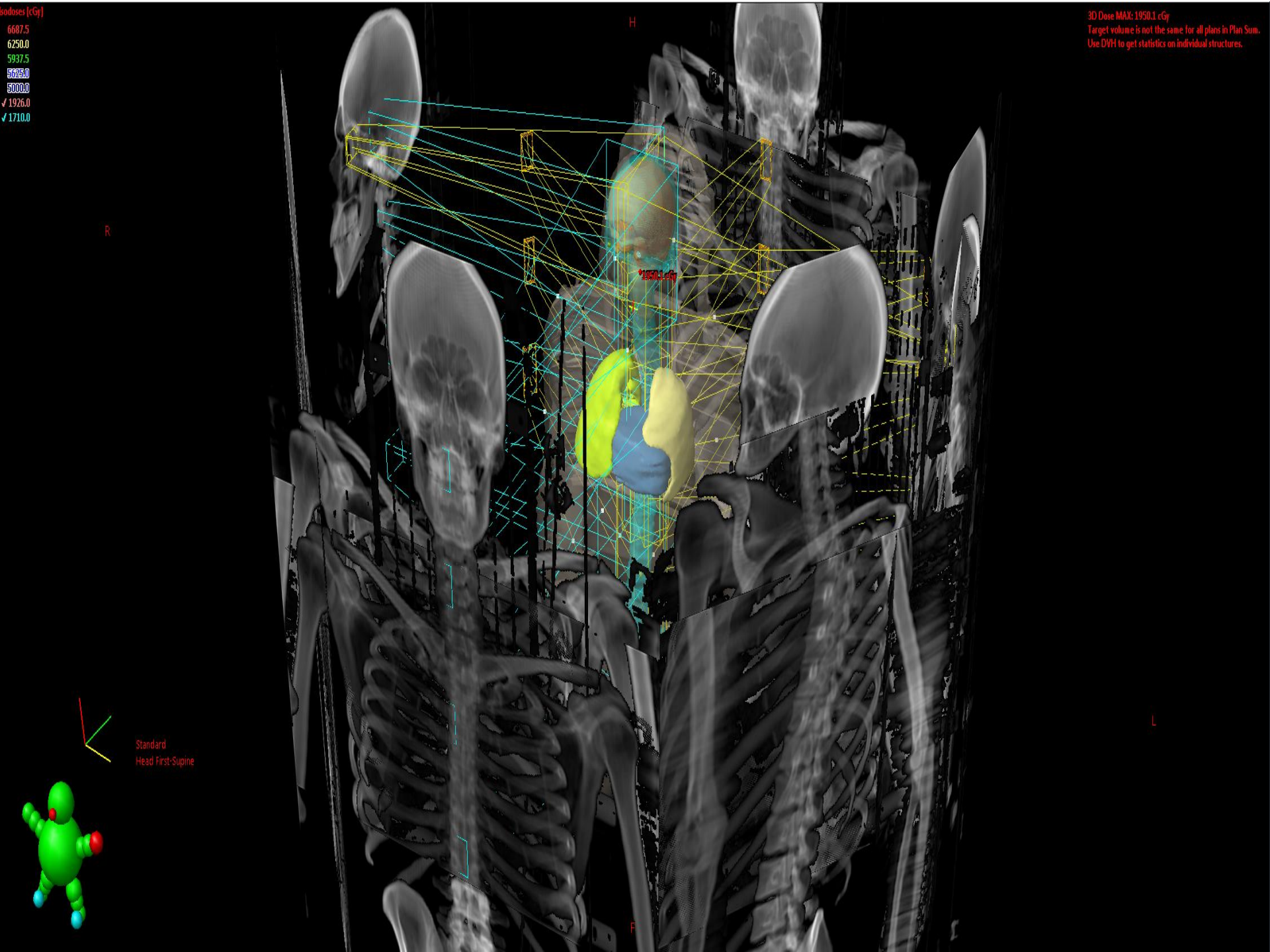
Craniospinal radiotherapy

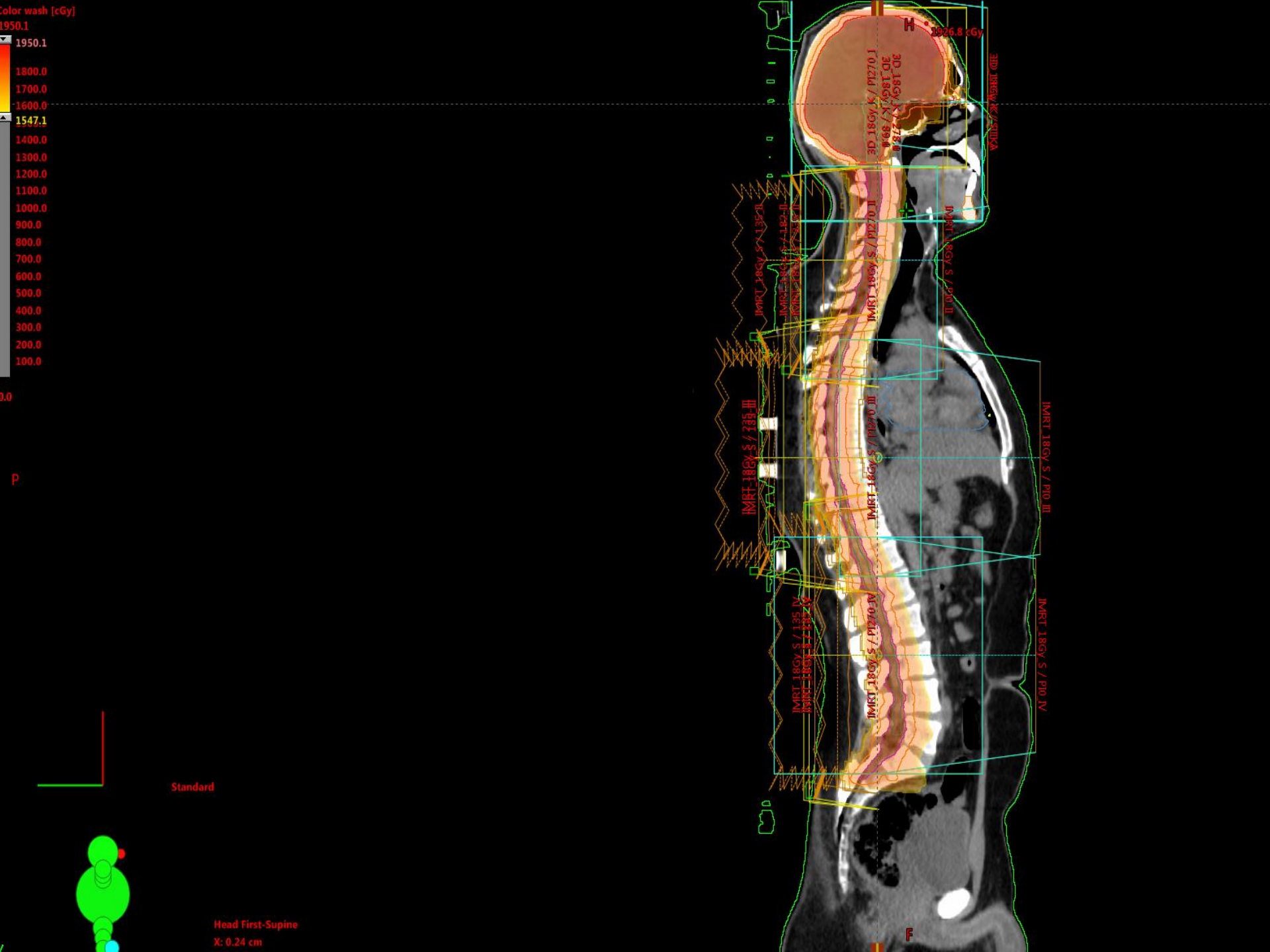
- When planning a boost to the region of the posterior cranial fossa, it is accepted that the entire cerebellum is included in the target volume, due to the risk of meningeal spread of the primary tumor.
- Boost is carried out with highly precise techniques in order to reduce the dose to non-target structures

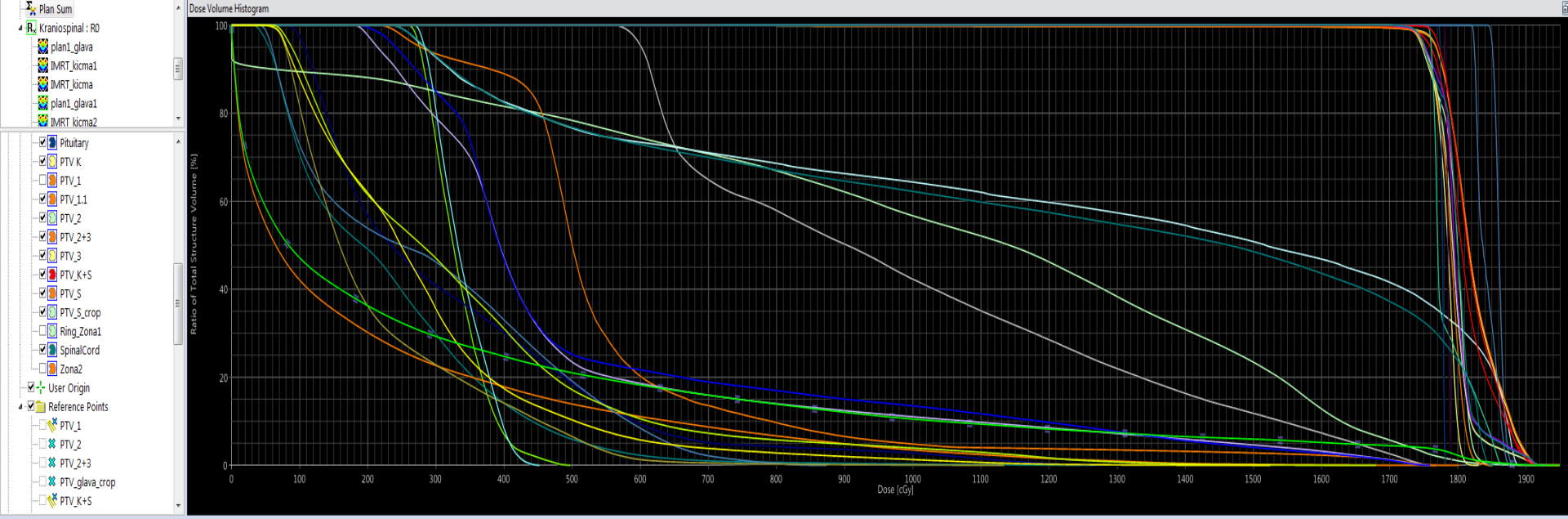


Thanks to dr Ivana Tomić - radiation oncologist at the Center for Radiation Oncology, UKC Kragujevac


CT Image
CT_2.3.2022
02.03.2022
CT_1
CT
11.02.2022
CT_2.3.2022
CT
02.03.2022
H
P
A
F
50.0 cm
X: 0.38 cm
(oncology\aca 08.03.2022 08:30)


Isodoses [cGy]
6687.5
6250.0
5937.5
5625.0
5000.0
1926.0
1710.0
H
R
L
F
3D Dose MAX: 1950.1 cGy
Target volume is not the same for all plans in Plan Sum.
Use DVH to get statistics on individual structures.
1950.1 cGy
Standard
Head First-Supine


Color wash [cGy]
1950.1
1950.1
1800.0
1700.0
1600.0
1547.1
1400.0
1300.0
1200.0
1100.0
1000.0
900.0
800.0
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0.0
P
H
1926.8 cGy
3D 18Gy S / 270 I
3D 18Gy S / 90 I
3D 18Gy S / 270 II
3D 18Gy S / 90 II
IMRT 18Gy S / 135 I
IMRT 18Gy S / 180 II
IMRT 18Gy S / 135 II
IMRT 18Gy S / 180 III
IMRT 18Gy S / 235 III
IMRT 18Gy S / 135 IV
IMRT 18Gy S / 180 IV
IMRT 18Gy S / 235 IV
IMRT 18Gy S / PTO II
IMRT 18Gy S / PTO III
IMRT 18Gy S / PTO IV
Standard
Head First-Supine
X: 0.24 cm
F



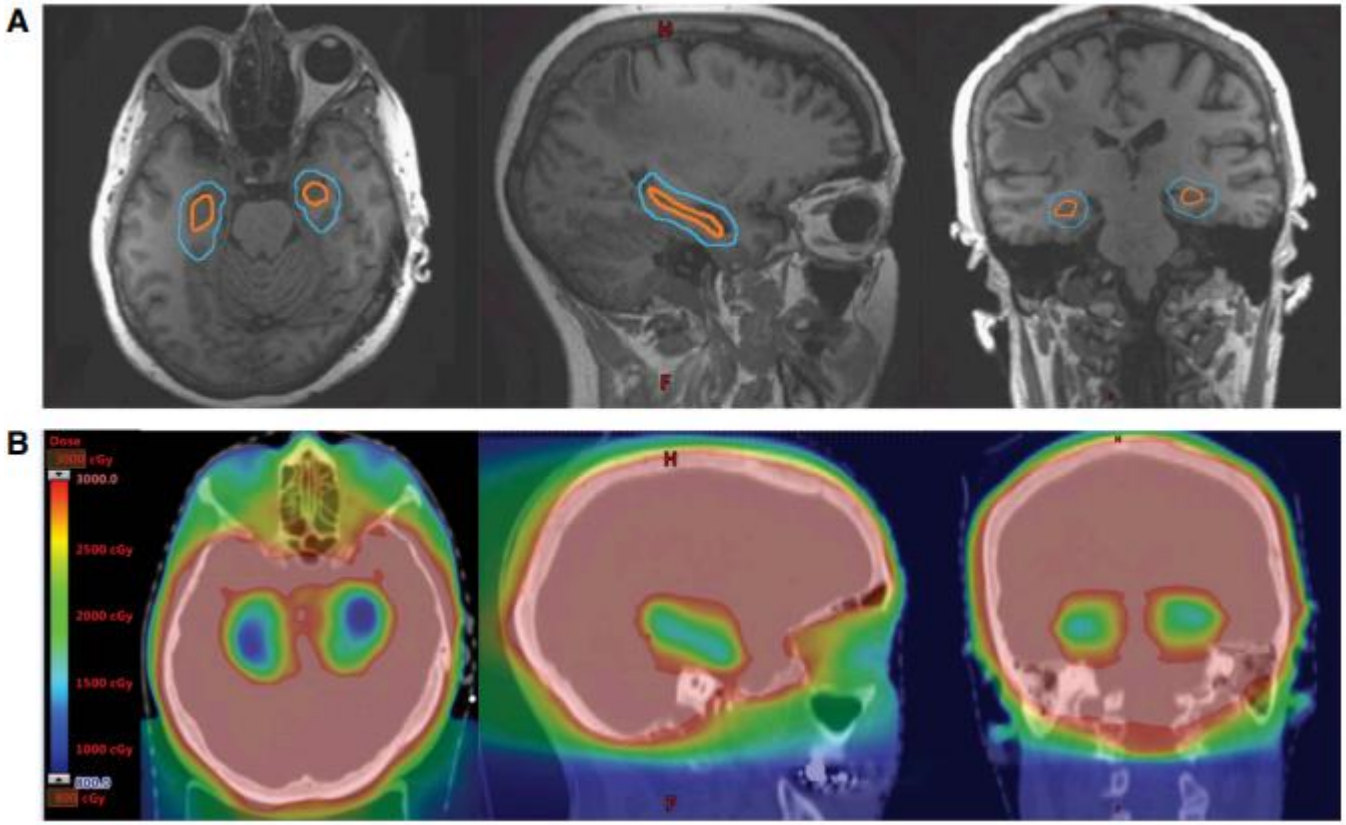
Dose | Reference Points | Dose Statistics

Show DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑	Liver	Approved	Plan Sum	1	2498.9	100.0	100.0	30.9	1268.6	226.9
☑	BODY	Approved	Plan Sum	1	85528.6	100.0	100.1	0.0	1950.1	315.5
☑	Lung_L	Approved	Plan Sum	1	1014.2	100.0	100.0	47.7	1525.2	280.1
☑	Lung_R	Approved	Plan Sum	1	1376.1	100.0	100.0	58.4	1681.2	335.4
☑	SpinalCord	Approved	Plan Sum	1	52.4	100.0	99.9	1673.4	1933.3	1800.6
☑	CTVk	Approved	Plan Sum	1	1515.6	100.0	100.0	403.4	1920.0	1819.9
☑	Lens_R	Approved	Plan Sum	1	0.2	100.0	98.8	258.3	497.7	332.2
☑	Lens_L	Approved	Plan Sum	1	0.2	100.0	99.9	268.2	451.8	338.5
☑	Eye_L	Approved	Plan Sum	1	8.8	100.0	100.1	229.9	1853.2	1213.1
☑	Eye_R	Approved	Plan Sum	1	9.0	100.0	100.1	234.8	1890.0	1253.7
☑	OpticNerve_L	Approved	Plan Sum	1	0.3	100.0	100.4	1819.4	1876.7	1841.4
☑	OpticNerve_R	Approved	Plan Sum	1	0.4	100.0	100.5	1845.3	1880.2	1860.7
☑	Pituitary	Approved	Plan Sum	1	0.0	100.0	101.9	1772.2	1782.1	1777.4
☑	Chiasm	Approved	Plan Sum	1	0.4	100.0	100.1	1779.5	1791.6	1785.5
☑	BrainStem	Approved	Plan Sum	1	24.0	100.0	100.0	1753.3	1866.9	1785.6
☑	Parotid_L	Approved	Plan Sum	1	27.4	100.0	100.1	182.5	1759.6	537.0
☑	Parotid_R	Approved	Plan Sum	1	25.3	100.0	100.1	178.2	1759.2	510.9
☑	Mandible	Approved	Plan Sum	1	68.0	100.0	99.9	193.2	1767.8	560.9
☑	Esophagus	Approved	Plan Sum	1	28.6	100.0	100.2	560.7	1754.7	980.9
☑	CTVs	Approved	Plan Sum	1	154.6	100.0	100.0	1622.4	1933.3	1798.3
☑	Heart	Approved	Plan Sum	1	894.7	100.0	100.0	40.0	873.4	289.1
☑	Kidney_L	Approved	Plan Sum	1	278.4	100.0	100.0	51.8	1134.8	214.4
☑	Kidney_R	Approved	Plan Sum	1	239.2	100.0	100.0	74.1	1283.7	318.8
☑	PTV_S_crop	Approved	Plan Sum	1	954.0	100.0	100.0	1637.0	1930.5	1794.0
☑	PTV K	Approved	Plan Sum	1	1926.8	100.0	100.0	291.8	1928.5	1818.4
☑	PTV_1	Approved	Plan Sum	1	2058.0	100.0	100.0	291.8	1950.1	1819.3
☑	PTV_2	Approved	Plan Sum	1	354.9	100.0	100.0	1684.0	1851.4	1794.2
☑	PTV_3	Approved	Plan Sum	1	479.6	100.0	100.0	1637.0	1831.4	1782.4
☑	PTV_K+S	Approved	Plan Sum	1	2899.6	100.0	100.0	291.8	1950.1	1810.0
☑	Ring_Zona1	Approved	Plan Sum	1	3886.7	100.0	99.7	0.0	1917.0	1009.3
☑	Zona2	Approved	Plan Sum	1	78041.4	100.0	100.1	0.0	1802.8	202.9
☑	PTV_2+3	Approved	Plan Sum	1	836.3	100.0	100.0	1637.0	1851.4	1787.4
☑	PTV_1.1	Approved	Plan Sum	1	2050.9	100.0	100.0	291.8	1950.1	1819.3
☑	PTV_S	Approved	Plan Sum	1	970.0	100.0	100.0	1463.0	1950.1	1793.5

Partial brain radiotherapy

- An alternative to WBRT and CSI, they frame the first stages of certain primary or secondary tumors of the CNS
- The goal of this type of radiotherapy is to spare radiosensitive brain structures (hippocampus, brain parenchyma).
- Hippocampal sparing WBRT
- Whole ventricular irradiation with primary tumor/tumor bed (phase I)
- Stereotactic techniques for tumors that do not have infiltrative growth of primary or secondary tumors of the CNS, with a maximum diameter of up to 3cm and a maximum volume of up to 40cm^3

Sparing of the hippocampal region



Brown PD, et al. Whole-Brain Radiotherapy for Brain Metastases: Evolution or Revolution? J Clin Oncol 2018;36(5):483-491.

Basic links in the implementation of radiotherapy treatment

- MDT decision
- First interview
- Preparation for CT simulation / processing
- CT simulation
- Delineation of organs at risk and target volumes
- Radiotherapy planning
- Accuracy check and plan verification
- Positioning
- Conducting treatment
- Quality assurance control
- Monitoring of side effects during and after completed treatment

Radiotherapy techniques

- Conventional 2D radiotherapy
- 3D - conformal radiotherapy (3D-CRT)
- Intensity Modulated Radiotherapy (IMRT)
- Volumetric Modulated Arc Radiotherapy (VMAT)
- Stereotactic radiosurgery
- Stereotactic radiotherapy
- Brachytherapy
- Proton therapy

Conventional 2D radiotherapy (2D-RT)

- Today it is mostly reserved for the palliative approach
- The simulation is performed on the Ro simulator, and the boundaries of the field are determined on the basis of bone structures
- To determine the position of the field, Frackfort's horizontal plane is used, which joins the points between the two external auditory meatus and the anterior infraorbital border. The lower boundary of the air field is the base of the skull
- Parallel opposition fields

3D conformal radiotherapy (3D-CRT)

- LINAC with multilamellar collimation systems
- The dose distribution within the target volume is homogeneous
- Radiotherapy planning is performed on the basis of a series of CT sections with co-registration with other imaging modalities (MR/PET).
- The virtual patient

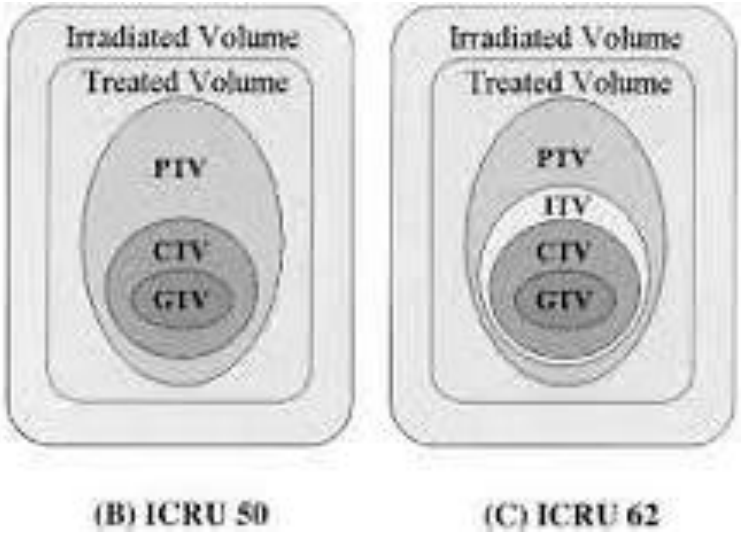
CT simulation and immobilization

- RT of the front 2/3 of the brain - supination
- RT of tumors of the occipital region, posterior cranial fossa and during craniospinal radiation - pronation
- Immobilization of the patient on the flat plate of the CT simulator stand, in the therapeutic position,
- Cuts of appropriate thickness (2,5-5mm)
- The region of interest, i.e. the volume in which the body surface, tumor and organs at risk should be displayed
- Contrast agent before performing CT imaging

- In order to define the geometry of the patient and connect this geometry with the geometry of the radiotherapy environment, the positions of reference (set up) markings are permanently marked on the patient's skin or the immobilization system (thermoplastic mask) at the points of projection of the laser beam, over which lead balls (drums) are glued, so that the reference markings are recognizable on CT scans

International Commission on Radiation Units and Measurments (ICRU 50 i ICRU 62)

- Gross Tumor Volume - GTV
- Clinical target Volume - CTV)
- Planning Target Volume - PTV
- Treatment volume - TV
- Irradiated volume - IV
- Organs at risk - OAR

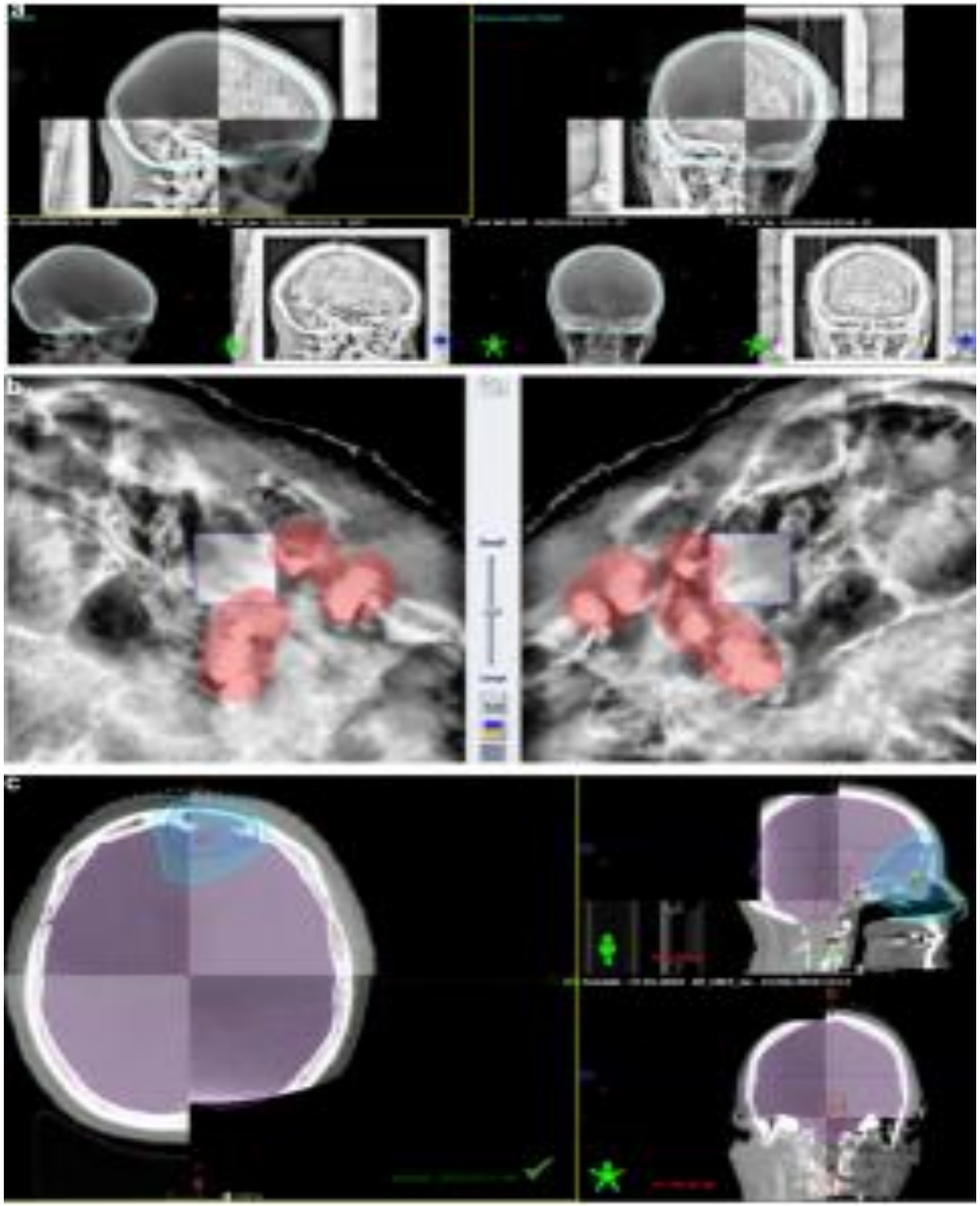


Radiotherapy planning and plan analysis

- It determines the ideal arrangement of beams that achieve a homogeneous distribution of the dose within the radiotherapy volumes with maximum sparing of the surrounding structures.
- The geometry of the beam and field is defined, the dose of radiation is prescribed, and its distribution is calculated based on that
- Analysis of DVH parameters

Verification of the accuracy of radiation performance

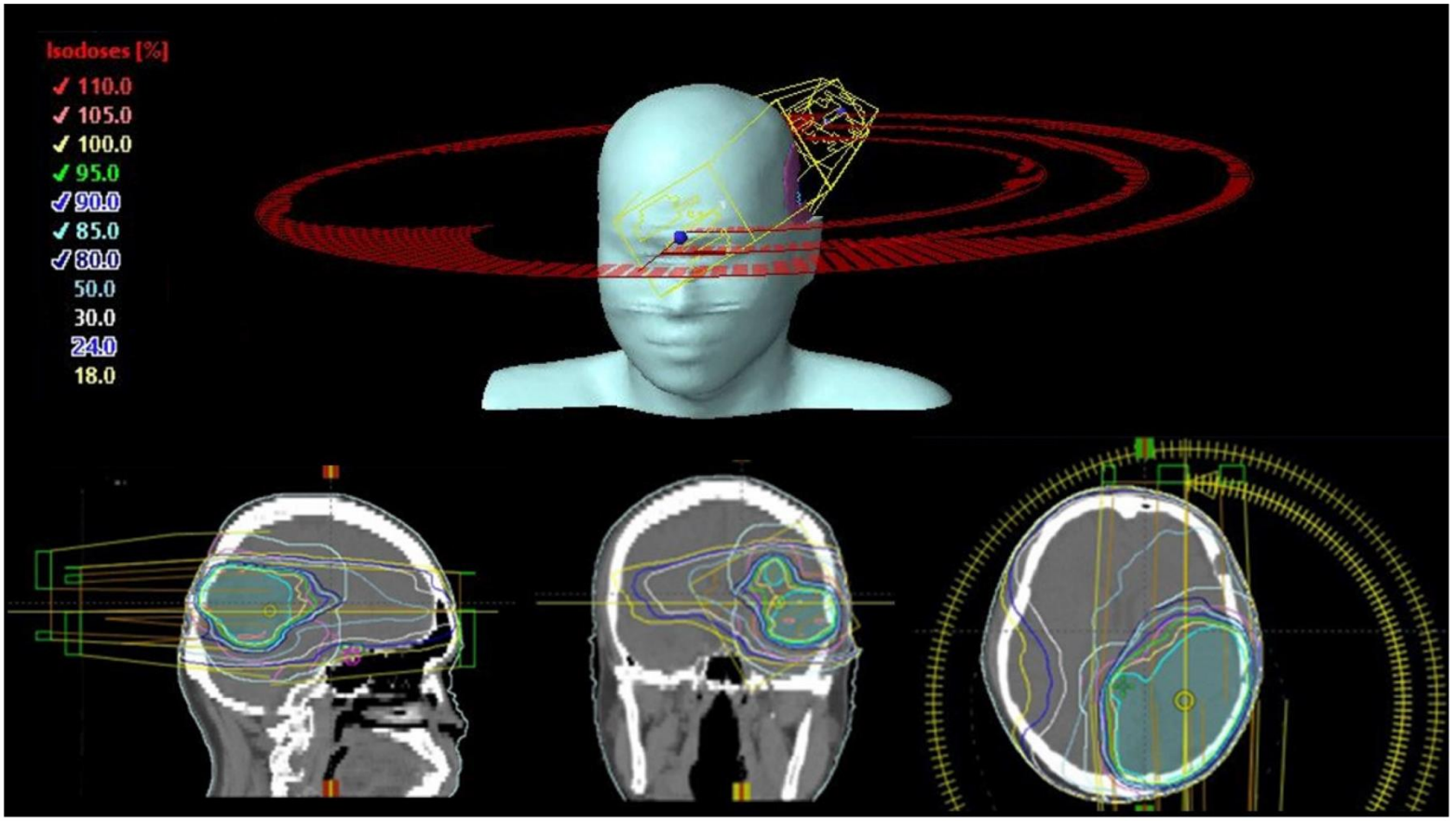
- Comparing the reference geometry of the radiation plane shown for each beam field on the corresponding digitally reconstructed radiographs (DRR) and the real geometry of the radiation plane shown on the portal graphics
- CONE beam CT



Legouté F, et al. Apport du guidage par l'image pour le repositionnement au cours de la radiothérapie des tumeurs encéphaliques [Interest of image-guided radiotherapy for brain tumors and positioning control]. Cancer Radiother 2018;22(6-7):593-601

IMRT

VMAT



Radiotherapy of CNS tumors

Low-grade gliomas

- pilocytic astrocytoma WHO grade I,
- subependymal giant cell astrocytoma WHO grade I,
- pleomorphic xanthoastrocytoma WHO grade II,
- diffuse astrocytoma IDH-mutated WHO grade II,
- oligodendroglioma IDH-mutated with 1p/19q codeletion WHO grade II

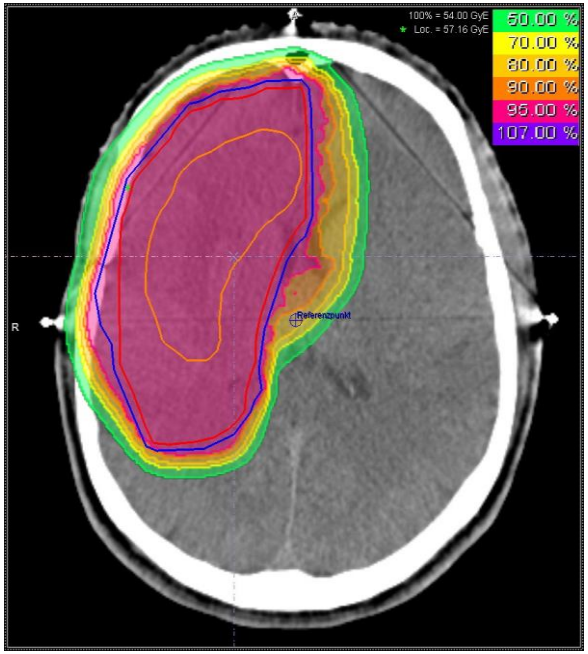
Summary of characteristic genetic features of six newly defined pLGG/GNTs in the 2021 WHO

2021 WHO Classification of Tumors of the CNS Tumor Type	Characteristic genetic feature(s)
Diffuse astrocytoma, MYB- or MYBL1-altered	*MYB* and *MYBL1* amplifications or fusions
Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)	MAPK pathway alterations (including *FGFR2* fusions)
Diffuse low-grade glioma, MAPK pathway-altered	MAPK pathway alterations (including *BRAF* p.V600E and *FGFR1* alterations)
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC)	methylation profile; frequent monosomy 14
Myxoid glioneuronal tumor	*PDGFRA* p. K385L/I
Multinodular and vacuolating neuronal tumor (MVNT)	MAPK pathway alterations (commonly *MAP2K1* and non-canonical *BRAF* mutations)

Bale TA, Rosenblum MK. The 2021 WHO Classification of Tumors of the Central Nervous System: An update on pediatric low-grade gliomas and glioneuronal tumors. Brain Pathol 2022;32(4):e13060.

Radiotherapy of CNS tumors

Maximum surgical resection
RT (unresectable tumors, residual symptomatic disease or disease progression especially when reoperation is not indicated): TD 50.4-54 Gy, in 28-30 fractions with a daily fraction of 1.8 Gy is standard
HT (not clearly defined)



Hauswald H, Rieken S, Ecker S, Kessel KA, Herfarth K, Debus J, Combs SE. First experiences in treatment of low-grade glioma grade I and II with proton therapy. Radiat Oncol.2012;7:189.

Radiotolerance OAR (QUANTEC)

Critical Structure	Volume	Dose/Volume	Max Dose	Toxicity Rate	Toxicity Endpoint
Brain			<60 Gy	<3%	Symptomatic necrosis
Brain			72 Gy	5%	Symptomatic necrosis
Brain			90 Gy	10%	Symptomatic necrosis
Brain stem			<54 Gy	<5%	Neuropathy or necrosis
Brain stem	D1-10 cc	<= 59 Gy		<5%	Neuropathy or necrosis
Brain stem			<64 Gy	<5%	Neuropathy or necrosis
Optic nerve/chiasm			<55 Gy	<3%	Optic neuropathy
Optic nerve/chiasm			55-60 Gy	3-7%	Optic neuropathy
Optic nerve/chiasm			>60 Gy	>7-20%	Optic neuropathy
Spinal cord			50 Gy	0.2%	Myelopathy
Spinal cord			60 Gy	6%	Myelopathy
Spinal cord			69 Gy	50%	Myelopathy

Prognostic Factors for Survival in Adult Patients With Cerebral Low-Grade Glioma

By Francesco Pignatti, Martin van den Bent, Desmond Curran, Channa Debruyne, Richard Sylvester, Patrick Therasse, Denes Áfra, Philippe Cornu, Michel Bolla, Charles Vecht, and Abul B.M.F. Karim for the European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group and Radiotherapy Cooperative Group

Table 4. Prognostic Factors for Survival in Adults Patients with Cerebral LGG: Multivariate Model Construction and Validation

	Construction Set (n = 281)			Validation Set (n = 253)		
Prognostic Factor (reference level)	HR	95% CI	P	HR	95% CI	P
Age at randomization						
< 40 years	1			1		
≥ 40 years	1.26	1.06-1.48	.0077	1.43	1.17-1.74	.0005
Largest diameter of the tumor						
< 6 cm	1			1		
≥ 6 cm	1.39	1.16-1.66	.0003	1.23	1.02-1.50	.0350
Tumor crossing midline						
No	1			1		
Yes	1.37	1.15-1.63	.0005	1.43	1.11-1.84	.0051
Histology type						
Oligo/mixed	1			1		
Astrocytoma	1.30	1.08-1.56	.0050	1.46	1.18-1.82	.0006
Neurologic deficit						
Absent	1			1		
Present	1.35	1.13-1.62	.0013	1.29	1.02-1.63	.0310

NOTE. Forty-one and 35 observations were excluded from the construction and validation sets, respectively, due to missing data.

Pignatti F, et al. Prognostic factors for survival in adul patients with cerebral low-grade glioma. J Clin Oncol 2002;20(8):2076–84.

Research Article

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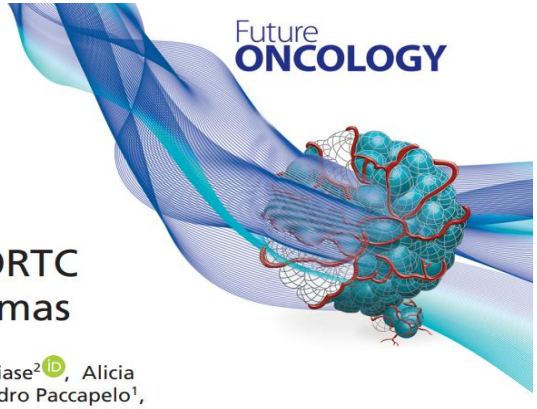

Concordance between RTOG and EORTC prognostic criteria in low-grade gliomas

Enrico Franceschi*[,1], Antonella Mura[1], Giuseppe Lamberti[1], Dario De Biase[2], Alicia Tosoni[1], Monica Di Battista[1], Chiara Argento[1], Michela Visani[3], Alexandro Paccapelo[1], Stefania Bartolini[1] & Alba Ariela Brandes[1]

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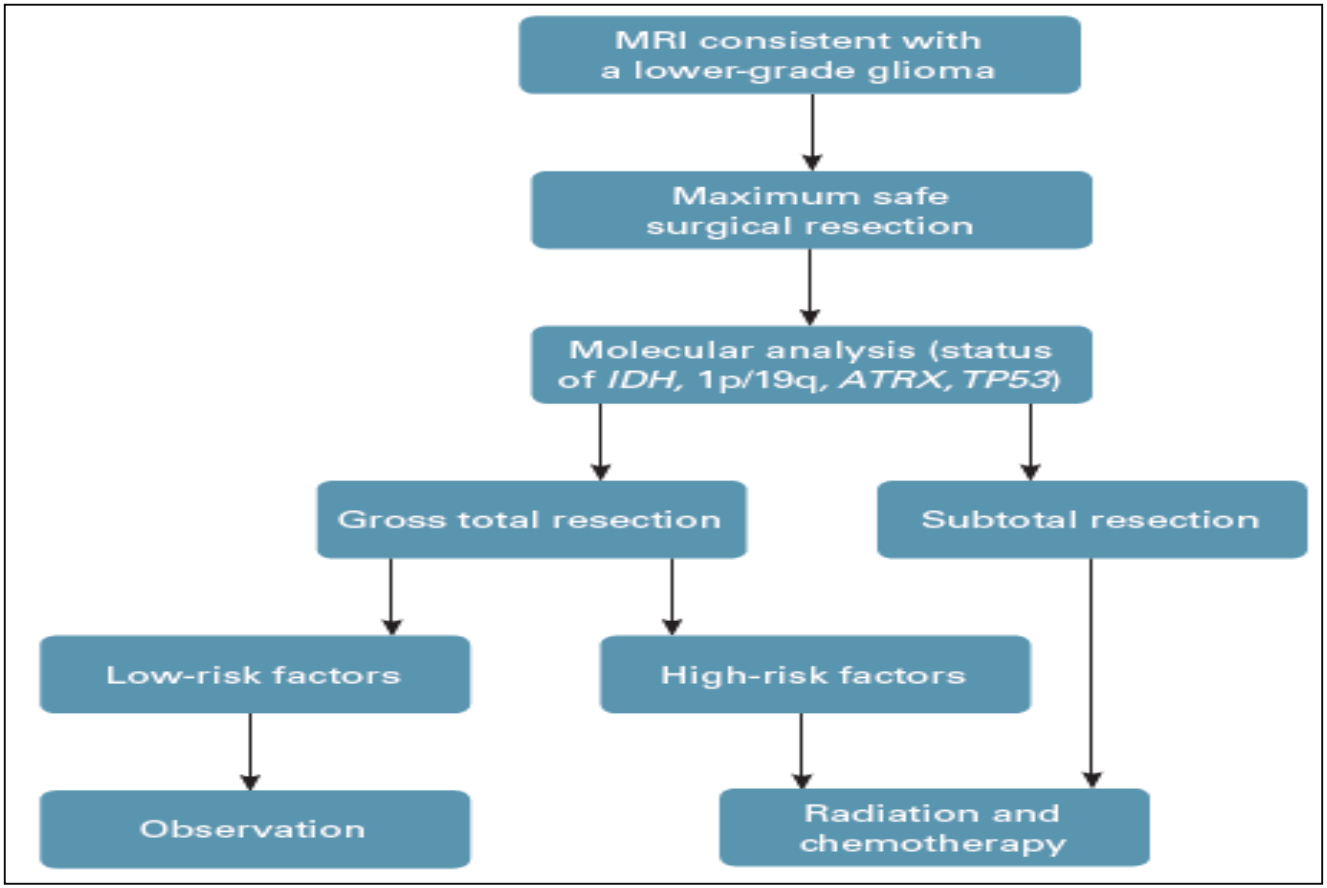
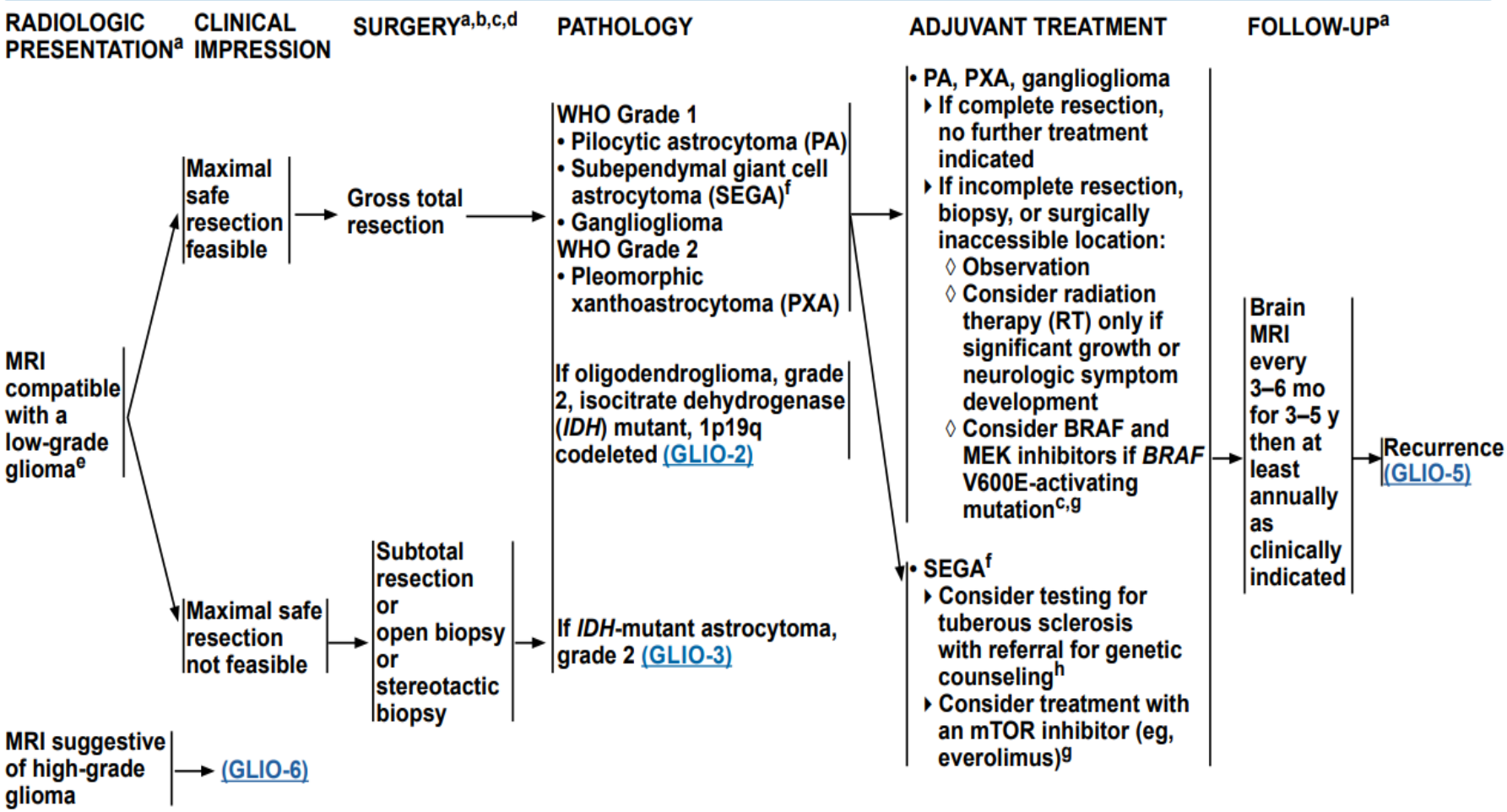
Summary points

- Low-grade gliomas (LGGs) are a heterogeneous group of primary brain tumors.
- The European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) criteria are used to evaluate LGG risk factors and choosing the best treatment after surgery.
- According to RTOG criteria, patients are considered low risk if they are both <40 years old and underwent total resection of their tumor. Otherwise (age ≥40 or incomplete resection), they are considered high-risk patients.
- EORTC criteria are made of five items: age ≥40 years, presence of neurological deficits before surgery, tumor diameter ≥6 cm, tumor crossing the midline and astrocytoma histology. The patients with up to two criteria are considered at low risk; otherwise, they are high-risk patients.
- Ninety-nine patients with enough data to be assessed according to both RTOG and EORTC criteria.
- The concordance between RTOG and EORTC criteria overall was poor: 50.5% ($K = 0.127$; $p = 0.021$).
- Only two subgroups showed high level of concordance: high-risk patients according to EORTC criteria were high risk also by RTOG criteria (concordance: 97.5%) and low-risk patients according to RTOG criteria were low risk also by EORTC criteria (concordance: 90.9%).
- Given the low concordance rate between RTOG and EORTC criteria, clinical trials based on different risk criteria should not be compared.

Therapeutic algorithm for the treatment of low-grade glioma



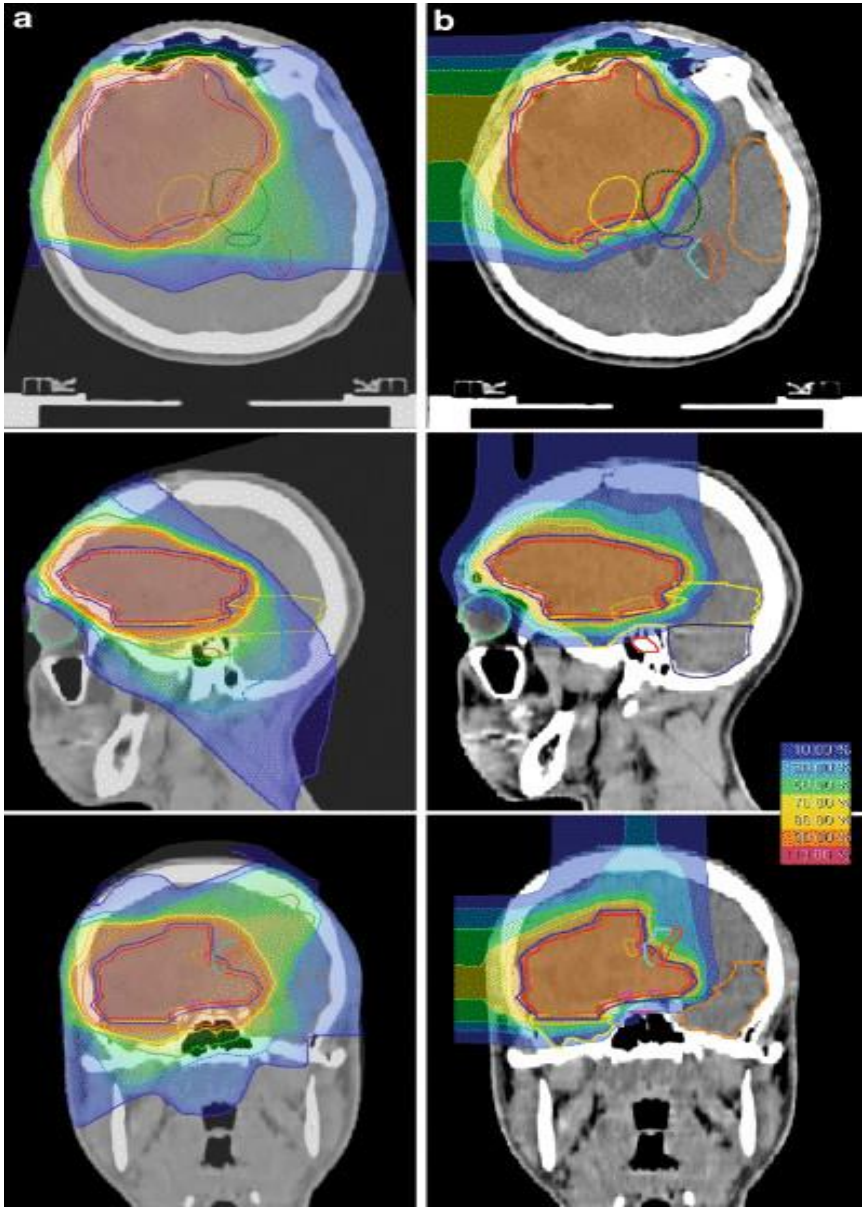
Dixit K, Raizer J. Newer Strategies for the Management of Low-Grade Gliomas. Oncology (Williston Park) 2017;31(9):680-2, 684-5.



[a] Principles of Brain and Spine Tumor Imaging (BRAIN-A).

Target volumes of low-grade tumors

- **GTV**: MRI co-registered with radiotherapy CT is used
- GTV is defined as the margin of abnormality of the high-signal region on T2W sequence and includes regions of peritumoral edema. There is a correlation of this region with the low density region on radiotherapy CT
- **CTV**: 1.5 cm margin around the GTV
- **PTV**: Adequate margin, usually 0.5cm



Harrabi SB,et al. Dosimetric advantages of proton therapy over conventional radiotherapy with photons in young patients and adults with low-grade glioma. Strahlenther Onkol 2016;192(11):759-69.

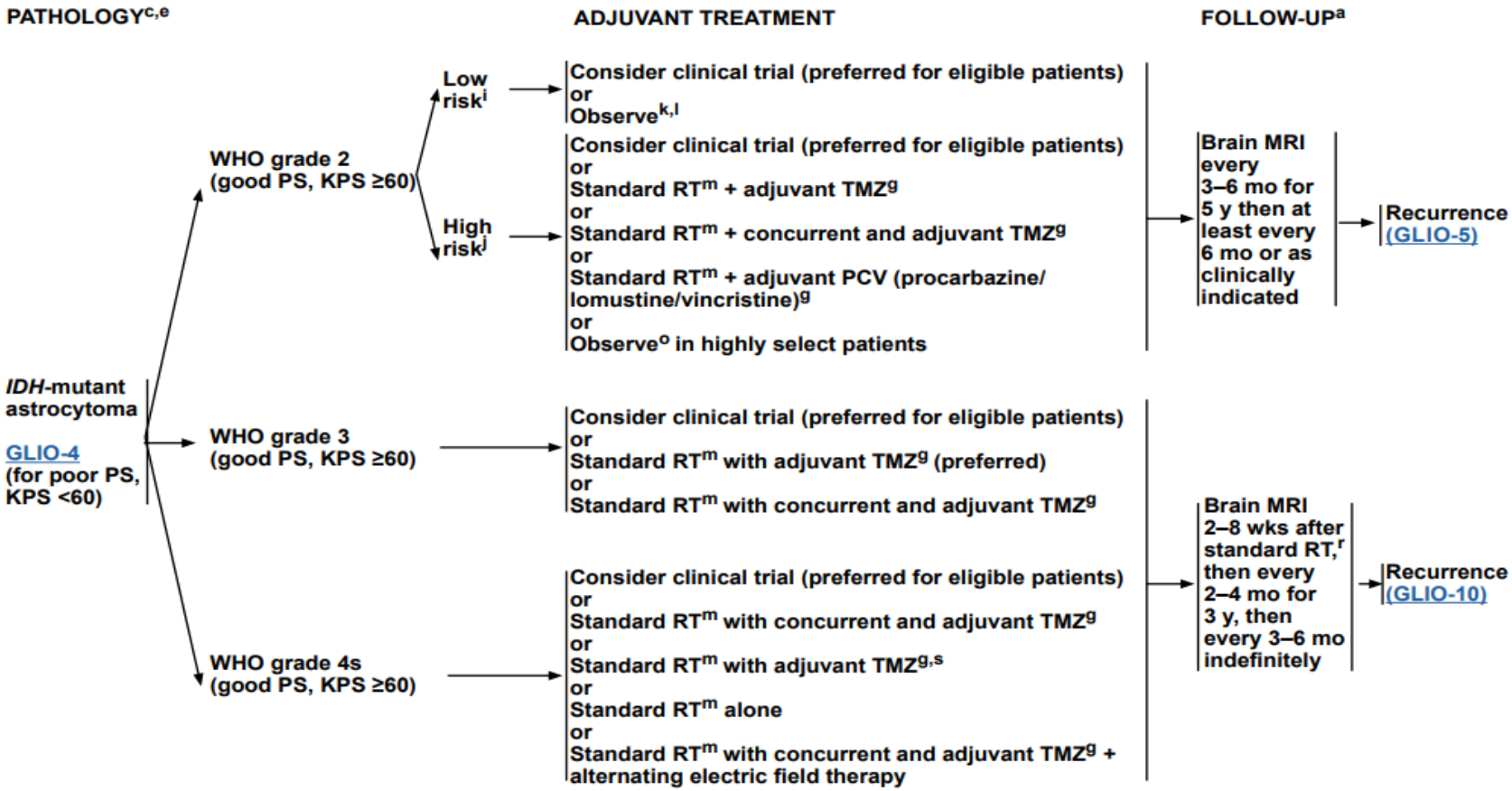
Radiotherapy of CNS tumors

- **High-grade gliomas**
- anaplastic astrocytoma IDH-mutated WHO grade III,
- anaplastic pleomorphic xanthoastrocytoma WHO grade III,
- anaplastic oligodendroglioma IDH-mutated with 1p/19q codeletion WHO grade III,
- glioblastoma IDH-wildtype
- IDH – mutated astrocytoma grade IV

- Surgery (maximum tumor resection)
- HT (according to the CCNU or BCNU protocol or concomitantly with temozolomide, which is also continued in the adjuvant approach)
- RT (6 weeks from surgery) TD 54-59.4 Gy in 30-33 fractions
- Immunotherapy (VEGF - bevacizumab and VEGF receptor agonist - cediranib)

Glioblastoma

- GB IDH-wildtype (about 90% of cases) - includes primary or de novo glioblastoma and is predominant in people over 55 years of age



Continued
Footnotes (GLIO-4)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Adult Glioma: High-Grade

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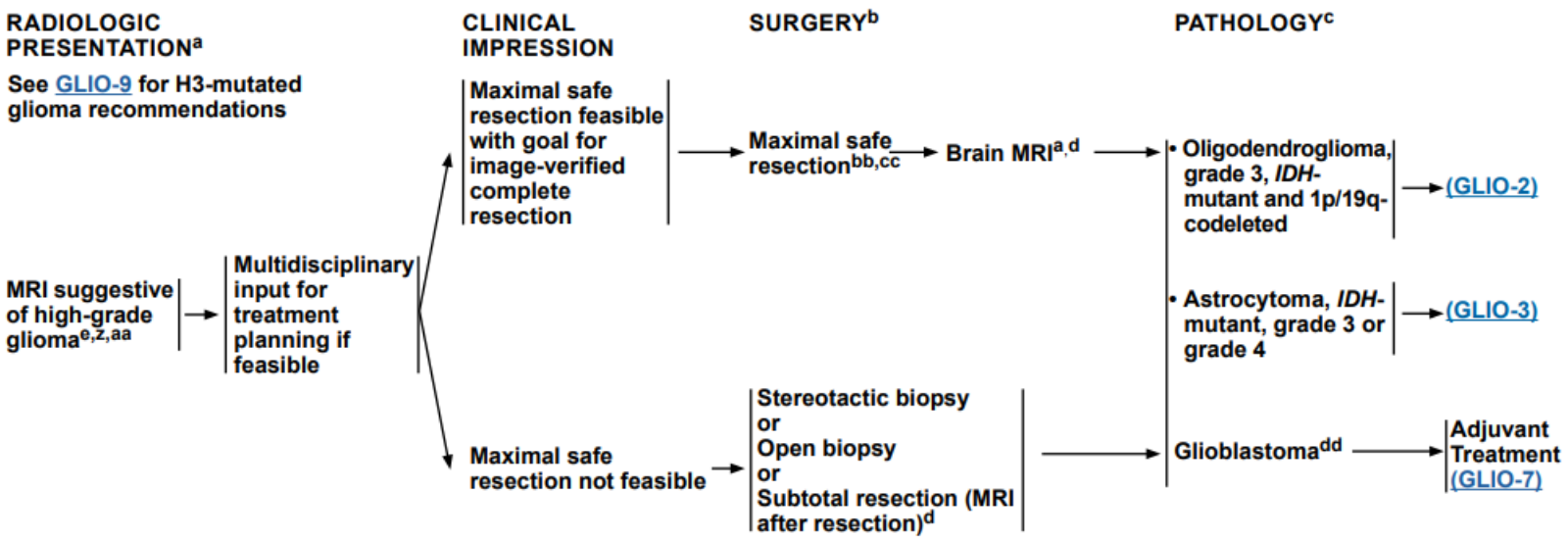

Glioblastoma treatment

- **Laser Interstitial Thermal Therapy (LITT)** destruction of tumor cells by the effect of localized high temperature with the help of radiofrequency waves, ultrasound, microwaves and magnetic nanoparticles.
- **Tumor Treating Fields (TTF)** is a technology of creating alternative electrical fields of low intensity (1–3 V/cm) and medium frequency (100–300 KHz) that lead to the interruption of cell division.
- **Immunotherapy**
- **Checkpoint inhibitors** (nivolumab, pembrolizumab, durvalumab, atezolizumab, and pidilizumab)
- **T-Cell Therapy** where T-cells are programmed to express chimeric antigen receptors (CARs).
- **Viral therapy** is a part of immunotherapy in which an oncolytic virus exerts an effect on various mechanisms including direct oncolysis, virus-induced antitumor response, and immunoregulation.
- **Vaccine**. Dendritic cell vaccine activates CD8+ and CD4+ T-lymphocytes, resulting in tumor destruction
- **Radiotherapy**
- Postoperative RT: TD 60 Gy in 30 fractions concomitant with chemotherapy with temozolomide, an oral alkylating agent that crosses the blood-brain barrier, at a dose of 75 mg/m2.
- After completion, adjuvant chemotherapy is carried out up to a total of VI cycles at a dose of 150-200 mg/m2 temozolomide for 5 days, and cycles of 28 days. Alternative drugs are cisplatin, carboplatin, etoposide, irinotecan.
- Palliative RT: TD 45Gy in 15 fractions or as palliative with TD30 Gy in 6 fractions.

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Adult Glioma: Glioblastoma

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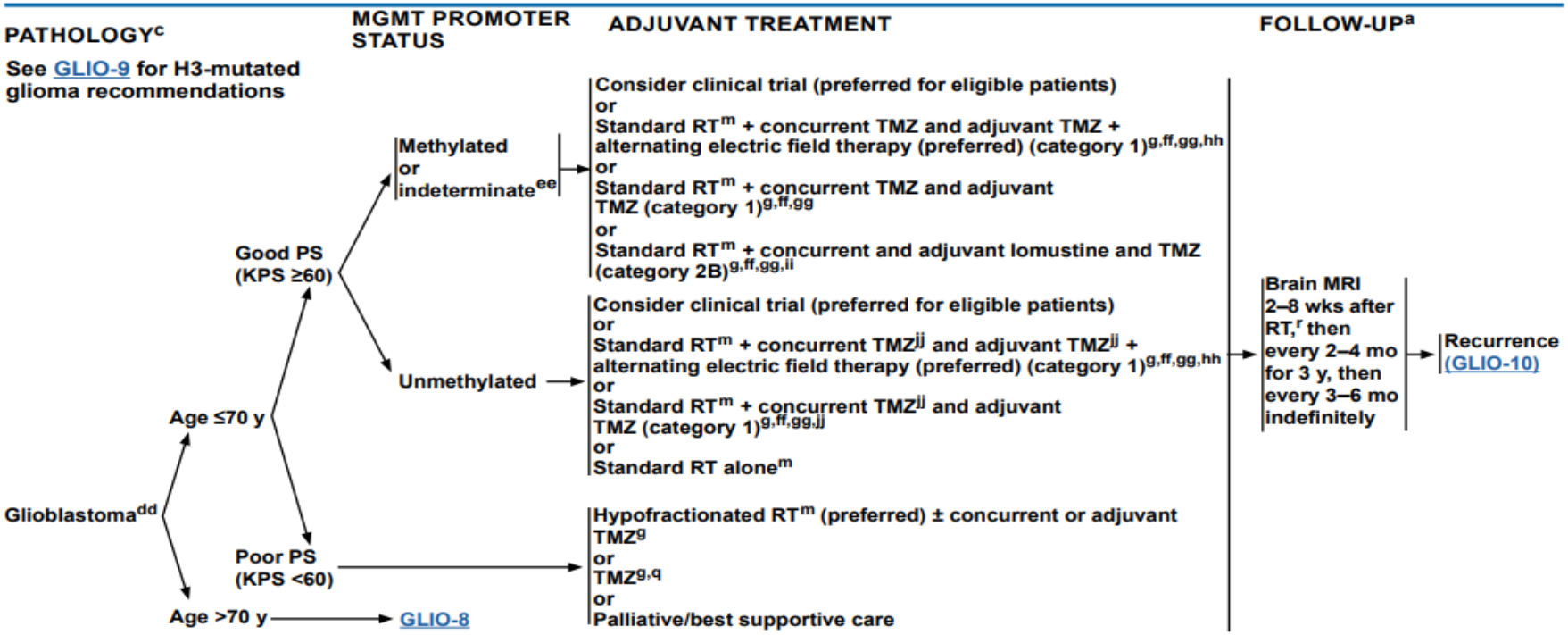
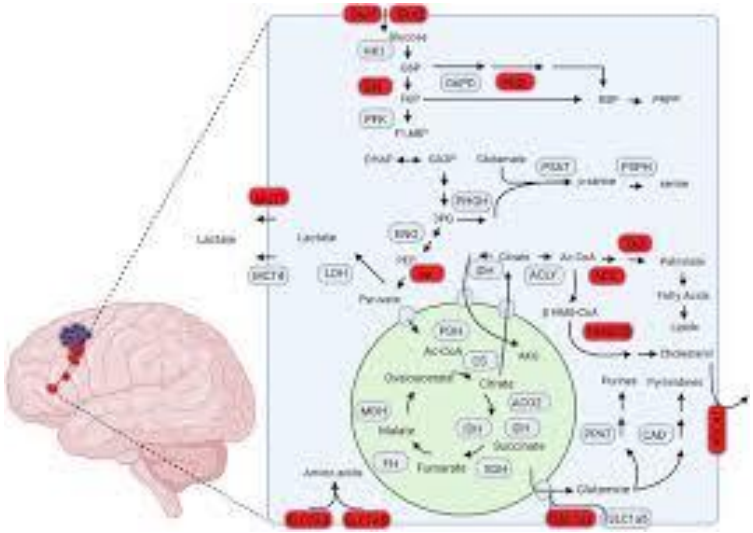


Key points in the pathogenesis of glioblastoma

- IDH mutation
- Notch signaling pathway
- Ceramide signaling
- VEGF signaling pathway
- PDGF signaling pathway
- EGFR signaling pathway
- PI3K/AKT/mTOR signaling pathway
- Phosphate and Tensin Homolog (PTEN) signaling pathway
- SHH signaling pathway



Tang X, et al. Targeting Glioblastoma Stem Cells: A Review on Biomarkers, Signal Pathways and Targeted Therapy. Front Oncol 2021;11:701291.

Target volumes for high-grade gliomas

- **GTV**: postoperative MRI co-registered with radiotherapy CT
- GTV is defined as contrast-enhanced abnormality on T1 sequence and includes gross residual disease and/or tumor bed after surgical resection, excluding peritumoral edema. Postoperative imaging will show changes in the operative region that are difficult to distinguish from tumors and should be included in the GTV
- **CTV**:

Phase 1: 2.5 cm margin around GTV, up to TD 50 Gy in 25 fractions

(or TD 40 Gy in 20 fractions)

Phase 2: 1.5cm margin in the same direction with TD 10 Gy in 5 fractions

(or 20 Gy in 10 fractions)

- **PTV**: Adequate margin, usually 0.5cm

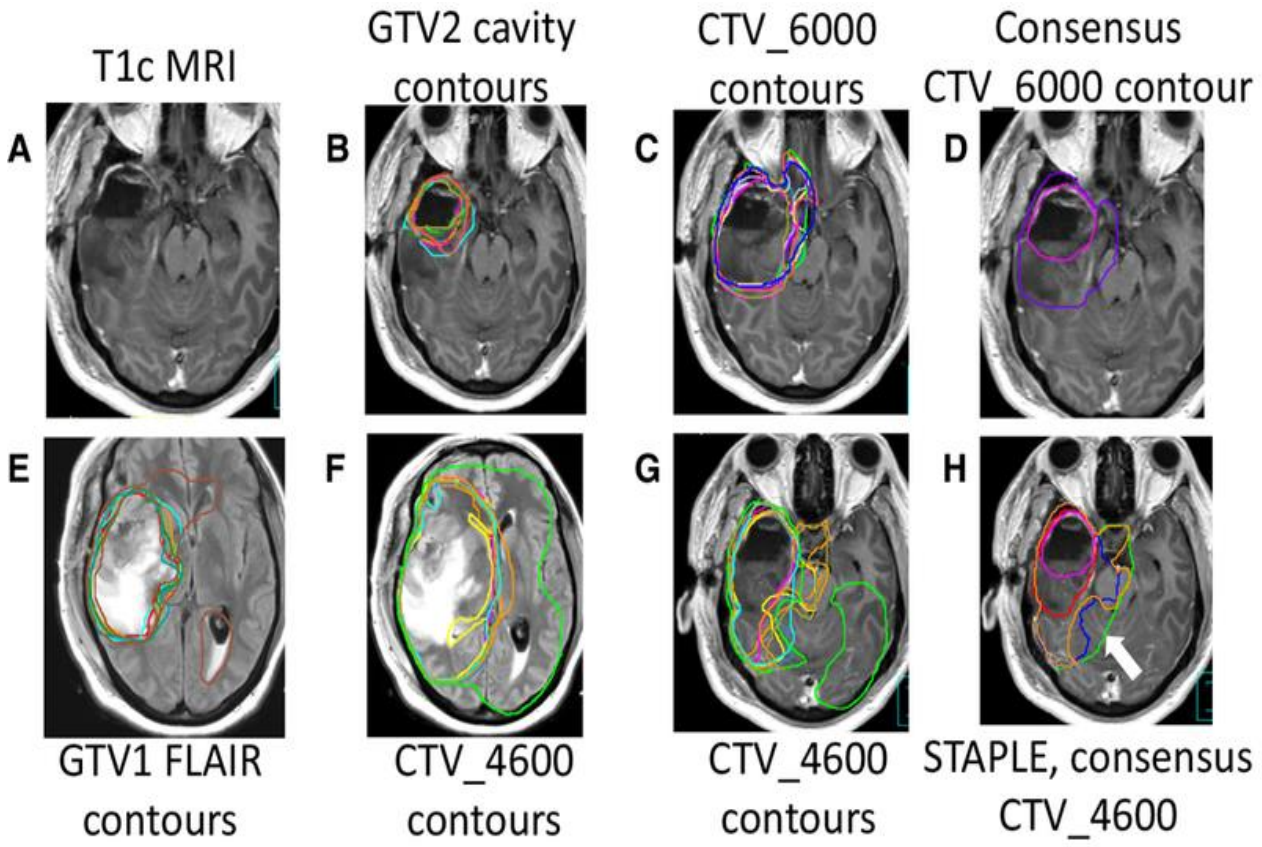
or

Hypofractionated regimen

40 Gy in 15 fractions without systemic therapy - elderly patients

34 Gy in 10 fractions

25 Gy in 5 fractions



Glioblatom temporalno desno
(A, B) panels show the contrast-enhanced T1 MRI with GTV2 contours (cavity plus enhancement).
(C) CTV_6000 contours demonstrate variability at the interface with the brainstem and optic structures.
(D) the STAPLE GTV2 cavity contour in pink and the consensus CTV_6000 contour.
(E, F) show T2 FLAIR MRI images with submitted GTV1 (FLAIR) contours and CTV_4600 contours.
(G) CTV_4600 contours are demonstrated at level of brainstem and optic nerves with significant variation.
(H) CTV1 expansion (without anatomic trimming) in green and mathematical STAPLE contours in blue. The space between the green and orange consensus CTV_4600 contour reflects anatomic trimming off the cerebellum (white arrow) due to cerebellar falx, while maintaining inclusion of optic and brainstem tissue in direct anatomic contiguity with the right temporal T2 FLAIR signal. (*These principles may also be applied to a simultaneous integrated boost approach of 50 Gy and 60 Gy all given in 30 fractions)

Kruser TJ, Bosch WR, Badiyan SN, Bovi JA, Ghia AJ, Kim MM, Solanki AA, Sachdev S, Tsien C, Wang TJC, Mehta MP, McMullen KP. NRG brain tumor specialists consensus guidelines for glioblastoma

Stereotactic Radiosurgery and Hypofractionated Radiotherapy for Glioblastoma

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Melissa I. Azoulay, MD*
Iris C. Gibbs, MD*
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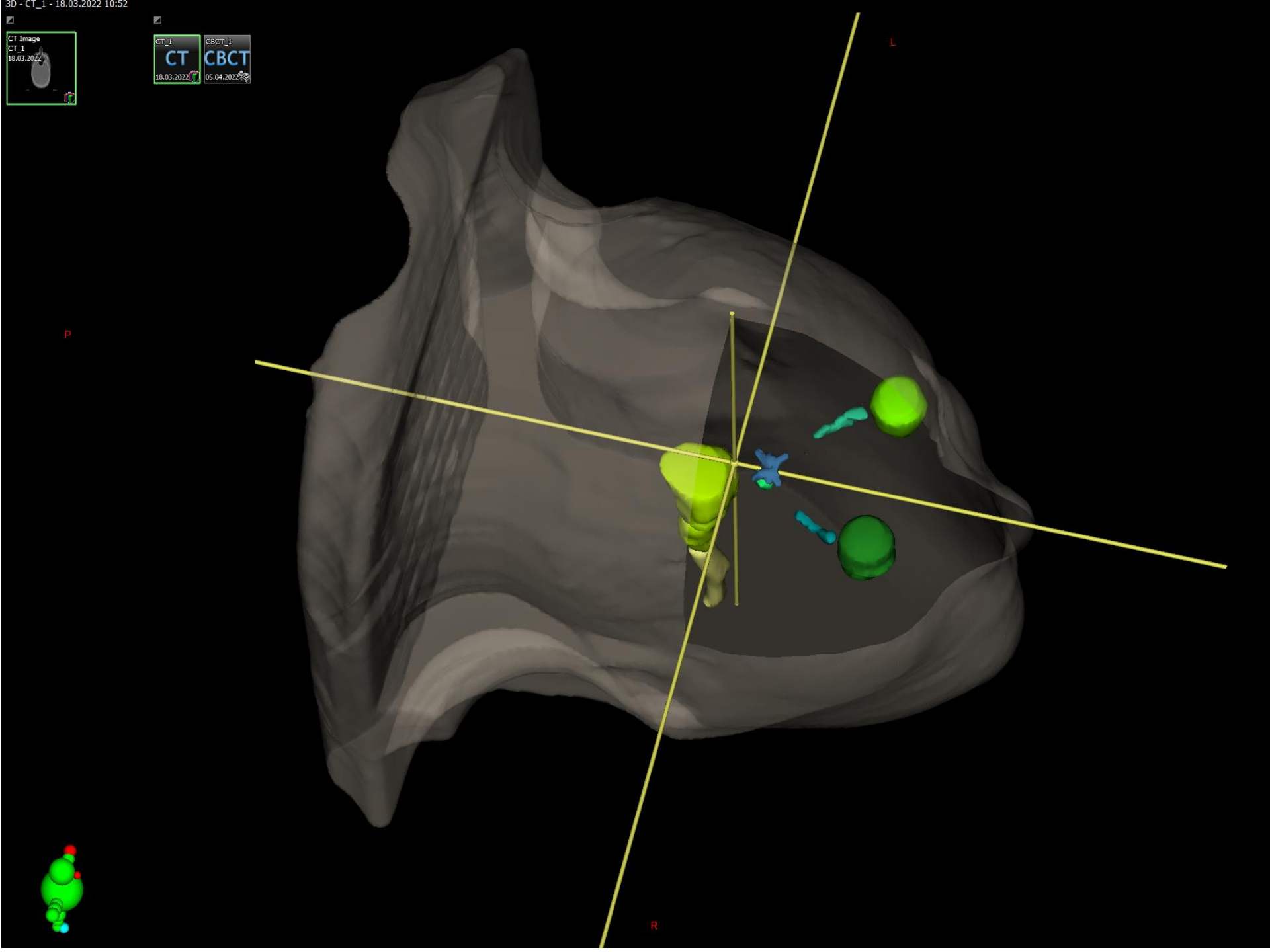
Glioblastoma is the most common primary brain tumor in adults. Standard therapy depends on patient age and performance status but principally involves surgical resection followed by a 6-wk course of radiation therapy given concurrently with temozolomide chemotherapy. Despite such treatment, prognosis remains poor, with a median survival of 16 mo. Challenges in achieving local control, maintaining quality of life, and limiting toxicity plague treatment strategies for this disease. Radiotherapy dose intensification through hypofractionation and stereotactic radiosurgery is a promising strategy that has been explored to meet these challenges. We review the use of hypofractionated radiotherapy and stereotactic radiosurgery for patients with newly diagnosed and recurrent glioblastoma.

KEY WORDS: Glioblastoma, Hypofractionation, Radiation, Radiosurgery

Neurosurgery 0:1–11, 2017 DOI:10.1093/neuros/nyx115 www.neurosurgery-online.com

TABLE 3. Series of Hypofractionated Radiotherapy (HFRT)/Stereotactic Radiosurgery (SRS) for Newly Diagnosed GBM

Authors	Year	Type of study	Number of patients	Tumor size eligibility	Surgery	HFRT/SRS dose	Systemic Therapy with HFRT/SRS	Median follow-up (months)	Median overall survival (months)	Radionecrosis	Notes
Nieder[12]	1999	Phase 1	19	Median 4 cm	47% GTR/STR 53% biopsy	5 Gy × 5, 6 Gy × 5, 7 Gy × 5	–	–	7	0%	Unacceptable toxicity with 6-7 Gy × 5; 5 Gy × 5 was tolerable but conferred no PFS or OS benefit
Hulshof[9]	2000	Prospective, nonrandomized	155	No limit	18% GTR 64% STR 18% biopsy	2 Gy × 33, 5 Gy × 8, 7 Gy × 4	–	–	7 (2 Gy per fx), 5.6 (5 Gy per fx), 6.6 (7 Gy per fx)	–	
Floyd[8]	2004	Pilot	18	<6 cm	–	5 Gy × 10 to GTV + cavity, 3 Gy × 10 to edema	–	–	7	17%	All recurrences were within 2 cm of the operative bed; study terminated due to high incidence of radionecrosis
Roa[5]	2004	Phase III	95	–	39% biopsy 52% STR 9% GTR	2.67 Gy × 15 vs 2 Gy × 30	–	–	5.6 mos vs 5.1 mos	–	Included patients > 60 with KPS > 50
Lipani[10]	2008	Retrospective	20	–	55% GTR 40% STR 5% biopsy	mean 6.12 Gy × 5.65	40% ACNU/VCR	16.45	16	–	
Panet-Raymond[13]	2009	Retrospective	35	Excluded tumors within 1.5 cm of chiasm or brainstem	37% GTR 37% STR 26% biopsy	3 Gy × 20 to GTV, 2 Gy × 20 to PTV	Concurrent and adjuvant TMZ	12.6	14.4	38%	Pattern of failure was central, within 2 cm of GTV; HFRT with TMZ is safe
Morganti[11]	2010	Phase I	19	–	63% GTR 31% STR 5% biopsy	2.4-2.6 Gy × 25 to GTV + cavity, 1.8 Gy × 25 to edema	Concurrent and adjuvant TMZ	23	20	0%	Dose-limiting toxicity was not reached at these dose fractionations with TMZ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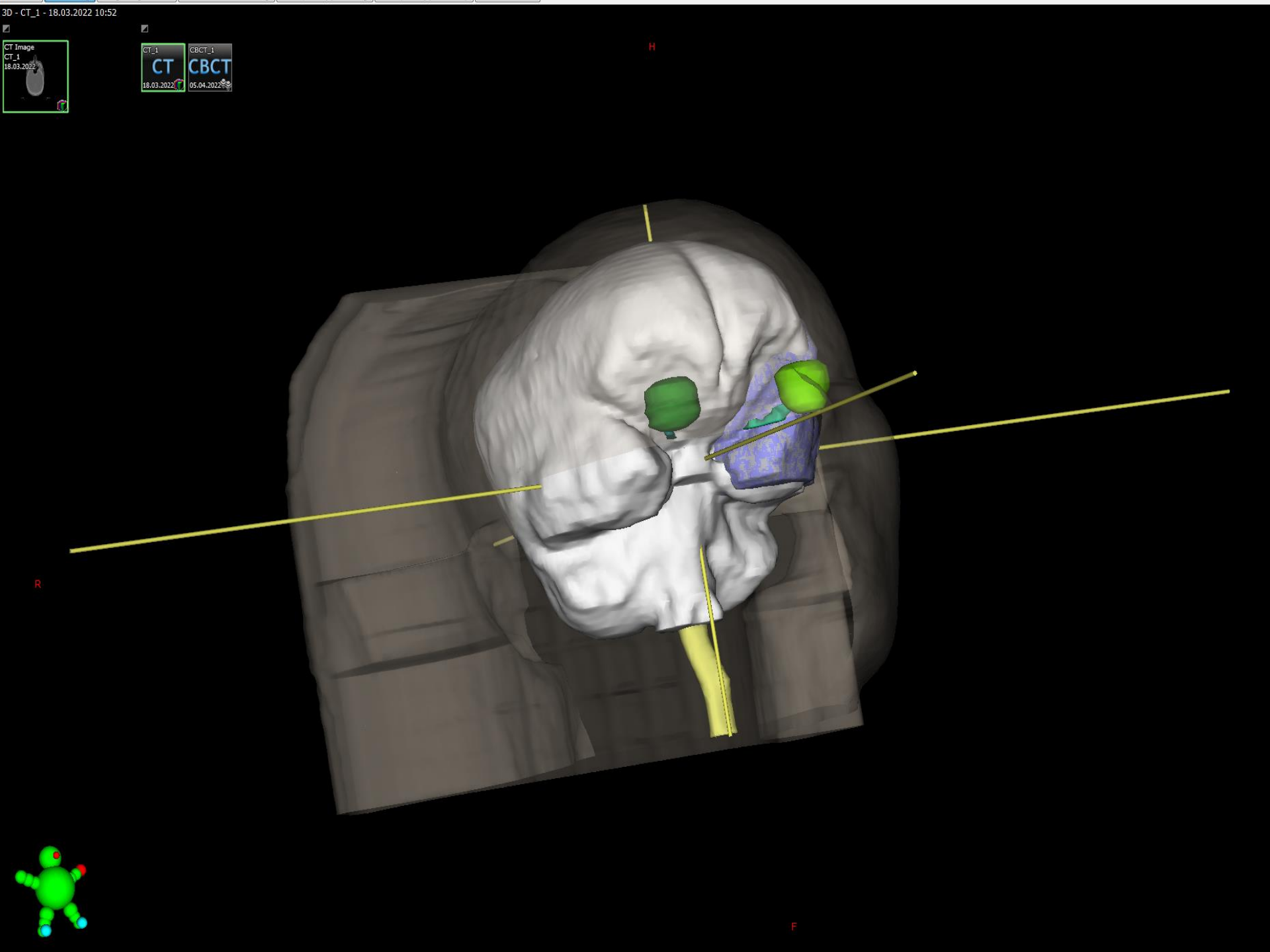
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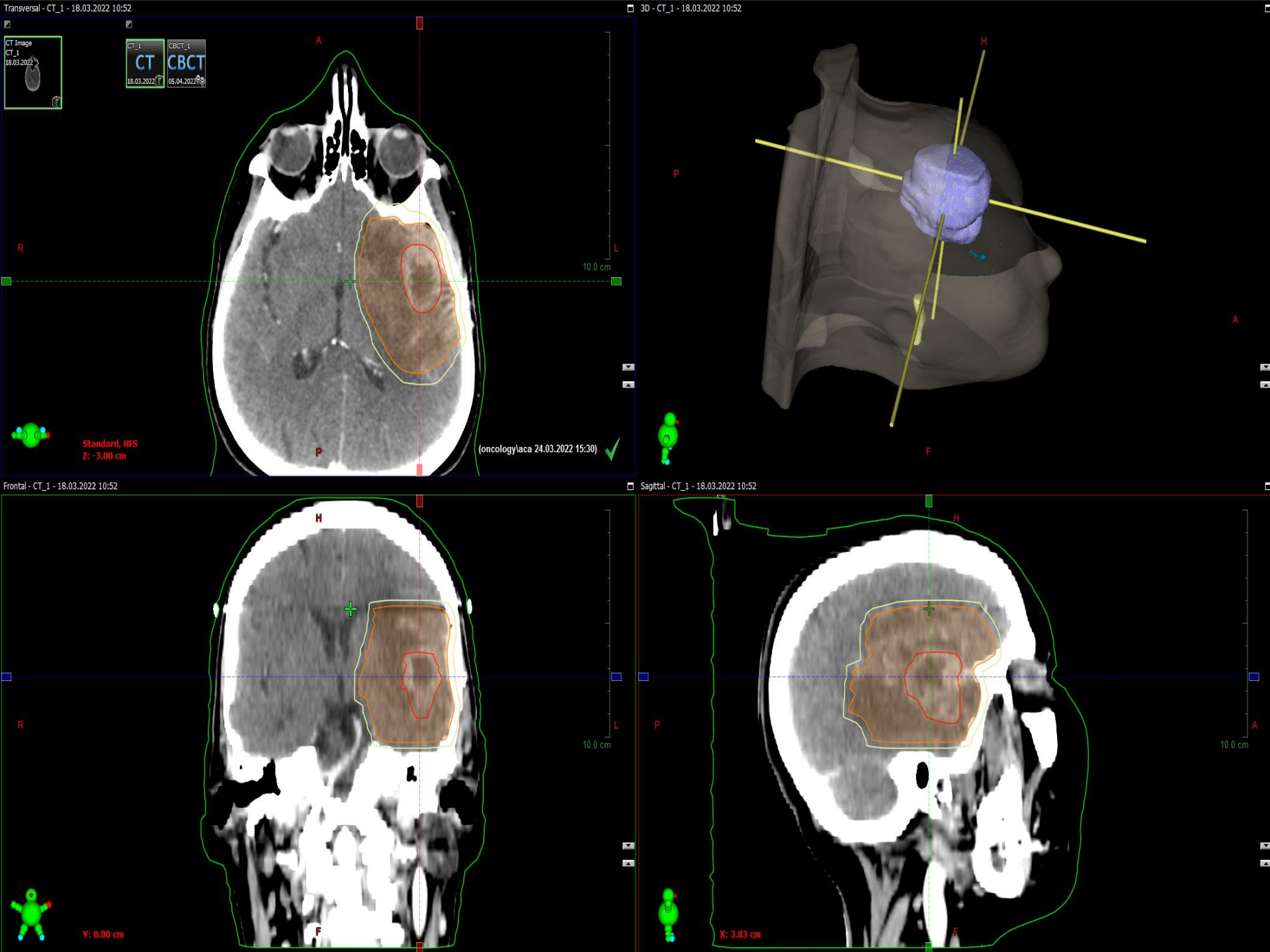
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3D - CT_1 - 18.03.2022 10:52
Frontal - CT_1 - 18.03.2022 10:52
Sagittal - CT_1 - 18.03.2022 10:52
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10.0 cm
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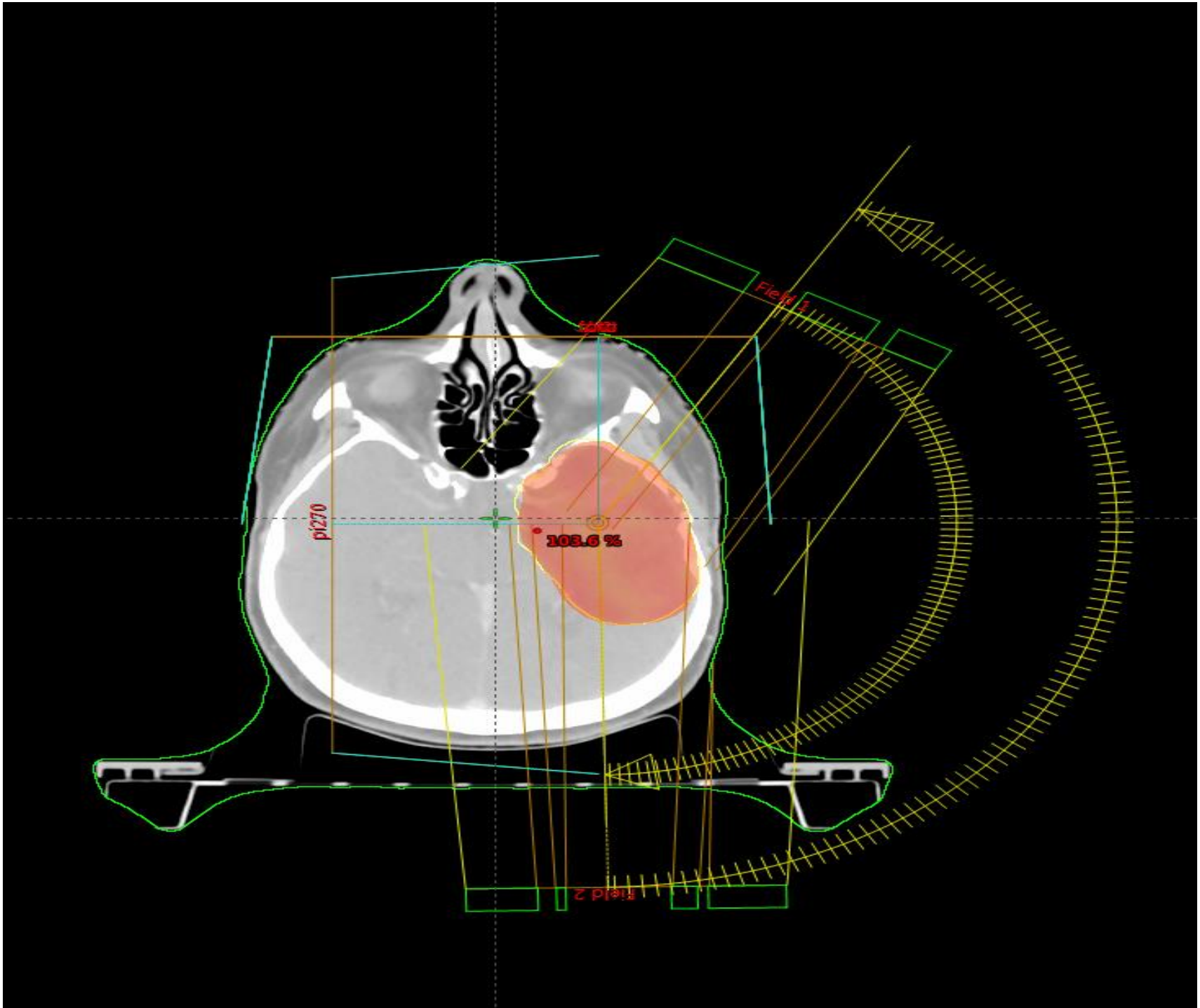
Y: 0.00 cm
X: 3.83 cm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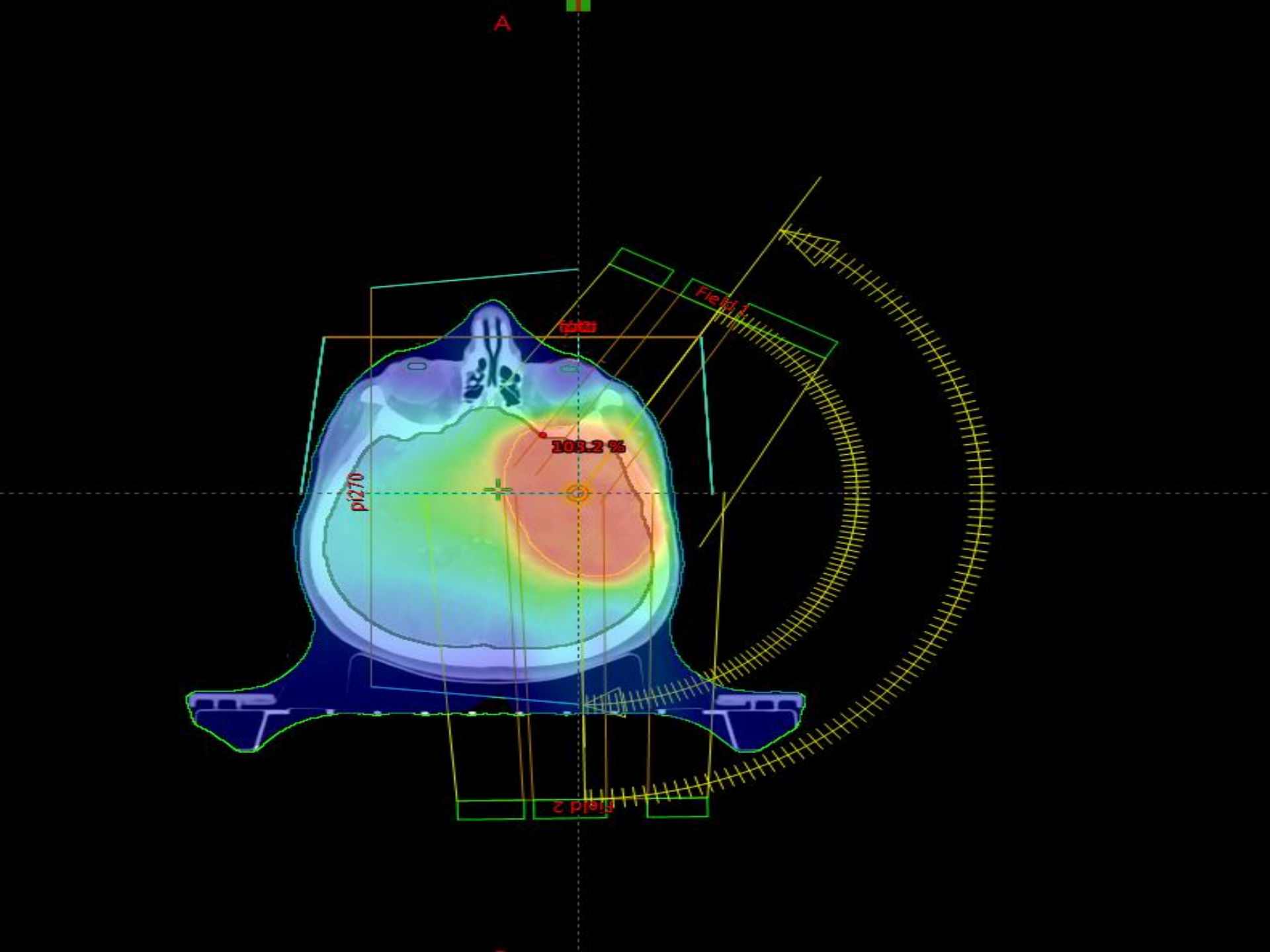
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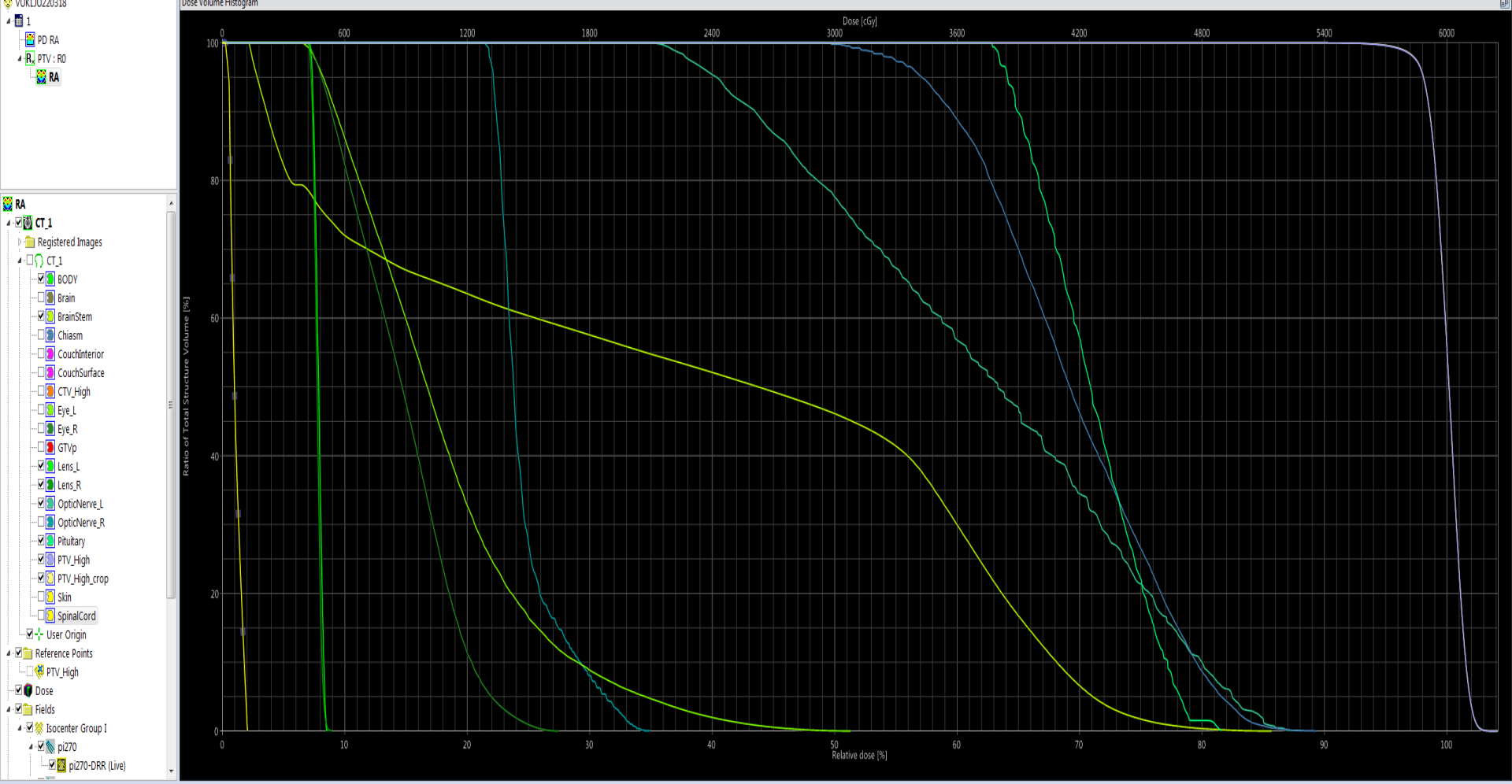
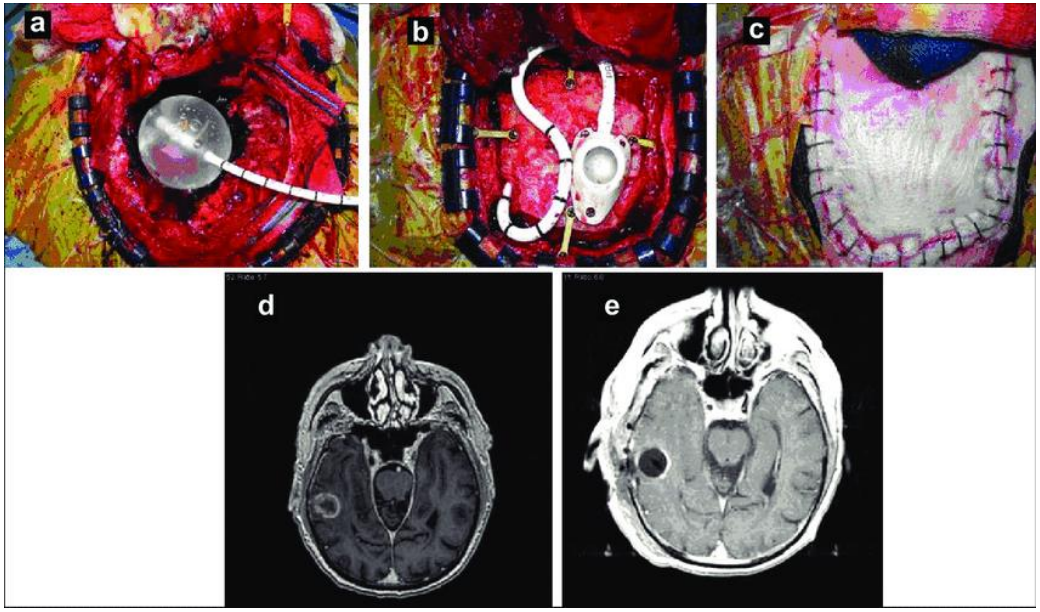


Dose | Reference Points | Dose Statistics

Show DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [%]	Max Dose [%]	Mean Dose [%]
☐	Brain	Approved	RA	1						
☐	BODY	Approved	RA	1	5547.8	100.0	99.9	0.0	104.2	16.7
☑	BrainStem	Approved	RA	1	15.8	100.0	100.2	2.1	85.7	37.7
☑	SpinalCord	Approved	RA	1	3.4	100.0	100.5	0.2	2.1	1.1
☑	Pituitary	Approved	RA	1	0.2	100.0	99.2	62.8	81.6	71.0
☑	Chiasm	Approved	RA	1	0.2	100.0	99.3	49.2	89.3	69.4
☑	OpticNerve_R	Approved	RA	1	0.1	100.0	98.3	21.5	34.9	24.7
☑	OpticNerve_L	Approved	RA	1	0.3	100.0	100.2	35.4	88.2	62.4
☑	Lens_R	Approved	RA	1	0.1	100.0	99.7	7.0	9.0	7.7
☑	Lens_L	Approved	RA	1	0.1	100.0	100.1	7.1	8.6	7.9
☑	Eye_R	Approved	RA	1	5.3	100.0	100.0	6.8	27.5	14.7
☑	Eye_L	Approved	RA	1	5.1	100.0	100.0	6.4	51.4	18.1
☐	GTVp	Approved	RA	1						
☐	CTV_High	Approved	RA	1						
☑	PTV_High	Approved	RA	1	199.9	100.0	100.0	85.2	104.2	100.1
☐	Skin	Approved	RA	1						
☑	PTV_High_crop	Approved	RA	1	199.8	100.0	100.0	85.2	104.2	100.1

Brachytherapy in high grade glioma

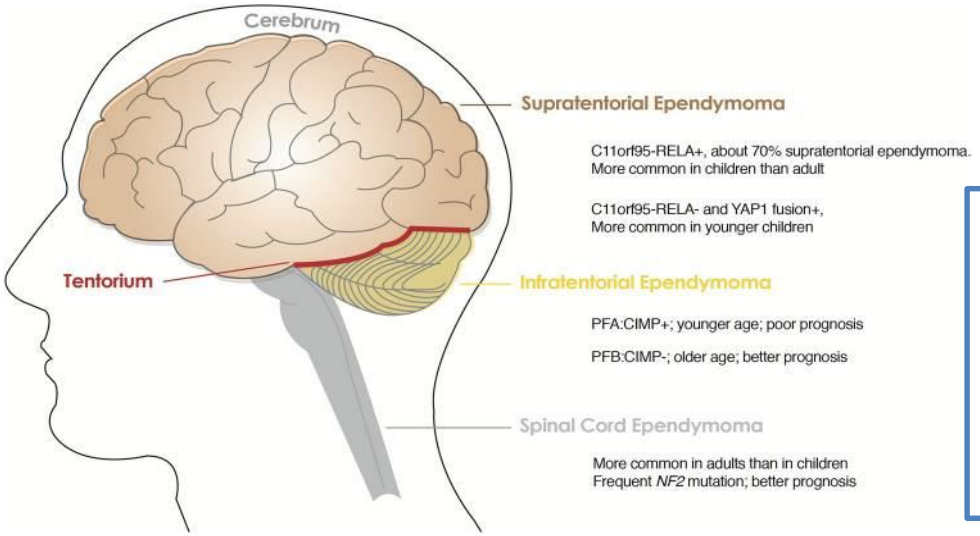
- Boost after EBRT
- Glia Site Radiation Therapy System (Cytyc, Marlborough, MA)
- 1-2 weeks after surgery after the placed catheters are filled with aqueous solution ^{125}I.
- TD of 40 to 60 Gy in 3 to 6 days, after which the device is displaced



Wernicke AG, et al. Feasibility and safety of GliaSite brachytherapy in treatment of CNS tumors following neurosurgical resection. J Cancer Res Ther 2010;6(1):65-74.

Radiotherapy of ependymoma

- Subependymom (WHO grade I)
- Myxopapillary neependymom (WHO grade I)
- Ependymom (WHO grade II)
- Anaplastic ependymoma (WHO grade III)
- RELA fusion-positive ependymoma (WHO grade II or III)



Molecular-biological characteristics of supratentorial, intratentorial and ependymoma of the spinal cord WHO grades II and III.
- Anywhere in the CNS (most commonly within the IV ventricle)
- Low-grade supratentorial → local RT
- High-grade supra and infraten → CS RT + boost
- Low-grade infratentorial - a controversy?

Wu J, Armstrong TS, Gilbert MR. Biology and management of ependymomas. Neuro Oncol 2016;18(7):902-13.)

Neuro-Oncology
23(8), 1231–1251, 2021 | doi:10.1093/neuonc/noab106 | Advance Access date 29 June 2021

The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

David N. Louis, Arie Perry, Pieter Wesseling, Daniel J. Brat, Ian A. Cree, Dominique Figarella-Branger, Cynthia Hawkins, H. K. Ng, Stefan M. Pfister, Guido Reifenberger, Riccardo Soffietti, Andreas von Deimling, and David W. Ellison

Supratentorial ependymomas	*ZFTA, RELA, YAP1, MAML2*
Posterior fossa ependymomas	H3 K27me3, *EZHIP* (methylome)
Spinal ependymomas	*NF2, MYCN*

Treatment of ependymoma

- Surgical resection
- RT
- Craniospinal RT with a TD of 35 to 45 Gy with a boost to areas of primary tumor and active disease up to a total dose of TD of 50.4 to 54 Gy
- HT – limited efficacy, high-grade tumors, resistant to other treatment modalities
- Surgery (subtotal resection) + II Cy (HT) + second-look operation

Delineation of target volumes in radiotherapy of ependymoma

- GTV: defined as tumor or residual tumor shown on pre- or post-operative MRI
- CTV: margin of 1-1.5cm
- PTV: a margin of 0.5 cm

Medulloblastoma

WNT-activated
SHH-activated
non WNT -
non SHH

- Tendency to spread via cerebrospinal fluid
- Extracranial metastases
- 5-year survival for medulloblastoma 60-70%

Neuro-Oncology
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Medulloblastoma, WNT-activated	*CTNNB1*, *APC*
Medulloblastoma, SHH-activated	*TP53*, *PTCH1*, *SUFU*, *SMO*, *MYCN*, *GLI2* (methylome)
Medulloblastoma, non-WNT/non-SHH	*MYC*, *MYCN*, *PRDM6*, *KDM6A* (methylome)

Radiotherapy of medulloblastoma

- WNT-activated
- SHH-activated
- non WNT - non SHH

- Rarely in adults - older than 40 years.
- Mostly in children
- CSF spread → 1/3 of patients
- Unlike other CNS tumors – bone metastases
- CS RT + boost
- Chemotherapy - multiagents (Cisplatin, Cyclophosphamide, Etoposide, Vincristine, Lomustine, "8 in 1")
- Treatment:
- Surgery
- RT

Risk	Craniospinal dose	Boost to the posterior cranial fossa
Standard	23,4 Gy / 13 fractions	54-55,8 Gy
High	36-39,6 Gy / 20-22 fractions	54-55,8 Gy

- Adjuvant CHT

Risk groups

- **Standard risk group** (age >3 years, postoperative residual tumor <1.5 cm^2, no signs of dissemination). The percentage of five-year survival without disease progression is 80%.
- **High-risk group** (age < 3 years, postoperative residual tumor >1.5 cm^2, metastatic disease, subtotal resection or biopsy only, male sex). Local relapse often occurs.

Tumors of the brain stem

- They include tumors of the midbrain, pons and medulla. They can be divided into focal (5-10%), dorsal exophytic (10-20%), cervicomedullary (5-10%) and diffuse tumors (75-85%).
- Focal, dorsal exophytic and cervicomedullary tumors are usually low grade astrocytomas.
- Treatment:
- Surgical excision
- RT reserved for inoperable tumors

Tumors of the brain stem

- Most children with brainstem tumors have an H3 K27M-mutated diffuse midline glioma, usually a high-grade astrocytoma. They have a typical MRI finding, and a biopsy is usually risky and contraindicated.
- The prognosis of these children is poor with a median survival of about 9 months and a small number of children with longer survival. Therapy is a big challenge and palliative care should be included in the early stages of the disease
- Because of the often relatively short survival time, RT should be started quickly
- Involved field radiotherapy is the primary treatment for midline diffuse infiltrative gliomas.
- GTV (MRI T2/FLAIR) with a uniform margin of 2 cm in all directions along the potential region of spread, superiorly, inferiorly, and posteriorly along the brainstem.
- RT with TD 54 Gy in 30 fractions

Radiotherapy techniques

Patient position and immobilization

- It is most often performed in supination with a suitable immobilization mask

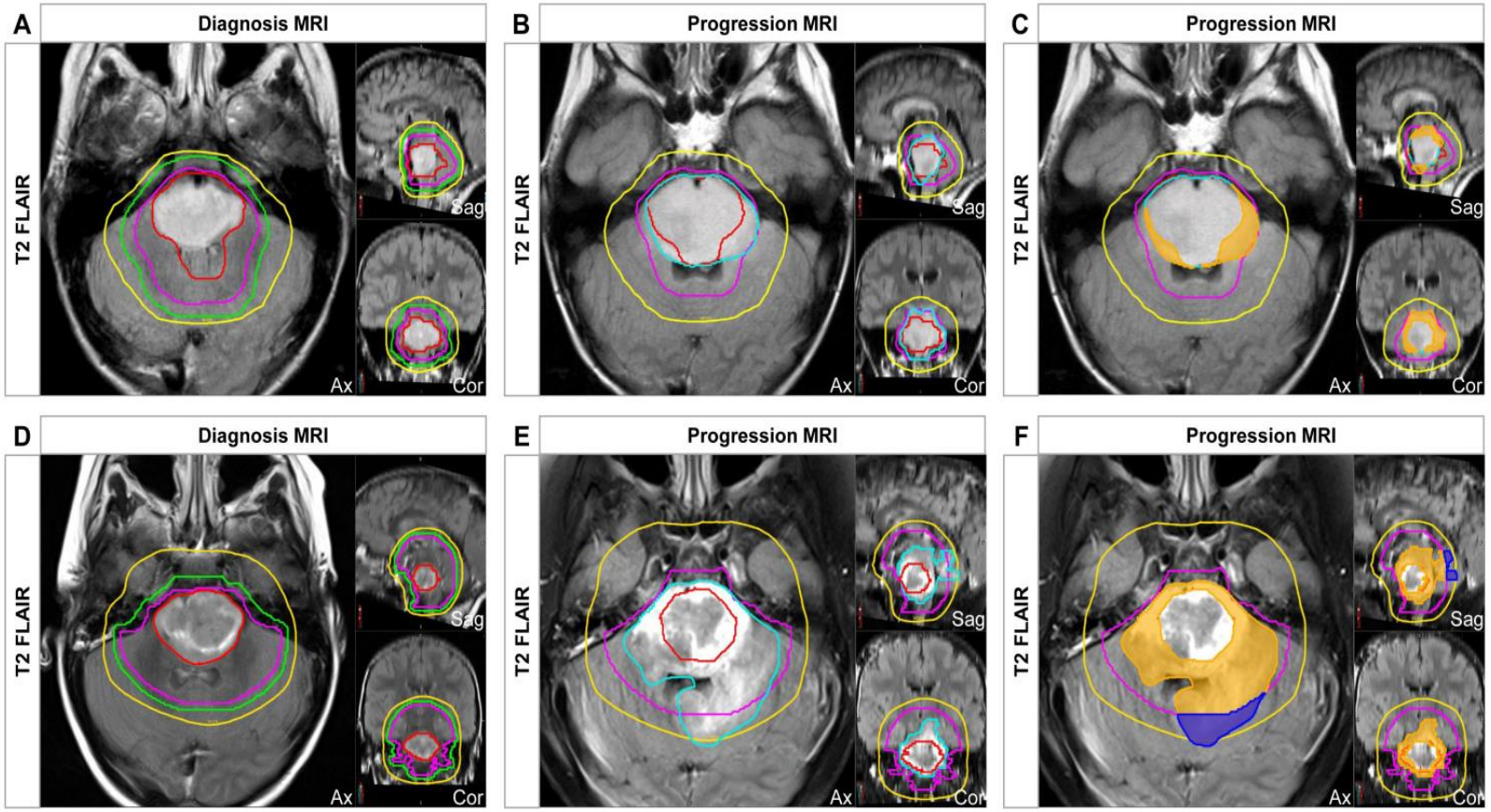
Clinical target volume

The GTV is defined on the diagnostic MRI scan with a margin of 2 cm along the potential region of spread superiorly, inferiorly and posteriorly along the brainstem.

Since the brain stem is poorly visualized on CT, MRI fusion is always recommended whenever possible

Radiotherapy techniques

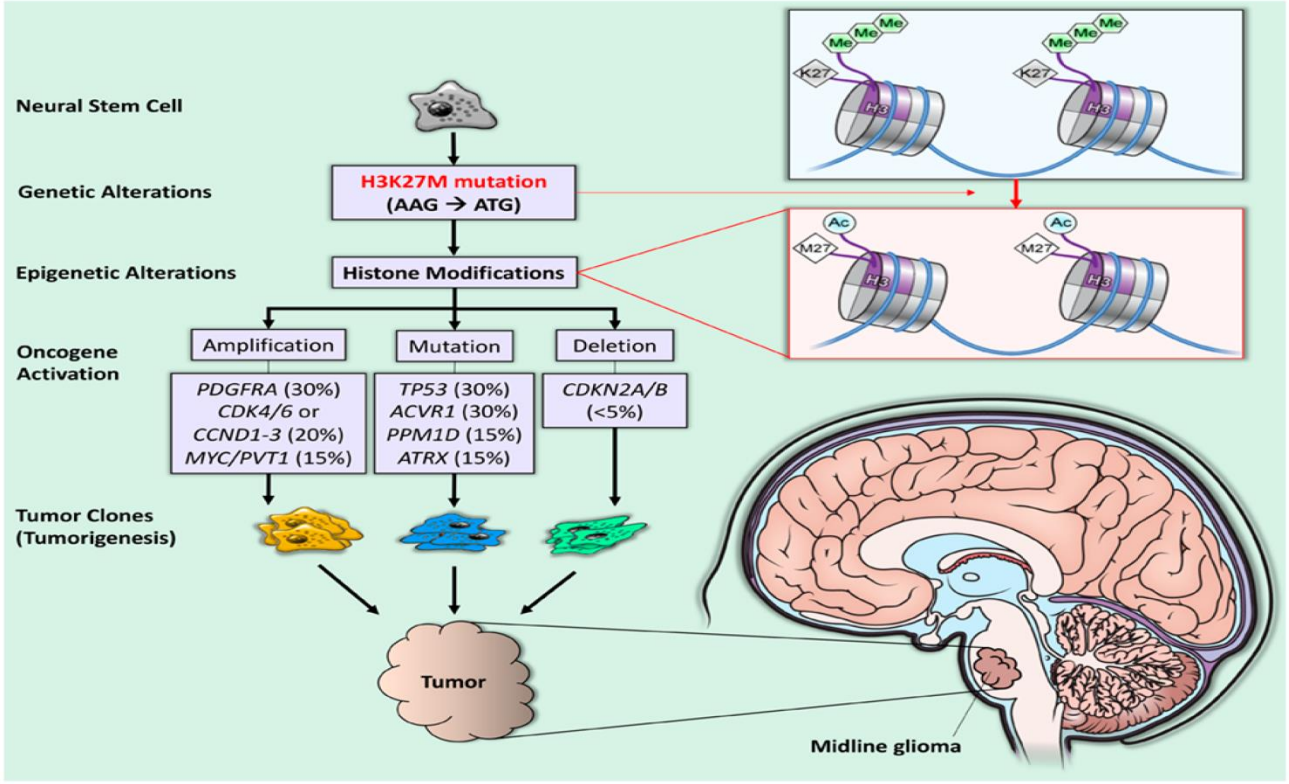
TD 54Gy / 30 fractions with 1,8 Gy daily



Tinkle CL, et al . Defining Optimal Target Volumes of Conformal Radiation Therapy for Diffuse Intrinsic Pontine Glioma. Int J Radiat Oncol Biol Phys. 2020;106(4):838-47.

Tumors of the brainstem

- Chemotherapy did not show benefit
- Conventional radiotherapy provides useful palliation in 75% of children
- PFS usually less than 6 months
- Hyperfractionated or accelerated RT does not improve treatment outcome



Argersinger DP, et al. New Developments in the Pathogenesis, Therapeutic Targeting, and Treatment of H3K27M-Mutant Diffuse Midline Glioma. Cancers (Basel) 2021;13(21):5280.

Radiotherapy of meningioma

- Benign (grade I): few mitosis, slow growth, rare relapse, 10-year progression-free survival is 80%,
- Atypical (grade II): more aggressive than benign, more mitoses, 7-8 times higher risk of relapse than grade I, 10-year progression-free survival is 40-60%,
- Anaplastic (grade III): invasive, poor prognosis; median relapse-free survival is less than 2 years

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The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

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Meningiomas	*NF2*, *AKT1*, *TRAF7*, *SMO*, *PIK3CA*; *KLF4*, *SMARCE1*, *BAP1* in subtypes; H3K27me3; *TERT* promoter, *CDKN2A/B* in CNS WHO grade 3

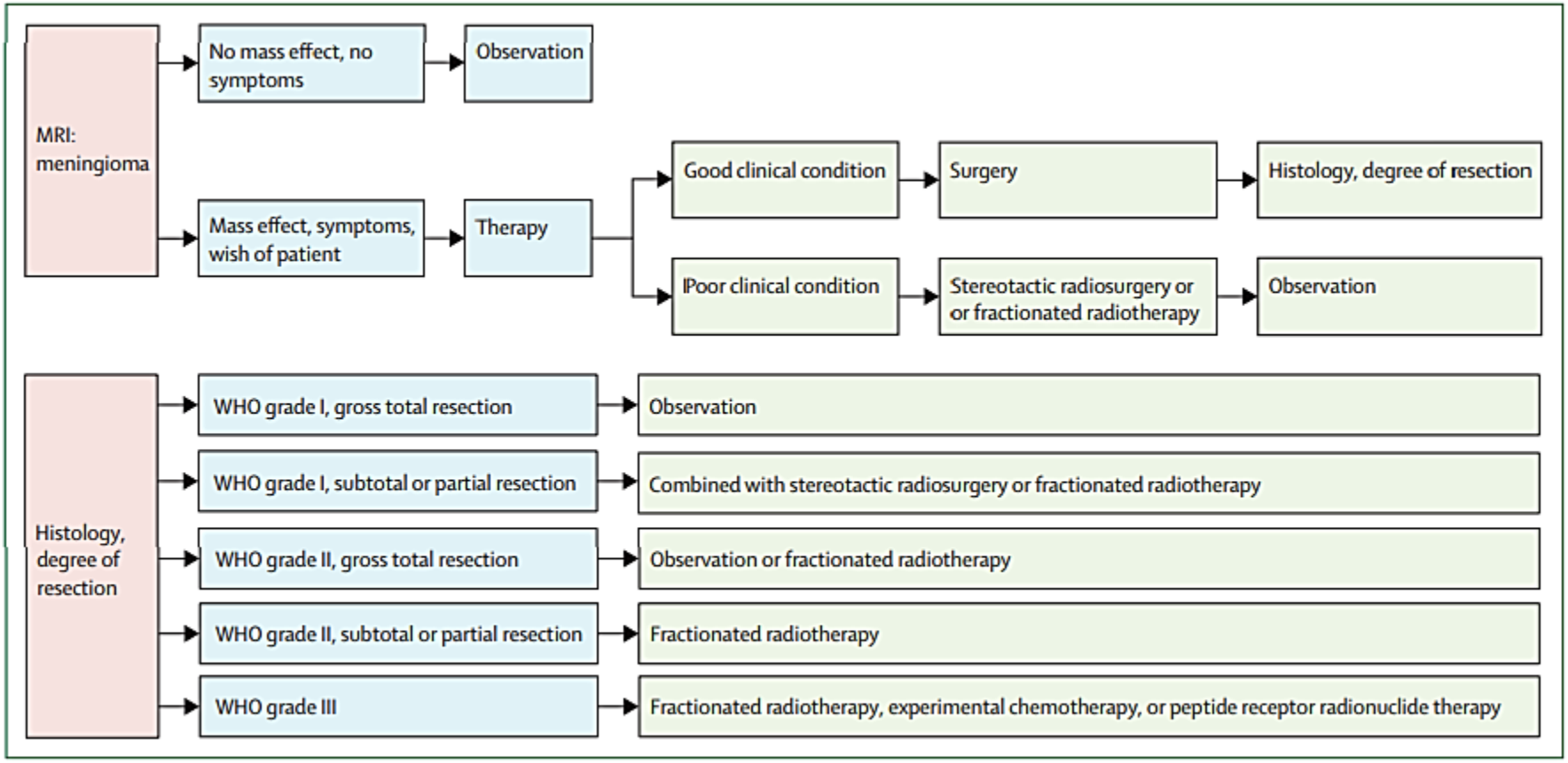

Figure 1: **Recommendations for the therapeutic management of meningiomas of WHO grades I–III**

Goldbrunner R, et al. EANO guidelines for the diagnosis and treatment of meningiomas. Lancet Oncol 2016;17(9):e383-91.

Treatment of meningioma

- **Surgery**
- **Radiotherapy**: unresectable or incompletely resectable tumors due to localization (skull base, cavernous sinus, cerebellopontine angle), the patient does not agree to surgery or it is medically contraindicated. Adjuvant approach in subtotal resection of benign and all atypical and malignant meningiomas
- Dosage prescription:
- Meningioma grade I: 50-54 Gy in 25-30 fractions
- Meningioma grade II and III: 60 Gy in 30-33 fractions
- Meningioma of the optic nerve: 50-54 Gy in 25-30 fractions
- Stereotaxic radiosurgery: 12-20 Gy in one fraction depending on the proximity of critical structures (12 Gy for tumors close to critical structures such as the brainstem, 15-20 Gy if the tumor is not close to extremely critical structures). Doses depend on the size of the tumor: 18 Gy (<1 cm), 16 Gy (1-3 cm), 12-14 Gy (>3 cm)

- **CHT**: in tumor progression after RT and in case of recurrent disease (cyclophosphamide, adriamycin, vincristine, interferon-alpha)

Delineation of target volumes in meningioma radiotherapy

- There is no consensus for the inclusion of the dura, areas of bone hyperostosis, or involved bone in the target volume
- Brain invasion is rare and the volume of brain involved in CTV should be minimal.
- GTV: contrast-binding tumor on MRI (T2W sequence)
- CTV: CTV with a margin of 0.5 cm
- PTV: CTV with a margin of 0.5 cm

Radiotherapy of tumors of the sellar region

Craniopharyngioma WHO gr I

Benign tumor of epithelial origin - remnant of Rathke's sac

Surgery

Total resection - curative → postoperative morbidity and mortality

GTR is not always feasible

Recommendation → limited surgical decompression + postoperative RT

Recurrent tumor with a large cystic component

Intracavitary brachytherapy (Beta emitters ^{32}P and ^{90}Yt and Gamma-Beta emitters ^{186}Ph and ^{198}Au)

Pituitary adenoma

Surgical resection for Tu above then 1 cm – the therapy of choice

Radiotherapy after partial resection

Most patients - hormone replacement therapy with dopamine agonists (bromocriptine, Cabergoline, quinagolide, Pergolide) - reduction in tumor size and improvement of symptoms

RT: 50-54 Gy in 30 fractions, and dose per fraction 1.67-1.8 Gy

Tumors of the sellar region

Tumors of the sellar region
Adamantinomatous craniopharyngioma
Papillary craniopharyngioma
Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma
Pituitary adenoma/PitNET
Pituitary blastoma

Delineation of target volumes in radiotherapy of the sellar region

- GTV: is defined based on the preoperative MRI findings, taking into account the surrounding anatomical structures. GTV includes both cystic and solid tumor components
- CTV: GTV + 3-5 mm, due to the tendency of the tumor to adhere to the surrounding structures
- PTV: CTV + 5 mm

- The dose is 50-54 Gy in 30 fractions, and the dose per fraction is 1.67-1.8 Gy

Radiotherapy of intracranial germ cell tumors

- Germinomas
- Embryonic carcinoma
- Choriocarcinoma
- Endodermal sinus tumor
- Teratoma / teratocarcinoma
- Mixed germ cell tumors

Intracranial germ cell tumors

- More than 90% of germinomas can be cured with radiotherapy

- CSI is performed because of the risk of leptomeningeal dissemination. In order to minimize the late effects of the therapy, the CSI dose and the boost dose to the primary tumor were reduced
- According to SIOP protocol CSI 24Gy in 15 fractions with 1.6 Gy daily fractions
- Boost 16Gy in 10 fractions with 1.6 Gy daily fractions
- Germinomas have a tendency to spread subepidermally, which must be taken into account when planning the boost volume, with a 2cm margin around the GTV

Delineation of target volumes

- GTV: GTV before chemotherapy/surgery is defined as a contrast-enhancing lesion on T1 and T2 MRI sequences. The patient should be in remission at the time of radiotherapy, so there is no residual GTV.
- CTV: two CTVs are defined, the first representing tumor spread before chemotherapy, and the second indicating potential sites of spread including the entire ventricular system (eng. whole ventricle radiotherapy - WVRT).
- PTV: additional safety margin of 5 mm

Radiotherapy of central nervous system lymphoma

- PCNSL in immunocompetent and
- PCNSL in immunocompromised patients (occurring in congenital or acquired immunodeficiency)

- Diffuse large B-cell lymphoma (DLBCL) accounts for 95% of lymphomas that occur in this region.
- According to the Ann Arbor staging system, they are staged as CS IE stage

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Lymphomas
CNS lymphomas
Primary diffuse large B-cell lymphoma of the CNS
Immunodeficiency-associated CNS lymphoma
Lymphomatoid granulomatosis
Intravascular large B-cell lymphoma
Miscellaneous rare lymphomas in the CNS
MALT lymphoma of the dura
Other low-grade B-cell lymphomas of the CNS
Anaplastic large cell lymphoma (*ALK*+/*ALK*–)
T-cell and NK/T-cell lymphomas

RPA classes associated with length of survival (Memorial Sloan-Kettering Cancer Center)

- **Class 1** - patient age under 50 years with a median survival of 8.5 years
- **Class 2** - patient age over 50 years and KPS over 70, with a median survival of 3.2 years
- **Class 3** - patient age over 50 years and KPS below 70, with a median survival of 1.1 years

- CHT - standard in definitive treatment (with or without RT), salvage therapy in disease progression or recurrent disease and as definitive treatment in ocular lymphomas. High doses of methotrexate > 1g/m2.
- Surgical resection does not bring benefit
- RT after HT or as definitive treatment in patients unfit for chemotherapy (KPS≤40, creatinine clearance <50%) and as definitive treatment for ocular lymphomas.
- WBRT with or without boost dose administration

- If a CR response is achieved: WBRT with 24-36Gy (1.5-2Gy). Consider dose reduction or discontinuation of treatment in patients over 60 years of age due to possible serious neurotoxicity.
- If CR response not achieved: WBRT with 24-36Gy (1.8-2Gy) with boost to residual disease up to 45Gy (1.8-2Gy).

- If it was not possible to apply chemotherapy:
- Whole brain RT up to 45Gy (1.8-2Gy)

Delineation of target volumes

- Target volume: whole brain up to C2/C3 intervertebral space including posterior third of orbit, temporal bones and cribriform plate.
- Parallel opposition fields, energy 6-10 MV using blocks and MLC.
- For boost, 3D-CRT or IMRT with 3-5 beam fields is performed.
- Residual tumor on MRI represents CTV, and a margin of 1-1.5 cm should be added for CTV.
- An additional margin of safety is added to create PTV.

Radiotherapy of secondary tumors of the CNS

The treatment is multimodal and includes the use of systemic therapy, surgery, radiotherapy, chemotherapy, immunotherapy and target therapy.

Factors that determine treatment for metastases in the CNS are:
factors from the patient: neurological deficit, age and general condition of the patient.

Disease factors are: number of metastases, lesion size, localization, primary tumor status and extracranial disease.
A single metastasis is a single metastasis in the CNS without taking into account the status of extracranial disease.
A solitary metastasis is a single metastasis in the CNS in the absence of extracranial disease.

Primary Site	
Lung	20%–50%
Breast	5%–20%
Small cell lung cancer	15%
Melanoma	7%–10%
Renal cell carcinoma	4%–6%
Colon	2%–5%
Relevant Facts	
Median survival	<1 yr
Mean age	60 yr
Annual U.S. incidence	>170,000
Clinical incidence	30%

Radiotherapy of secondary tumors of the CNS

- WBRT with or without surgery
- WBRT with or without stereotactic radiosurgery,
- Surgery with or without RT (localized or WBRT)
- Stereotactic radiosurgery

Doses and fractionation

- WBRT:
- 12 Gy in 2 fractions
- 18 Gy in 3 fractions
- 20 Gy in 5 fractions, 4 Gy per fraction over one week
- 30 Gy in 10 fractions, 3 Gy per fraction, over 2 weeks
- Focal radiation: 40Gy in 20 fractions, during 4 weeks
- Stereotactic radiosurgery: 17 Gy in one fraction

Solitary CNS metastasis <3-4cm

- Surgery (unknown primary tumor, pronounced compressive effect)
- SRS (good general condition, inaccessible localization for surgical resection)
- SRS+WBRT (in patients assigned to a better prognostic group, better local control and longer survival, pay attention to neurogenic functions)

Multiple CNS metastases

- Oligometastatic disease (1-4 changes in the CNS)
- SBRT+WBRT (oligometastatic disease, each change <4cm, better prognostic group)
- If there is a high risk of damage to neurocognitive functions, in the prognostically better group, postpone WBRT with sparing of the hippocampus after SRS


THANK
YOU!