



**UNIVERSITY OF KRAGUJEVAC
FACULTY OF MEDICAL SCIENCES**



**CLINICAL RADIOTHERAPY APPLICATION
IN VULNERABLE PATIENTS GROUPS**

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Palliative radiotherapy

Indications

- pain reduction
- stabilization
- hemostasis
- deobstruction
- improving the quality of life



Emergency situations in radiotherapy

- CNS metastases
- Threatening pathological fracture
- Spinal cord compression (spinal canal stenosis)
- Superior vena cava Syndrome

Bone metastases

Single fields

- Spine, sacrum
- Ribs, calvaria

Parallel - opposite fields

- Pelvis, long bones
- Base of skull
- Dose and fractionation
- 30Gy / 10 fractions
- 20Gy / 5 fractions
- 8Gy / 1 fraction

Hemibody irradiation

- Lower half
- 8Gy in 1 fraction (9-10 MeV photons)
- Upper half
- 6-8Gy in 1 fraction (9-10 MeV photons)

CNS metastasis radiotherapy

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

The factors that determine the treatment of metastases in the CNS are:
presence of neurological deficit, age and general condition of the patient, number of metastases, size of the lesion, localization, status of the primary tumor 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%

CNS metastasis radiotherapy

- **Whole brain radiotherapy (WBRT) with or without surgery**
- **WBRT with or without stereotactic radiosurgery**
- **Surgery with or without RT (localized or WBRT)**
- **Stereotactic radiosurgery**

- Doses and fractionation

- **Whole brain radiotherapy:**
 - 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 radioterapy:** 40Gy in 20 fractions, during 4 weeks
- **Stereotactic radiosurgery:** 17 Gy in one fraction

Palliative radiotherapy of the chest

- Cough, chest pain or hemoptysis
 - Bone, lung or skin metastases
 - Vena cava syndrome (SVCS)
 - In patients with ECOG PS 0–1 who are not candidates for curative radiotherapy
-
- Effective in 60% of NSCLC patients and 80% of SCLC patients
 - TD 16Gy / 2 fractions or 10Gy / 1 fraction
 - ECOG PS 0 or 1 - consider also 20 Gy / 5 fractions, 30 Gy / 10 fractions or 36 Gy / 12 fractions

Palliative radiotherapy of head and neck tumors

- Locally/locoregionally advanced disease in order to relieve symptoms
- Bleeding
- Pain
- Obstruction of the aero-digestive tract
- Distant metastases (bones, endocranium)

Prohemostatic palliative radiotherapy

BT and/or EBRT

- Bladder cancer with massive hematuria
- Massive bleeding in gynecological cancer patients
- Rectorage
- Hemoptysis

RADIOTHERAPY OF THE GERIATRIC POPULATION

Challenges in radiotherapy treatment in the elderly

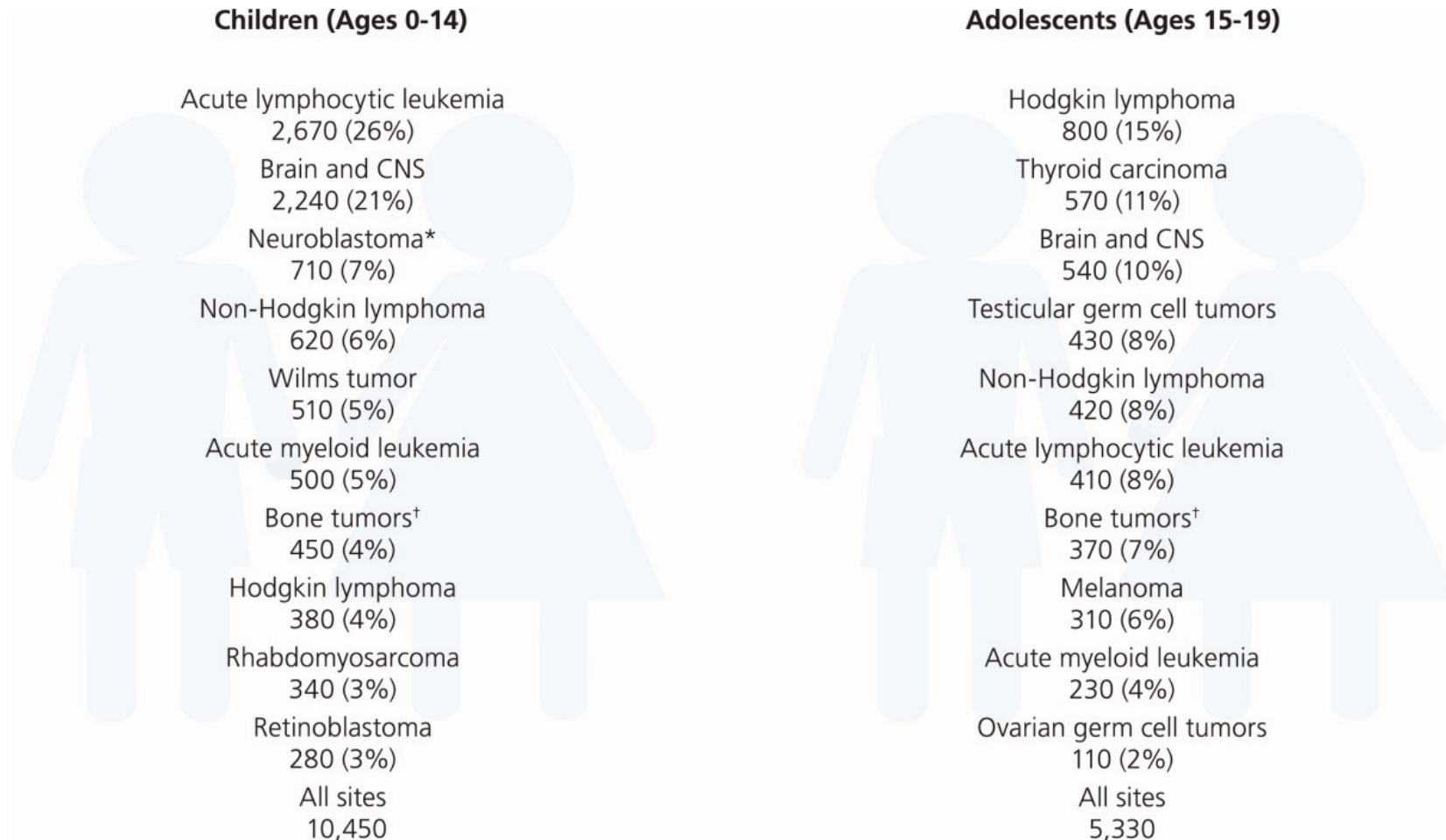
- General condition of the patient
- Characteristics of locoregional tumor growth
- Risk assessment due to comorbidities
- Assessment of functional reserves of organic systems

Radiotherapy specifics in the geriatric population

- Dose reduction
- Choosing the right radiotherapy technique
- The right choice of fractionation mode
- Decision on patient eligibility for RT
- Consider expected survival
- Implementation of RT in ambulatory or hospital settings

RADIOTHERAPY OF TUMORS IN PEDIATRIC POPULATION

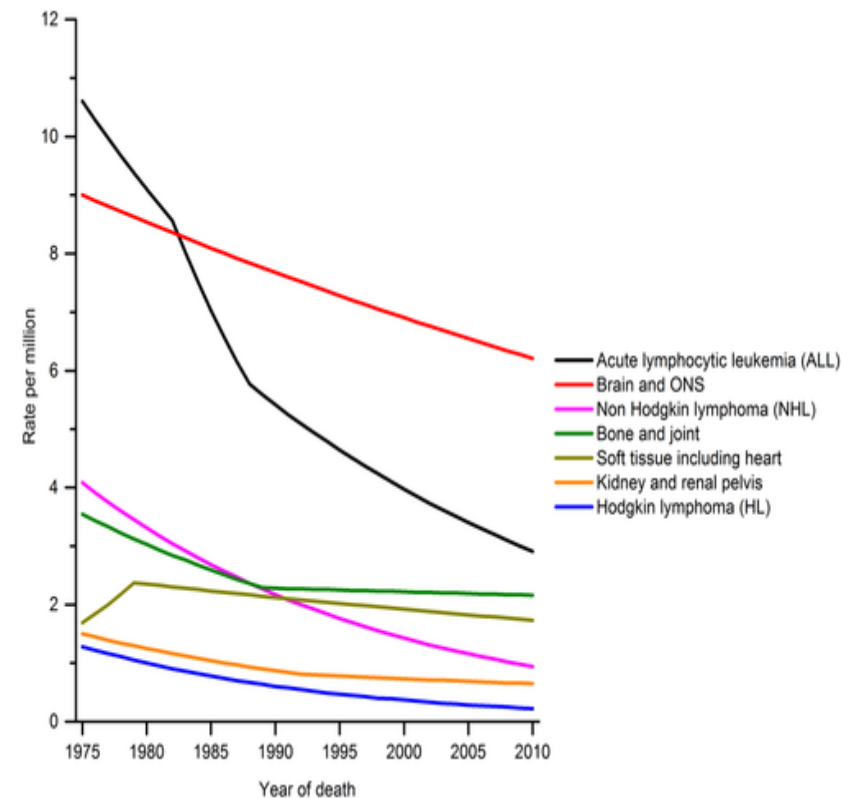
The most common tumors in children



Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014 Mar-Apr;64(2):83-103.

Epidemiology

- National Cancer Institute, the Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries- 15,780 new cases diagnosed annually
- Approximately 1 child in 500 will develop cancer before the age of 15



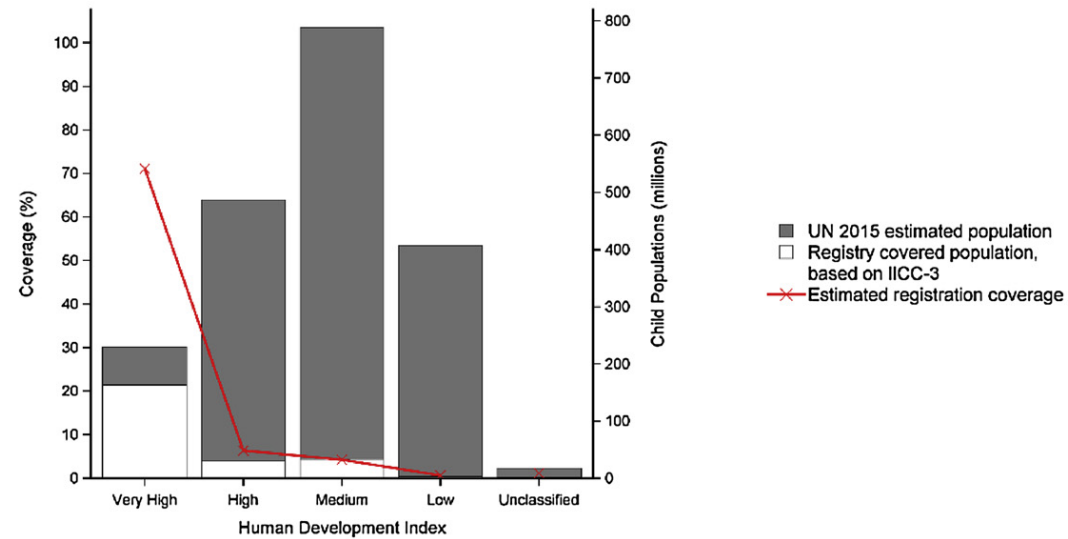
Trend stope mortaliteta

In 2015, a total of 360,114 childhood cancers were diagnosed in the world, of which 54% were diagnosed in Asia and 28% in Africa.

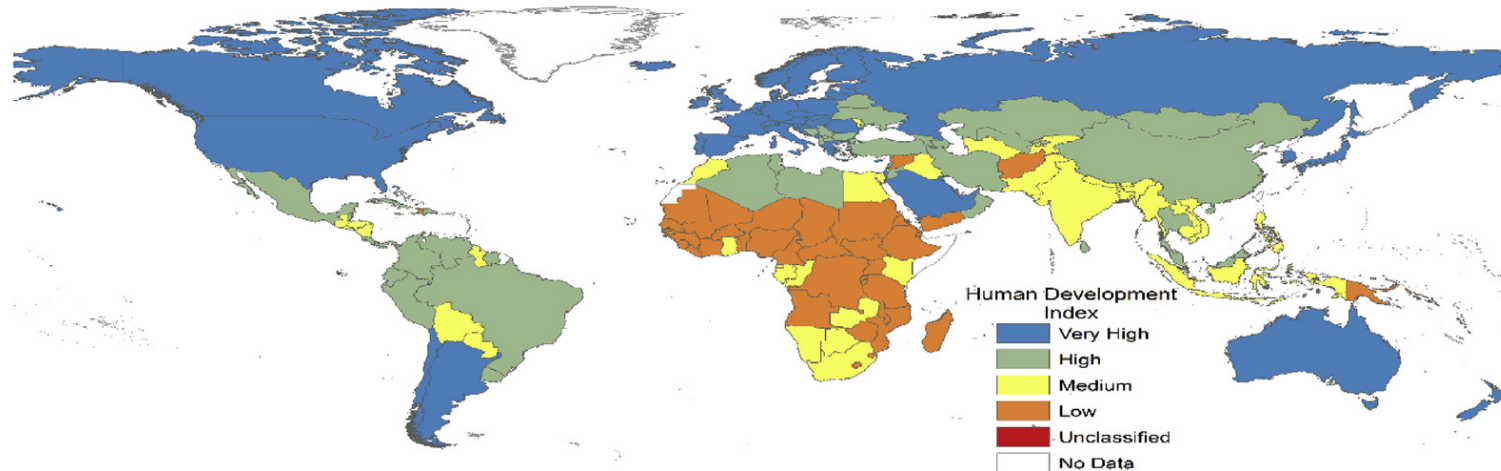
The estimated standardized rates ranged from
~178 cases per million in Europe and North America, to
~218 cases per million in West and Central Africa.

Distribution of newly diagnosed tumors in children

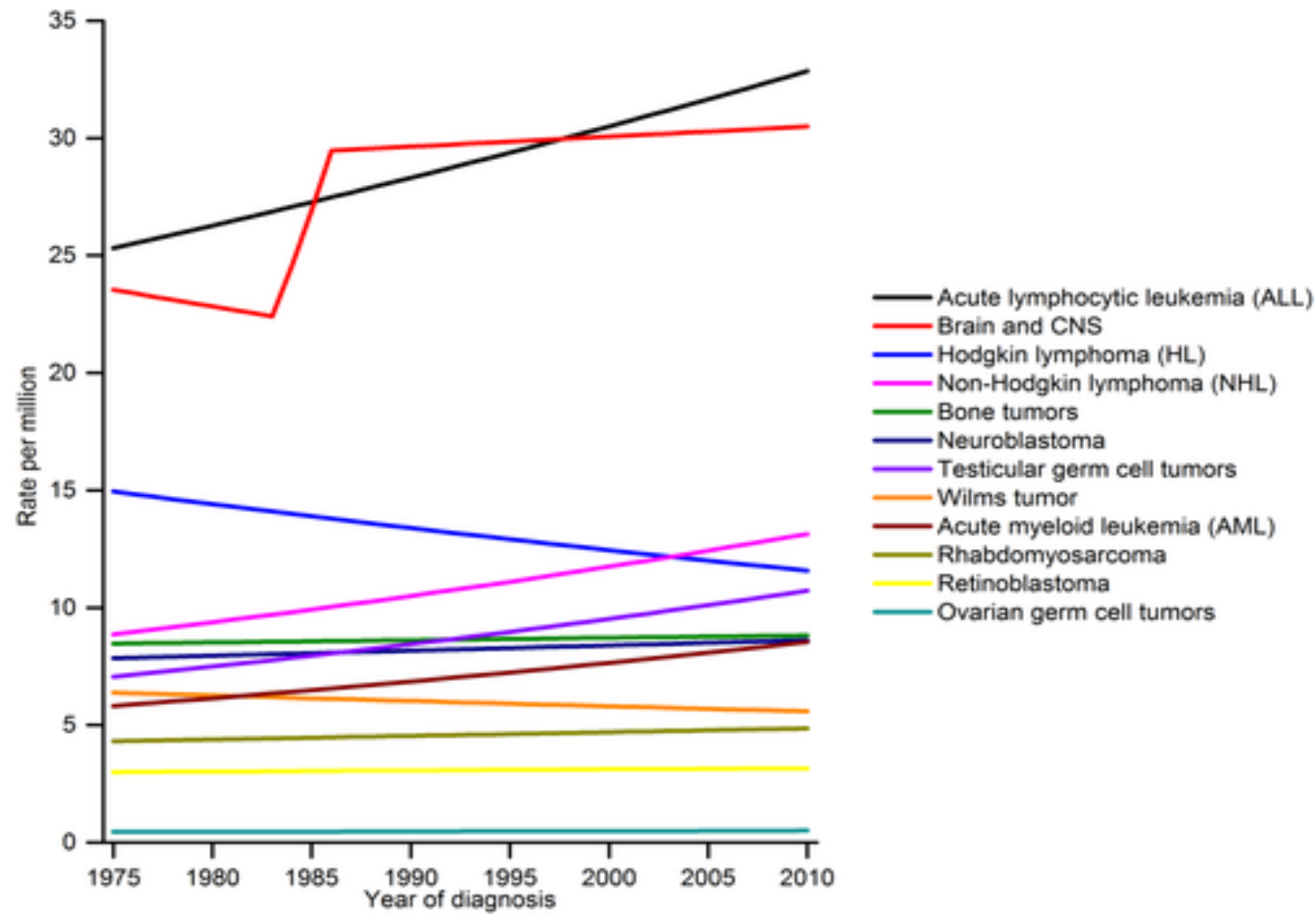
A



B



Incidence trends of pediatric tumors



- The prognosis of tumors in children is different from tumors in adults
- Most tumors in childhood are determined by high radiosensitivity
- Modern treatment regimens ensure longer survival and now more than 2/3 have long-term survival
- RT is used in 40-50% of children with tumors, in addition to CHT and surgery
- In addition to success in treatment, it is particularly important to apply all procedures to reduce late sequelae to the smallest possible extent
- **Late effects of RT**: soft tissue hypoplasia, bone growth retardation, CNS neuropsychological effects, and radiation-induced secondary tumors
- Use of **CHT associated with late effects** of therapy (late myocardial damage due to anthracycline administration, nephrotoxicity due to cisplatin and ifosfamide and secondary leukemia due to alkylating agents)

Radiotherapy of tumors in children - general aspects

- It is carried out in highly specialized centers
- The radiotherapy team consists of: a pediatric radiation oncologist, a medical physicist, a radiation technician and a nurse
- Smaller daily doses per fraction (1.2-1.8 Gy)

The patient and family are involved in the treatment process.

- RT in children up to 3-4 years of age requires the use of short-term general anesthesia
- Mandatory rigorous quality control
- Avoid using large fields whenever possible



HHS Public Access

Author manuscript

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Clin Oncol (R Coll Radiol). 2019 March ; 31(3): 199–207. doi:10.1016/j.clon.2019.01.002.

Pediatric Normal Tissue Effects in the Clinic (PENTEC): an international collaboration to analyze normal tissue radiation dose-volume-response relationships for pediatric cancer patients

Louis S. Constine^a, Cécile M. Ronckers^{b,c}, Chia-Ho Hua^d, Arthur Olch^e, Leontien C. M. Kremer^{b,c}, Andrew Jackson^f, Soren M. Bentzen^g

Highlights

- RT for pediatric cancer can cause long-term adverse normal tissue effects
- Radiation damage depends on the radiation dose and volume, and developmental status
- For some organs, chemotherapy can exacerbate the effects of radiation
- PENTEC seeks to increase knowledge about pediatric RT dose constraints for organs
- Radiation dosimetric data should be precisely reported in pediatric RT studies

Leukemias in childhood

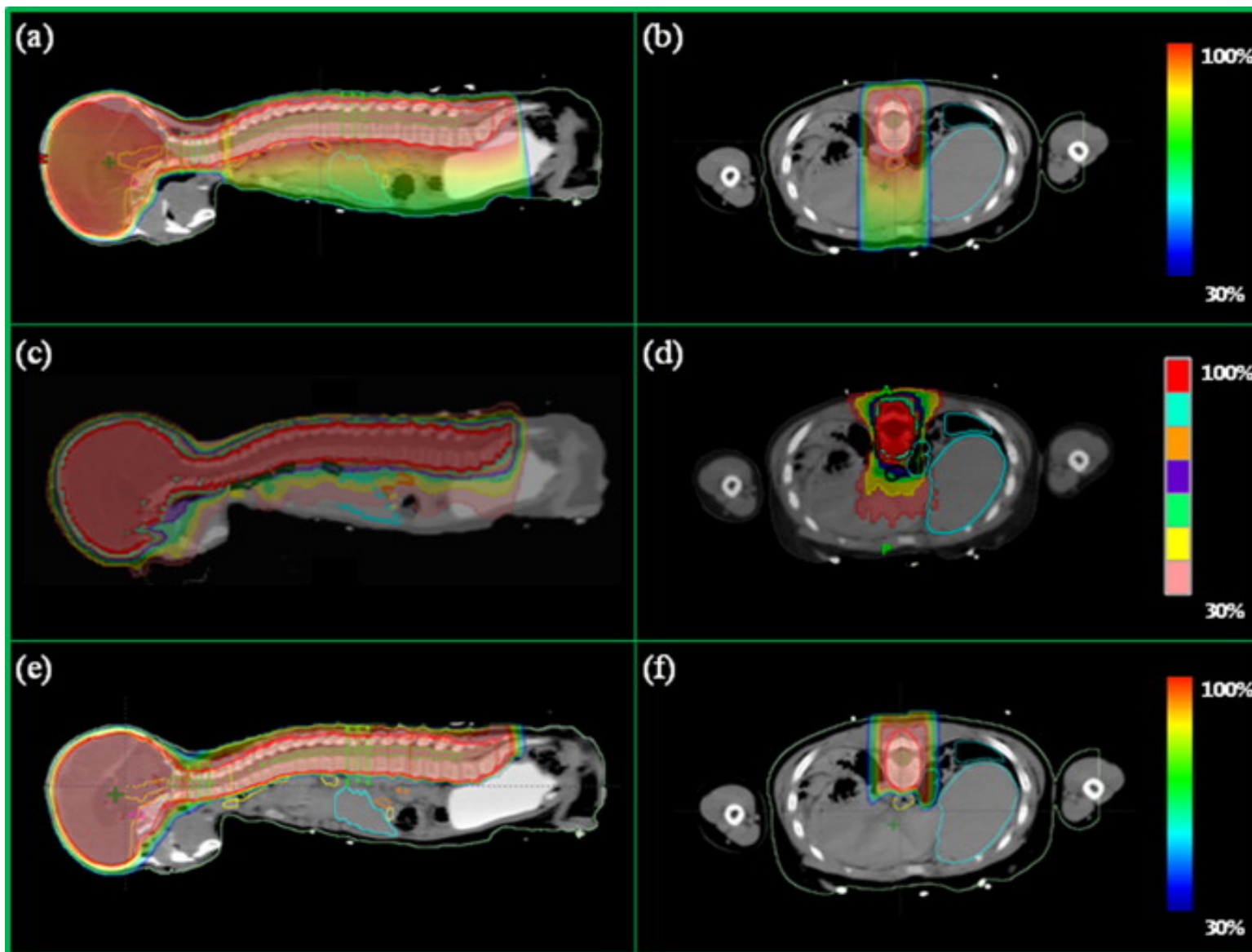
- The most common malignant disease in children (30% of childhood malignancies)
- 4000 new cases in the world annually
- ALL (80%), AML (15-20%), CML (5%)

Treatment of leukemia

- **Surgery** is not used
- **Systemic CHT**
- **Radiotherapy**
- Prophylactic WBRT of the CNS in 10-15% of patients with ALL (Intrathecal administration of CHT is preferred to avoid toxicity)
- Cranial and craniospinal RT in disease relapse

Cranial and craniospinal radiotherapy in leukemia patients

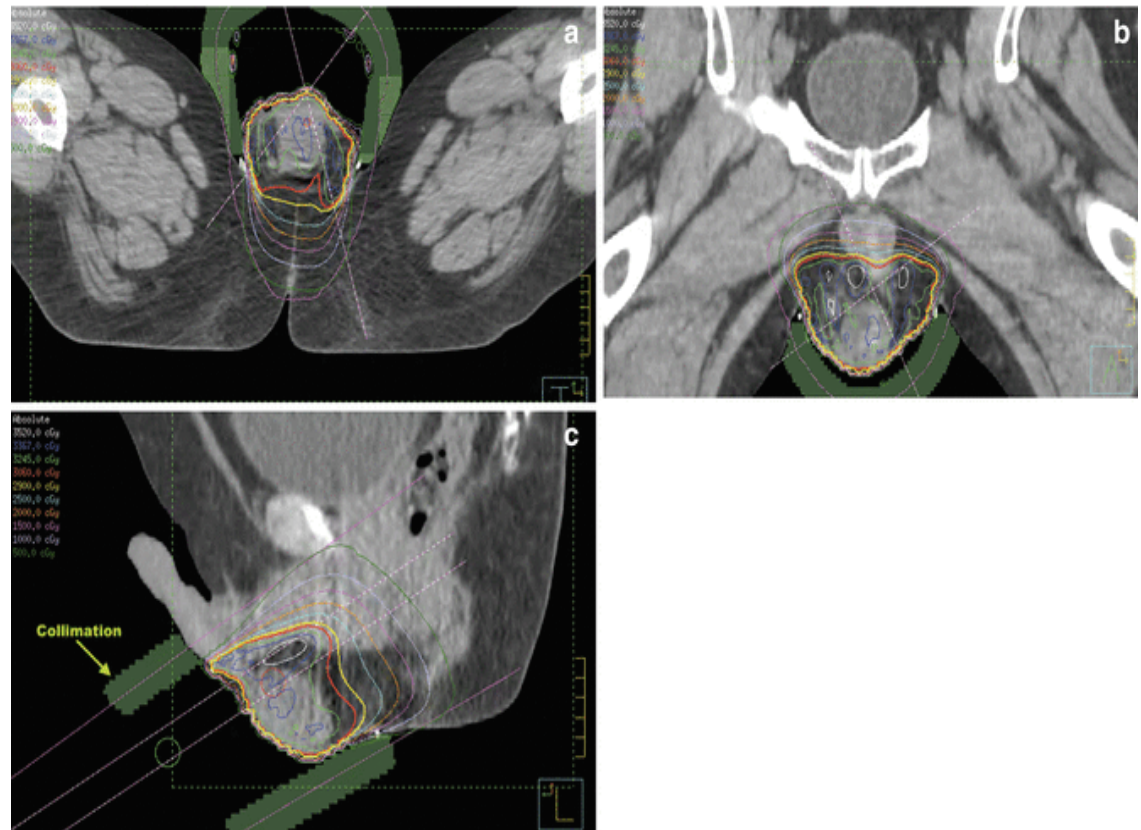
- Delineation of target volume structures for prophylactic and therapeutic RT
- CTV (entire endocranium, both retrobulbar spaces, skull base, C1-C2)
- CTVsp (dural sac with intervertebral openings, cranial border of the lower edge of CTVcr, caudal 2cm below the end of the dural space)
- PTV = CTV + 5mm
- OAR (eye lens, spinal vertebrae, spinal cord)
- Prophylactic dose 12 Gy (1.2 Gy per fraction)
- Therapeutic cranial dose 18 - 24 Gy (1.5 Gy per fraction)
- Spinal dose 6-18 Gy (1.8-2 Gy per fraction)



Yoon M, et al. Craniospinal irradiation techniques: a dosimetric comparison of proton beams with standard and advanced photon radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;81(3):637-46.

Testicular radiotherapy in leukemia patients

- Indications:
- Residual testicular disease persists after CHT
- Relapse of the testicles
- TD 24 Gy (2Gy per fraction)



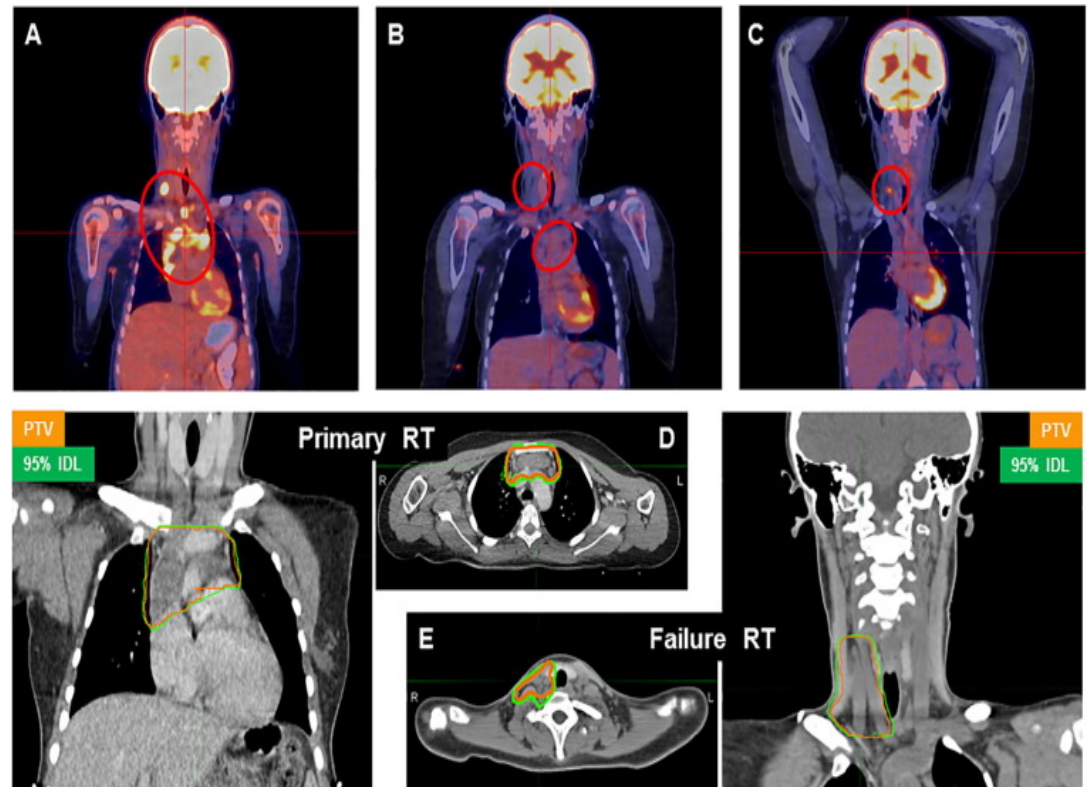
Dostupno na: Primary Testicular Lymphoma. At: <https://oncohemakey.com/primary-testicular-lymphoma/>

Hodgkin's lymphoma in childhood

- Over 80% older than 10 years
- Enlargement of neck LN, mediastinum, supraclavicular LN
- 25-30% B symptomatology
- 10% diagnosed in the IV stage

Treatment

- HT (MOPP, ABVD, ABVD/MOPP, GPOH-HD95, BEACOPP)
- PR or CR – RT applied



Tinkle CL, et al. Treatment patterns and disease outcomes for pediatric patients with refractory or recurrent Hodgkin lymphoma treated with curative-intent salvage radiotherapy. *Radiother Oncol* 2019;134:89-95.

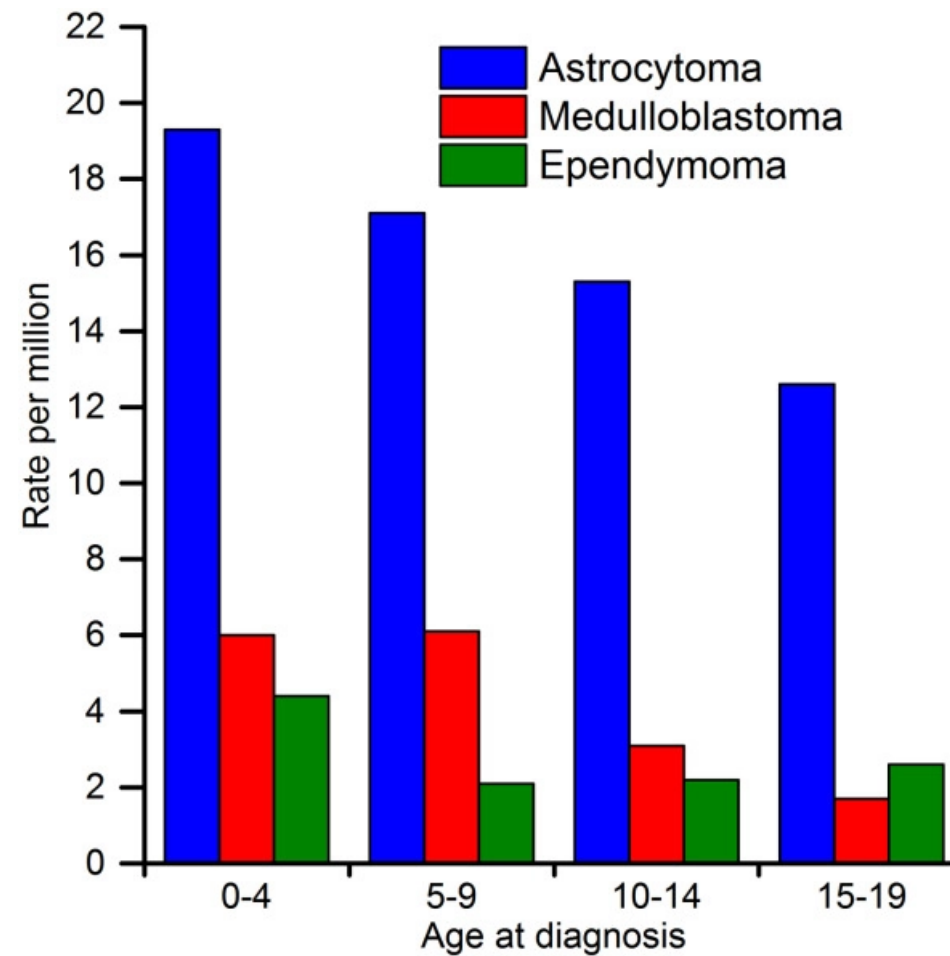
- **RT contraindications:** low risk patients, complete remission after HT
- **Indications for RT:**
- PR after HT = RT with TD 15-25 Gy (1.8 Gy per fraction)
- Intermediate and High risk patients = RT regardless of the achieved effect of CHT with TD 15-25 Gy

- Residual disease after HT= IF technique with TD 20-36 Gy
- Disease relapse after HT= IF technique with TD 20-36 Gy

Tumors of the central nervous system in childhood

- Brain tumors in children account for 20% of tumors in pediatric population
- The 5-year survival is about 50%, which is lower than for other pediatric tumors
- Cured children have sequelae either from the tumor or oncological treatment or both
- CHT has not yet contributed to a significant improvement in survival for most pediatric CNS tumors
- Neuro-oncology multidisciplinary team

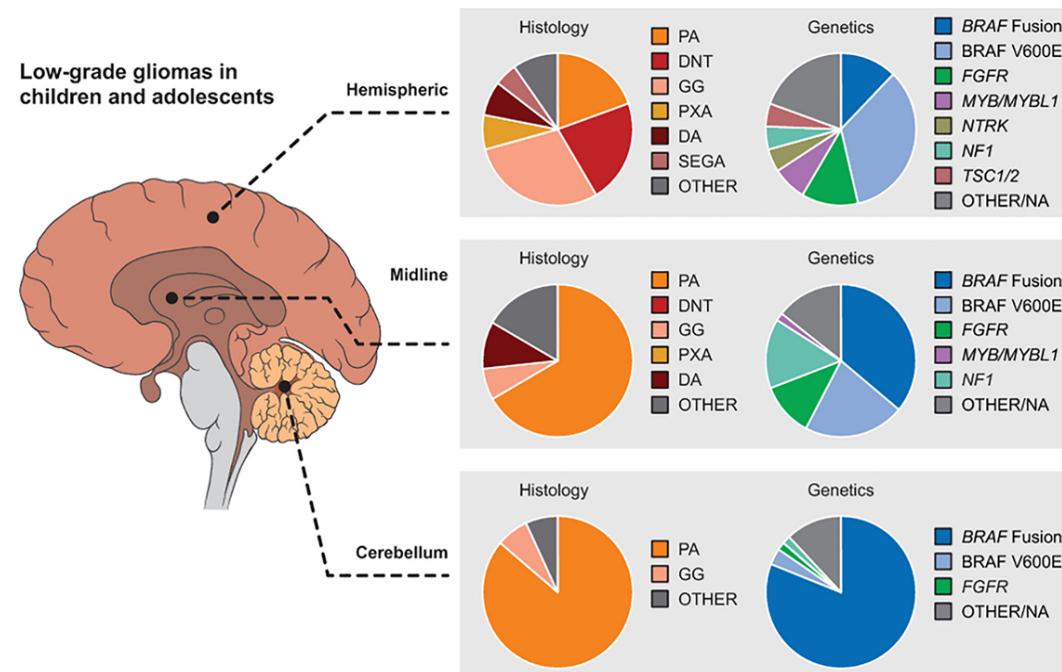
Frequency of certain tumors of the CNS in children



Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014 Mar-Apr;64(2):83-103.

Low-grade gliomas

Low-grade gliomas radiotherapy is based on precise imaging to define target volumes



Radiotherapy techniques for low-grade gliomas

Position and immobilization

Supination or pronation depending
on the anatomy, immobilization -
head mask

Target volumes

GTV - visible tumor on imaging (T2 or
"Flair" MRI, fusion with CT)

CTV – in case of surgical resection,
the brain tissue that surrounded
the tumor with a margin of 0.5
cm for potential spread

54Gy in 30 fractions with 1.8Gy per
day

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

Download

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)

Medulloblastoma

WNT-activated
SHH-activated
non SHH non
WNT

- Tendency to spread via cerebrospinal fluid
- 5-year survival for medulloblastoma 60-70% and similar supratentorial localized tumors 40-50%

Medulloblastoma

- Surgical resection followed by craniospinal RT with a boost dose applied to the primary tumor site
- Standard application of adjuvant chemotherapy (Vincristine, CCNU, Cisplatin)

More recent studies also consider prognostic groups: standard and high risk

Standard risk group (age >3 years, postoperative residual tumor <1.5 cm², no signs of dissemination). The percentage of five-year disease free survival is 80%.

High-risk group (age < 3 years, postoperative residual tumor >1.5 cm², metastatic disease, subtotal resection or biopsy only, male sex). Local relapse often occurs.

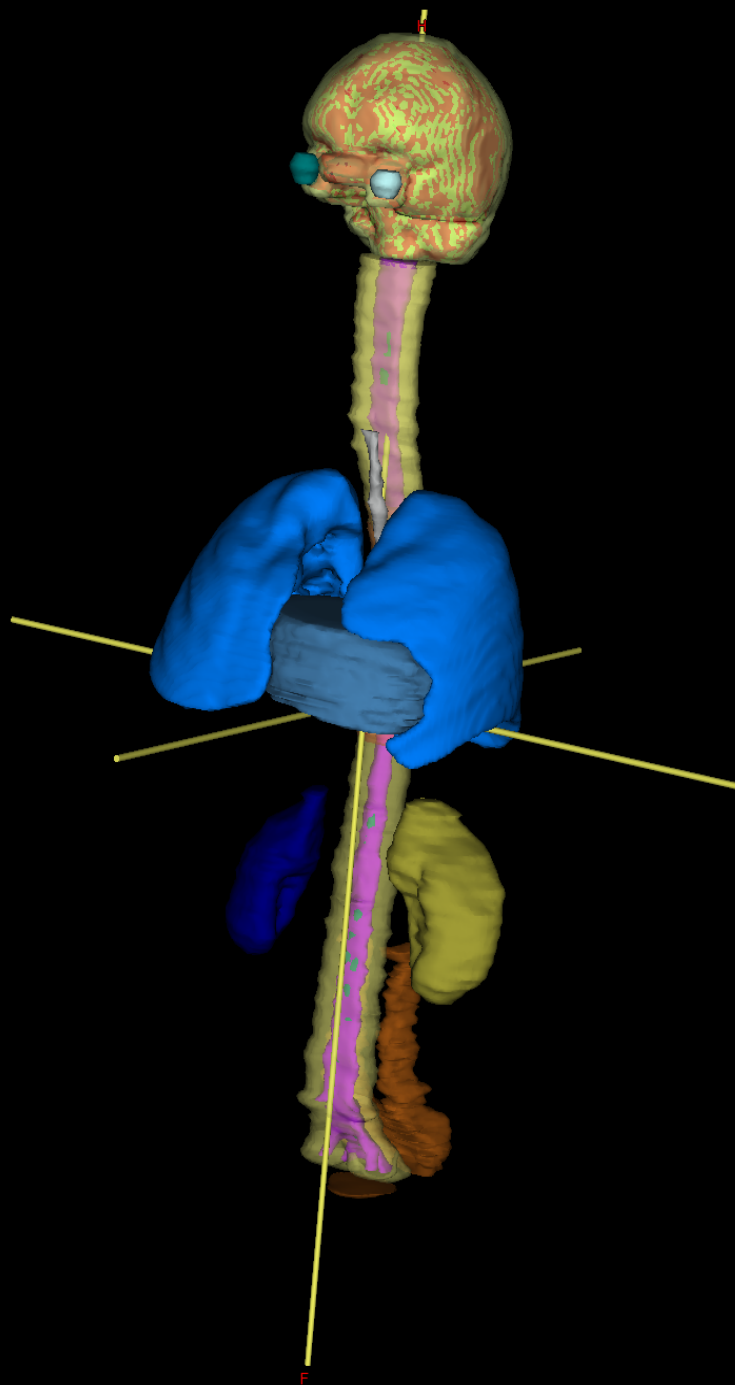
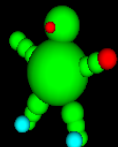
Risk	Craniospinal dose	Boost to the posterior cranial fossa
Standard	23,4 Gy in 13 fractions	54-55,8 Gy
High	36-39,6 Gy in 20-22 fractions	54-55,8 Gy

Craniospinal radiotherapy (CSRT) of medulloblastoma

- CSRT is one of the most complex radiotherapy technique
- Patient position and immobilization
- Most often, pronation with a head mask, although supination with immobilization of the body is also possible



R



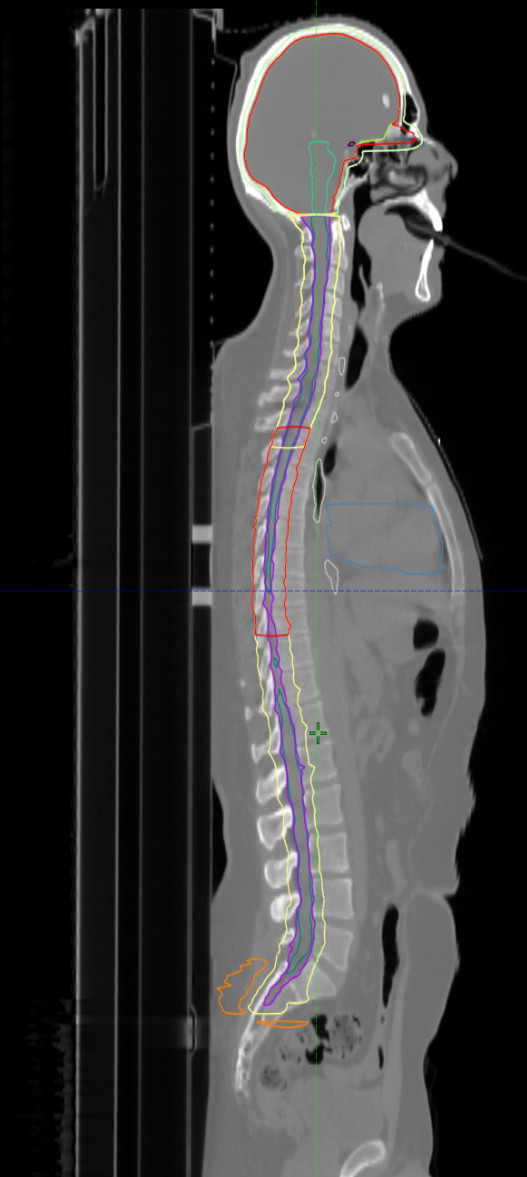


CT Image
CT_2.3.2022
02.03.2022

CT_1
CT
11.02.2022

CT_2.3.2022
CT
02.03.2022

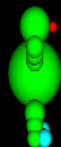
H



50.0 cm

P

A



X: 0.38 cm

F

(oncologylaca 08.03.2022 08:30)



Doses [cGy]

6687.5
6250.0
5937.5
5625.0
5000.0
✓ 1926.0
✓ 1710.0

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.

R

H

1950.1 cGy

L

F

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

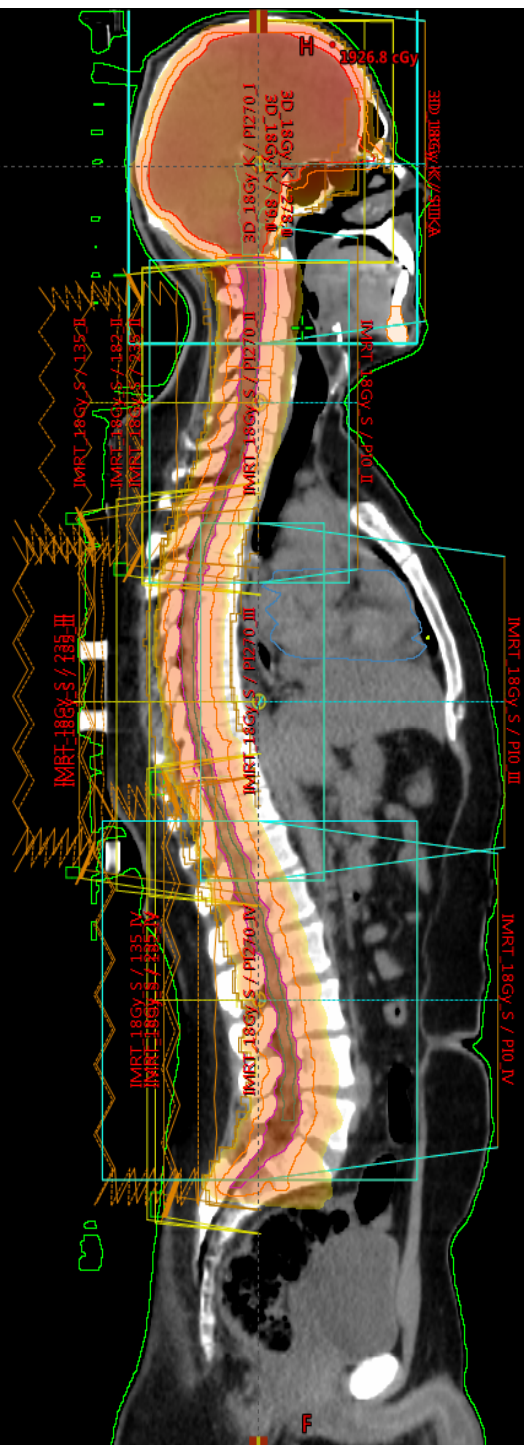
0.0

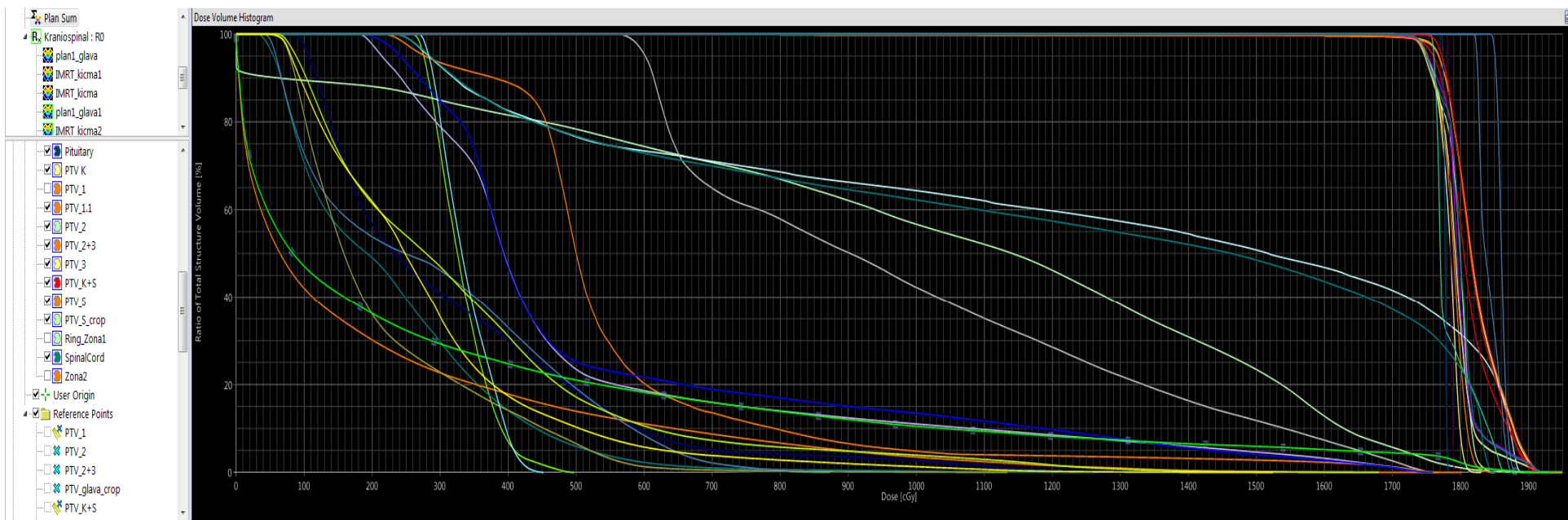
P

Standard

Head First-Supine

X: 0.24 cm

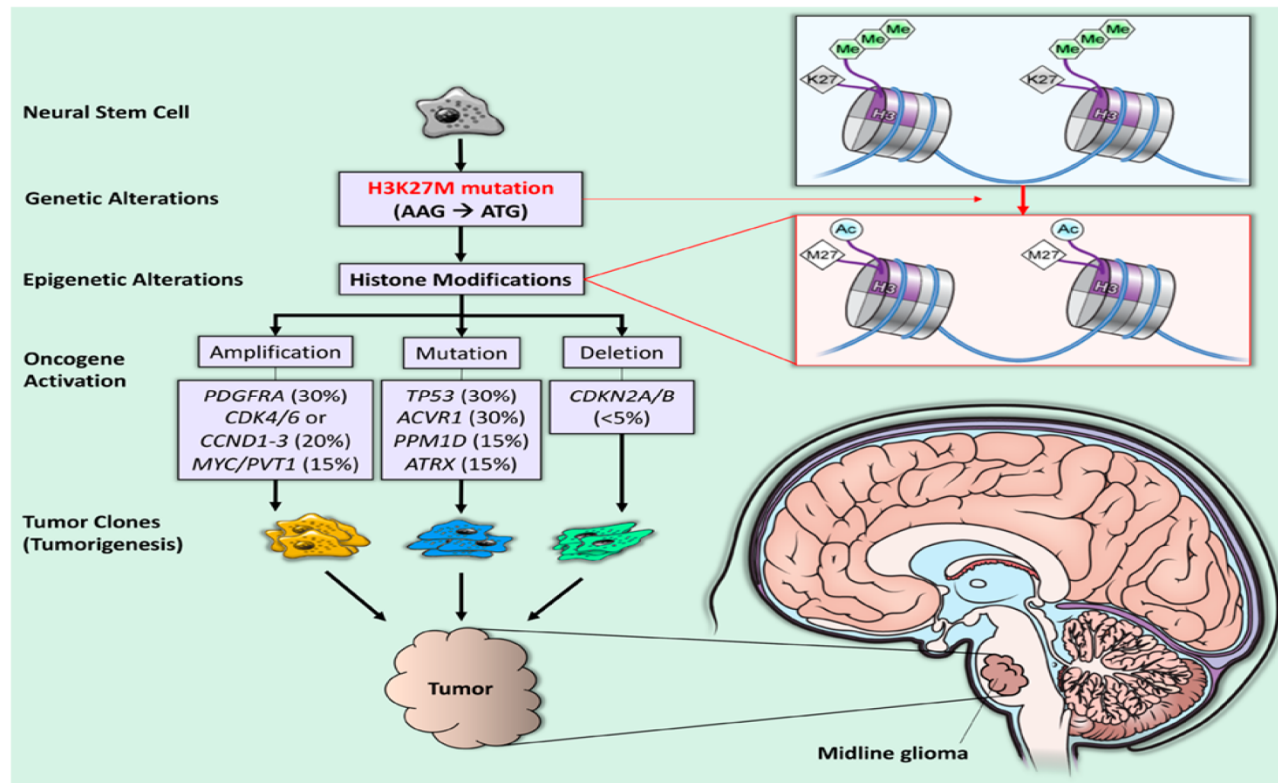




Dose Reference Points Dose Statistics											
Show DVH	Structure	Approval Status	Plan	Course	Volume [cm ³]	Dose Cover [%]	Sampling Cover [%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]	
<input checked="" type="checkbox"/>	Liver	Approved	Plan Sum	1	2498.9	100.0	100.0	30.9	1268.6	226.9	
<input checked="" type="checkbox"/>	BODY	Approved	Plan Sum	1	85528.6	100.0	100.1	0.0	1950.1	315.5	
<input checked="" type="checkbox"/>	Lung_L	Approved	Plan Sum	1	1014.2	100.0	100.0	47.7	1525.2	280.1	
<input checked="" type="checkbox"/>	Lung_R	Approved	Plan Sum	1	1376.1	100.0	100.0	58.4	1681.2	335.4	
<input checked="" type="checkbox"/>	SpinalCord	Approved	Plan Sum	1	52.4	100.0	99.9	1673.4	1933.3	1800.6	
<input checked="" type="checkbox"/>	CTVx	Approved	Plan Sum	1	1515.6	100.0	100.0	403.4	1920.0	1819.9	
<input checked="" type="checkbox"/>	Lens_R	Approved	Plan Sum	1	0.2	100.0	98.8	258.3	497.7	332.2	
<input checked="" type="checkbox"/>	Lens_L	Approved	Plan Sum	1	0.2	100.0	99.9	268.2	451.8	338.5	
<input checked="" type="checkbox"/>	Eye_L	Approved	Plan Sum	1	8.8	100.0	100.1	229.9	1853.2	1213.1	
<input checked="" type="checkbox"/>	Eye_R	Approved	Plan Sum	1	9.0	100.0	100.1	234.8	1890.0	1253.7	
<input checked="" type="checkbox"/>	OpticNerve_L	Approved	Plan Sum	1	0.3	100.0	100.4	1819.4	1876.7	1841.4	
<input checked="" type="checkbox"/>	OpticNerve_R	Approved	Plan Sum	1	0.4	100.0	100.5	1845.3	1880.2	1860.7	
<input checked="" type="checkbox"/>	Pituitary	Approved	Plan Sum	1	0.0	100.0	101.9	1772.2	1782.1	1777.4	
<input checked="" type="checkbox"/>	Chiasm	Approved	Plan Sum	1	0.4	100.0	100.1	1779.5	1791.6	1785.5	
<input checked="" type="checkbox"/>	BrainStem	Approved	Plan Sum	1	24.0	100.0	100.0	1753.3	1866.9	1785.6	
<input checked="" type="checkbox"/>	Parotid_L	Approved	Plan Sum	1	27.4	100.0	100.1	182.5	1759.6	537.0	
<input checked="" type="checkbox"/>	Parotid_R	Approved	Plan Sum	1	25.3	100.0	100.1	178.2	1759.2	510.9	
<input checked="" type="checkbox"/>	Mandible	Approved	Plan Sum	1	68.0	100.0	99.9	193.2	1767.8	560.9	
<input checked="" type="checkbox"/>	Esophagus	Approved	Plan Sum	1	28.6	100.0	100.2	560.7	1754.7	980.9	
<input checked="" type="checkbox"/>	CTVs	Approved	Plan Sum	1	154.6	100.0	100.0	1622.4	1933.3	1798.3	
<input checked="" type="checkbox"/>	Heart	Approved	Plan Sum	1	894.7	100.0	100.0	40.0	873.4	289.1	
<input checked="" type="checkbox"/>	Kidney_L	Approved	Plan Sum	1	278.4	100.0	100.0	51.8	1134.8	214.4	
<input checked="" type="checkbox"/>	Kidney_R	Approved	Plan Sum	1	239.2	100.0	100.0	74.1	1283.7	318.8	
<input checked="" type="checkbox"/>	PTV_S_crop	Approved	Plan Sum	1	954.0	100.0	100.0	1637.0	1930.5	1794.0	
<input checked="" type="checkbox"/>	PTV_K	Approved	Plan Sum	1	1926.8	100.0	100.0	291.8	1928.5	1818.4	
<input checked="" type="checkbox"/>	PTV_1	Approved	Plan Sum	1	2058.0	100.0	100.0	291.8	1950.1	1819.3	
<input checked="" type="checkbox"/>	PTV_2	Approved	Plan Sum	1	354.9	100.0	100.0	1684.0	1851.4	1794.2	
<input checked="" type="checkbox"/>	PTV_3	Approved	Plan Sum	1	479.6	100.0	100.0	1637.0	1831.4	1782.4	
<input checked="" type="checkbox"/>	PTV_K+S	Approved	Plan Sum	1	2899.6	100.0	100.0	291.8	1950.1	1810.0	
<input checked="" type="checkbox"/>	Ring_Zona1	Approved	Plan Sum	1	3886.7	100.0	99.7	0.0	1917.0	1009.3	
<input checked="" type="checkbox"/>	Zona2	Approved	Plan Sum	1	78041.4	100.0	100.1	0.0	1802.8	202.9	
<input checked="" type="checkbox"/>	PTV_2+3	Approved	Plan Sum	1	836.3	100.0	100.0	1637.0	1851.4	1787.4	
<input checked="" type="checkbox"/>	PTV_1.1	Approved	Plan Sum	1	2050.9	100.0	100.0	291.8	1950.1	1819.3	
<input checked="" type="checkbox"/>	PTV_5	Approved	Plan Sum	1	970.0	100.0	100.0	1463.0	1950.1	1793.5	

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



Brainstem tumors

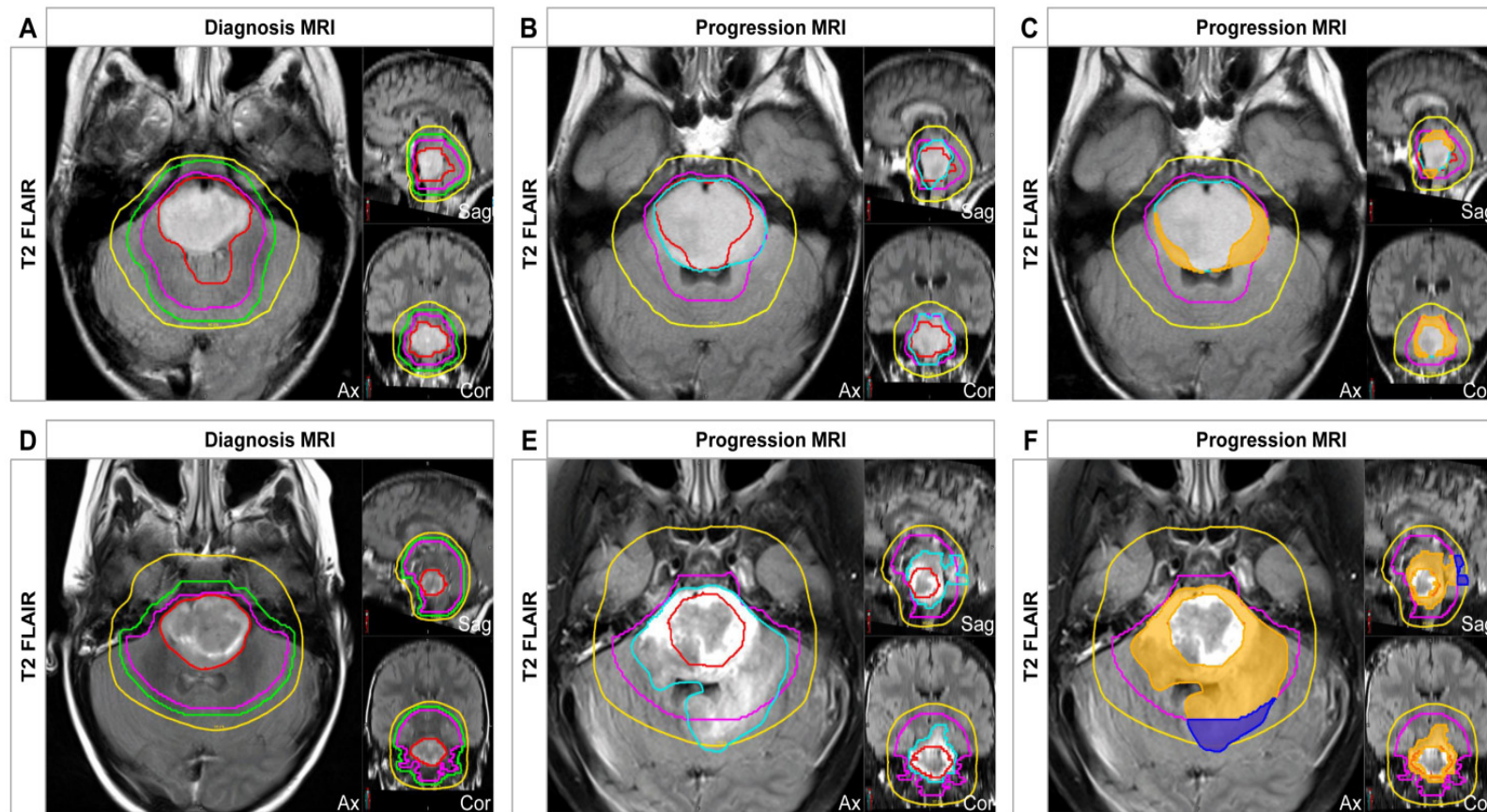
- Include tumors of the midbrain, pons and medulla.
- Focal (5-10%), dorsal exophytic (10-20%), cervicomedullary (5-10%) and diffuse tumors (75-85%).
- Focal, dorsal exophytic and cervicomedullary tumors are usually low grade astrocytomas.
- Treatment:
- **Surgical excision**
- **RT** reserved for inoperable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

Brainstem tumors

- Most children with brainstem tumors have an H3 K27M-mutated diffuse midline glioma, usually a high-grade astrocytoma.
- Typical MRI presentation, and a biopsy is usually risky and contraindicated.
- Poor prognosis - 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.

Radiotherapy techniques

TD54Gy in 30 fractions with 1.8Gy 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.

Rhabdomyosarcoma (RMS) in childhood

- Soft tissue sarcomas account for 7% of all childhood malignancies
- It is the most common soft tissue sarcoma in the first decade of life
- Localization: orbit, nasopharynx, extremities and urogenital system
- It metastasizes hematogenously, to the lungs, liver and bones, and lymphogenously to the regional lymph nodes.
- Three histopathological forms:
- **embryonic RMS** (80% of RMS, urogenital system, children up to 5 years of age, has a favorable prognosis)
- **alveolar RMS** (in children and adolescents, extremities, has a less favorable prognosis)
- **pleomorphic RMS** (in adults).

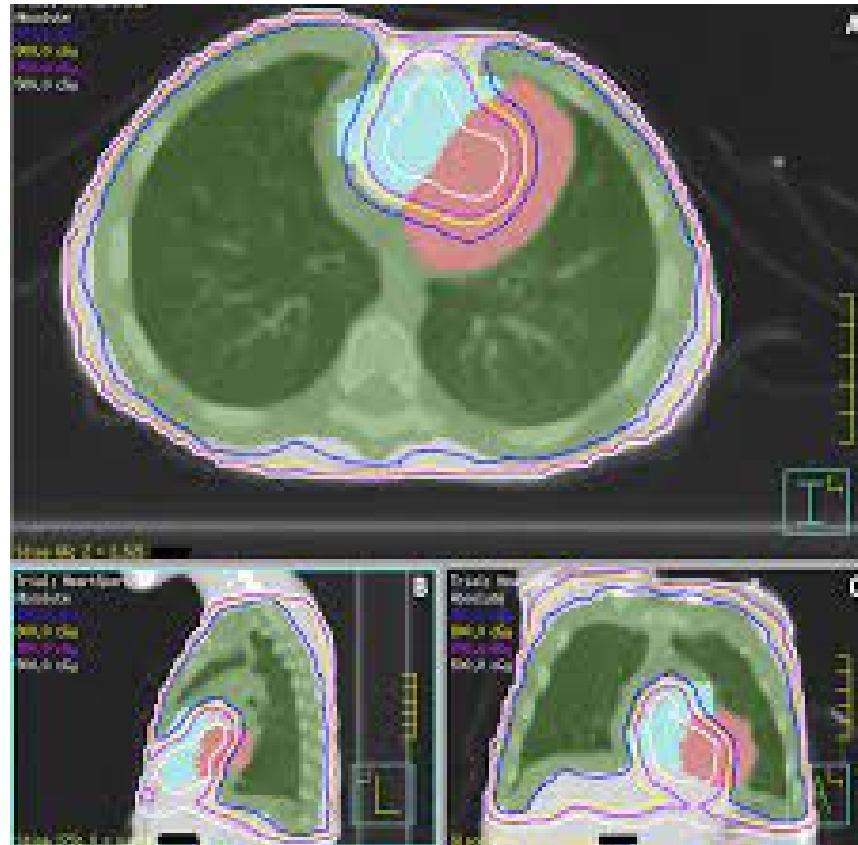
Intergroup Rhabdomyosarcoma Studies (IRS)

- **Group I** - the tumor was completely removed (R0), no malignant cells are present in the regional lymph nodes
- **Group II** - after removal of the tumor at the resection margin (R1), there are microscopic accumulations of residual tumor cells and/or extirpation of pathologically enlarged regional lymph nodes
- **Group III** - localized tumor that cannot be surgically removed in its entirety, macroscopic residual tumor is present at the resection margins (R2)
- **Group IV** - distant metastases are present

Treatment of rhabdomyosarcoma in childhood

- **Surgery**
 - **HT**
 - **RT** (The target volume is defined in accordance with the recommendations of IGRU 50 and IGRU 62)
 - The dose depends on the radicality of the surgical procedure and the locoregional stage of the disease
 - Microscopic residual disease (after R1 resection) – TD 41.4 Gy (1.8 Gy per fraction)
 - Macroscopically present tumor - TD from 50.4 to 54 Gy
 - Unfavorable histological type localized in the orbit - TD 45 Gy
 - Microscopic disease of favorable histological subtype, without spread to regional lymph nodes TD - 36 Gy
-
- GTV (Initial or residual tumor)
 - CTV= GTV + margin 1-2cm
 - PTV = CTV + margin 5-10 mm
 - OAR (depending on localization)

- Lung metastases:
- Whole lung irradiation (WLI) – TD 15 Gy in 10 fractions
- Whole lung irradiation (WLI) – TD 12 Gy in 8 fractions (in children up to 6 years old)



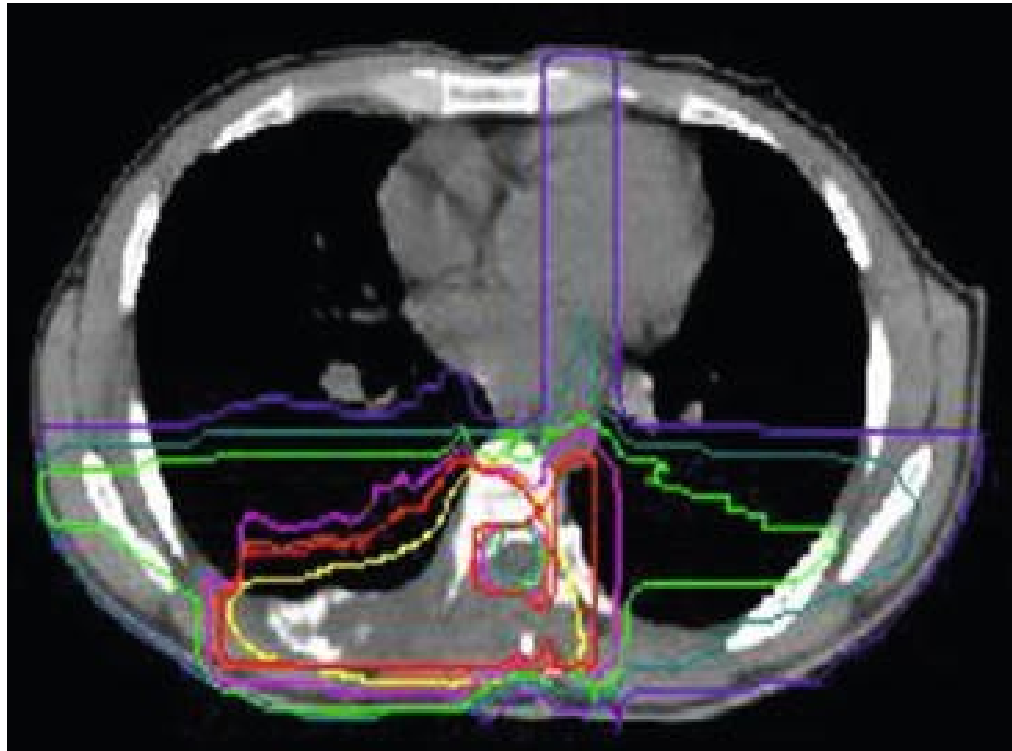
Kalaparakal JA, et al. Cardiac-Sparing Whole Lung IMRT in Patients With Pediatric Tumors and Lung Metastasis: Final Report of a Prospective Multicenter Clinical Trial. *Int J Radiat Oncol Biol Phys* 2019;103(1):28-37.

Bone tumors in children

- The most common solid tumors in adolescents and young adults are second in incidence, behind malignant diseases of the hematopoietic system.
- Half of bone tumors in childhood are malignant.
- **Osteosarcoma** (metaphyses of long bones of the extremity: distal femur, proximal tibia, proximal or middle part of femur, proximal humerus)
- **Ewing sarcoma** (bones of the pelvis, ribs, diaphyses of long bones of the lower limbs)

Bone tumors in children

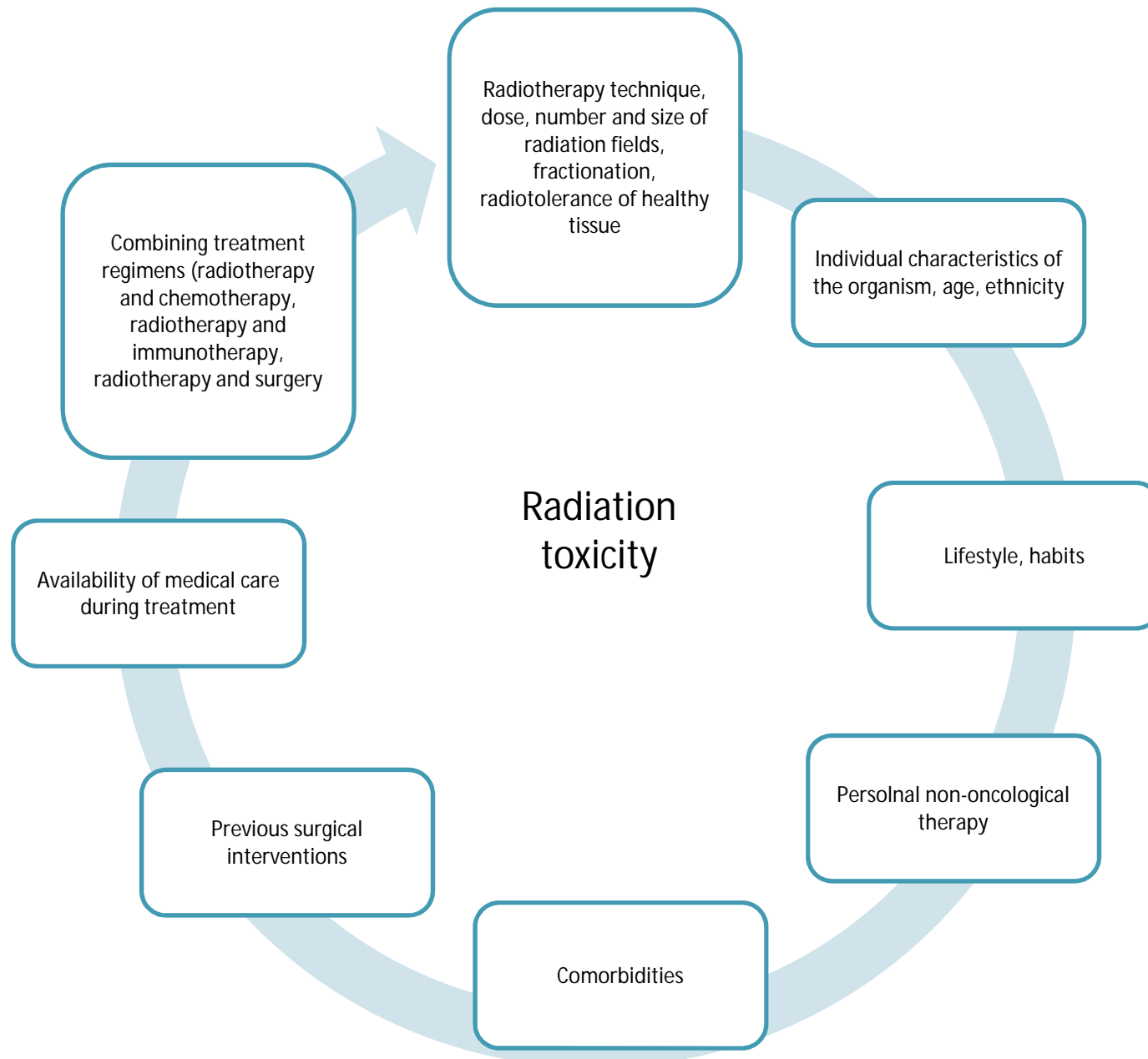
- The advantage of using protons over photons
- RT is carried out according to the same principles as in adults



Matsunobu A, et al; Working Group for Bone and Soft Tissue Sarcomas. Impact of carbon ion radiotherapy for unresectable osteosarcoma of the trunk. Cancer. 2012;118(18):4555-63.

RADIOTHERAPY SIDE EFFECTS

Risk factors for acute and chronic radiation toxicity



Radiation toxicity types

- **Acute** (from the beginning of RT to the 90th day)
- **Chronic** (from the 90th day, months and years after the treatment)
- Hypoplasia of parenchymal cells
- Changes in the microvascular network
- Changes in the connective stroma


- Radiotolerance of organs at risk
- Therapeutic complications
- Dose-volume effects of healthy tissues

The radiosensitivity of normal tissue depends on:

- kinetics of the cell cycle
- mitotic behavior of the cell
- cell differentiation

Organs at risk limits

- Standard fractionation
- Hypofractionation
- Stereotactic radiotherapy
- Radiosurgery

NIH-PA Author Manuscript		NIH Public Access
		Author Manuscript
		<i>Int J Radiat Oncol Biol Phys.</i> Author manuscript; available in PMC 2012 August 31.
		Published in final edited form as: <i>Int J Radiat Oncol Biol Phys.</i> 2010 March 1; 76(3 Suppl): S3–S9. doi:10.1016/j.ijrobp.2009.09.040.
		Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): An Introduction to the Scientific Issues
		Søren M. Bentzen, Ph.D., D.Sc. ^a , Louis S. Constine, M.D. ^b , Joseph O. Deasy, Ph.D. ^c , Avi Eisbruch, M.D. ^d , Andrew Jackson, Ph.D. ^e , Lawrence B. Marks, M.D. ^f , Randall K. Ten Haken, Ph.D. ^d , and Ellen D. Yorke, Ph.D. ^e

Efficiency of radiotherapy vs. radiation toxicity

- Time - Dose - Fraction Factor (TDF)
- Volume of irradiated tissue

Radiotolerance of OAR with conventional fractionation regimen

Radiation toxicity

Deterministic effects - there is a relationship between the absorbed dose and the damage caused

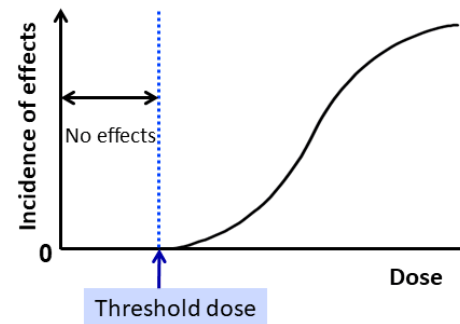
Stochastic effects - there is no correlation between absorbed dose and secondary tumor induction

Deterministic effects

(Hair loss, cataract, skin injury, etc.)

When a number of people were exposed to the same dose of radiation and certain symptoms appear in 1% of them, said dose is considered to be the threshold dose.

(2007 Recommendations of the International Commission on Radiological Protection (ICRP))

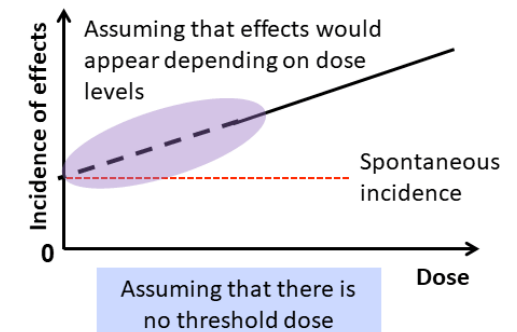


Stochastic effects

(Cancer, leukemia, hereditary effects, etc.)

Effects of radiation exposure under certain doses are not clear because effects of other cancer-promoting factors such as smoking and drinking habits are too large.

However, the ICRP specifies the standards for radiological protection for such low-dose exposures, assuming that they may have some effects as well.



Deterministic Effects (Tissue Reactions) and Stochastic Effects. Dostupno na:
<https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-01-04.html>

Criteria for assessing the presence and intensity of radiotherapy side effects

- Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0)
- Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC)
- Late Effects Normal Tissue Task Force (LENT)-Subjective, Objective, Management, Analytic (SOMA) scales

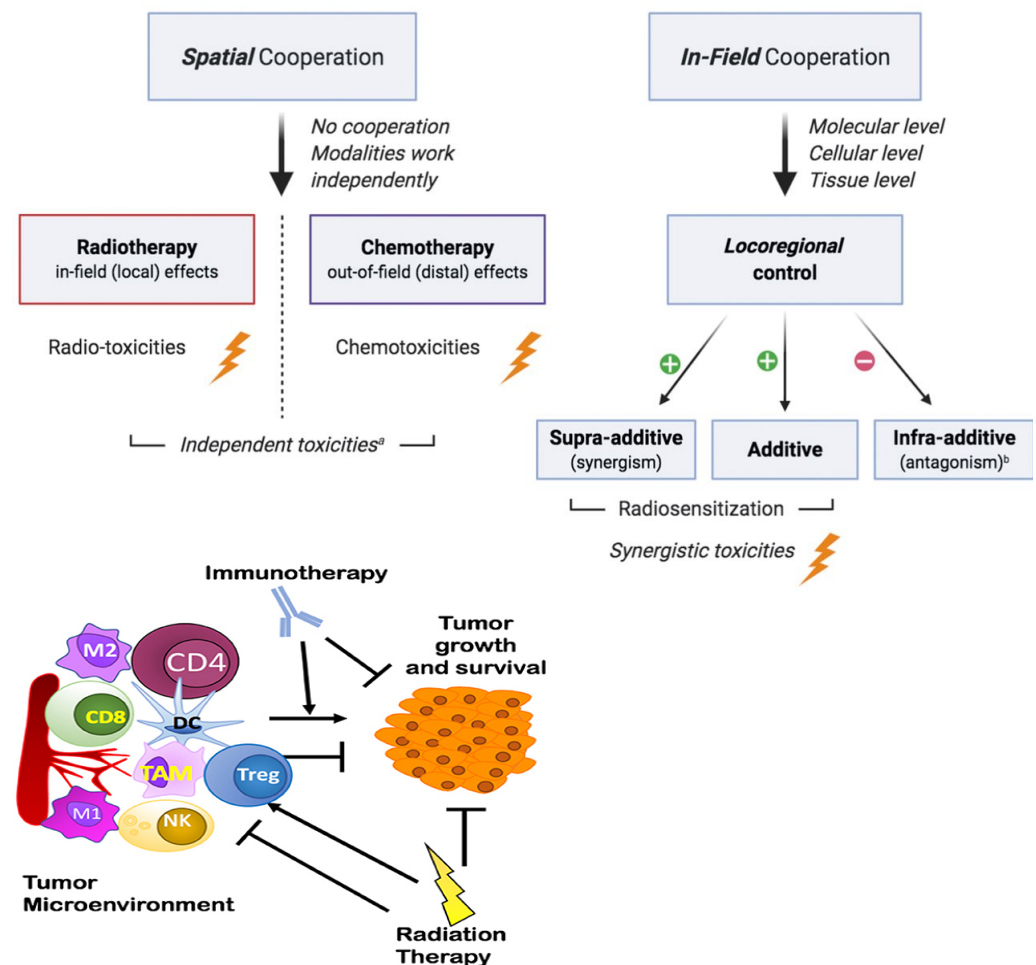
Combined treatment modalities and radiation toxicity

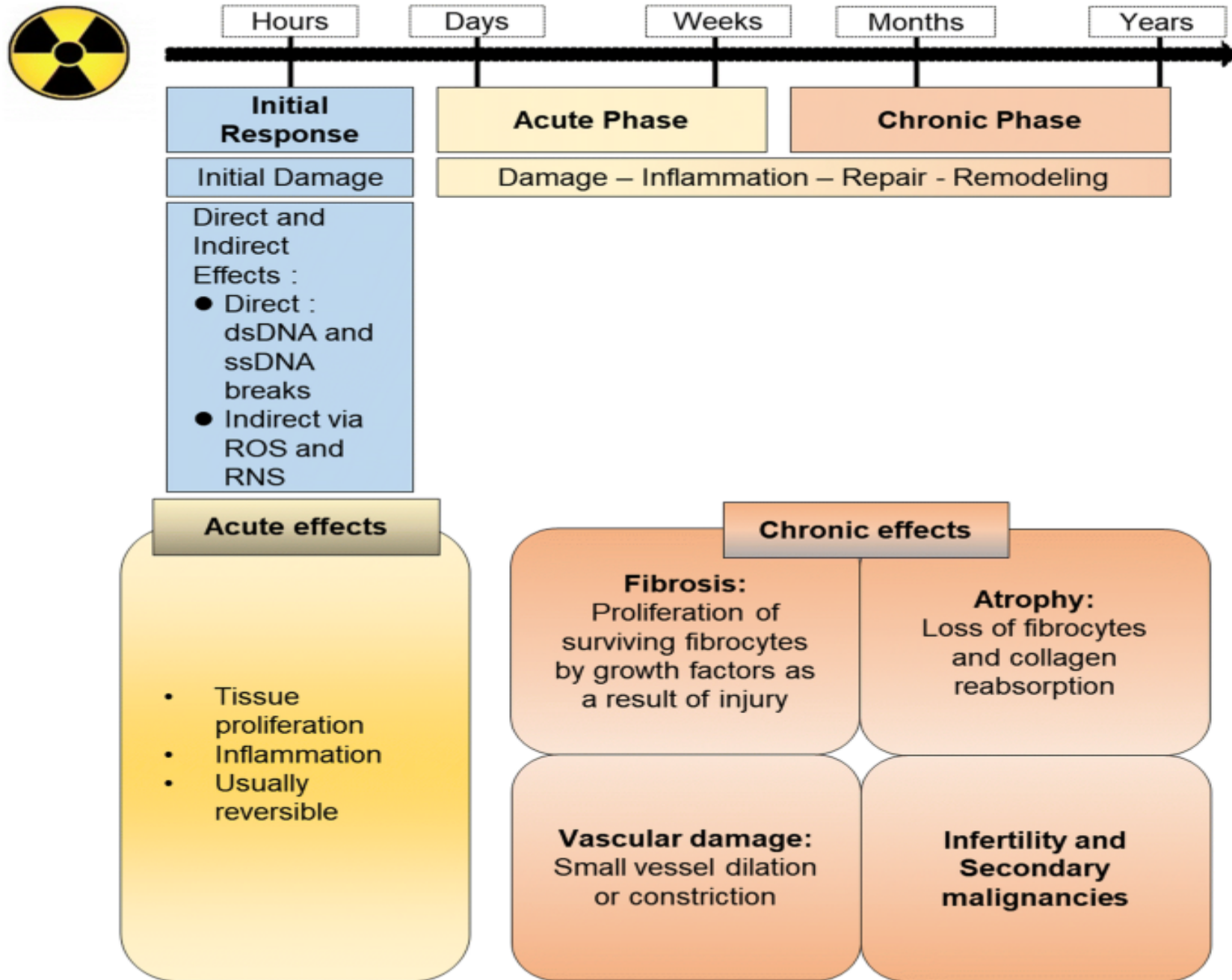
Surgery: increases the frequency of strictures, adhesions, dehiscence, fistulas, radionecrosis

Chemotherapy: most often potentiates the desired and unwanted effects of radiotherapy and vice versa, increases the frequency and intensity of acute and late complications of radiotherapy

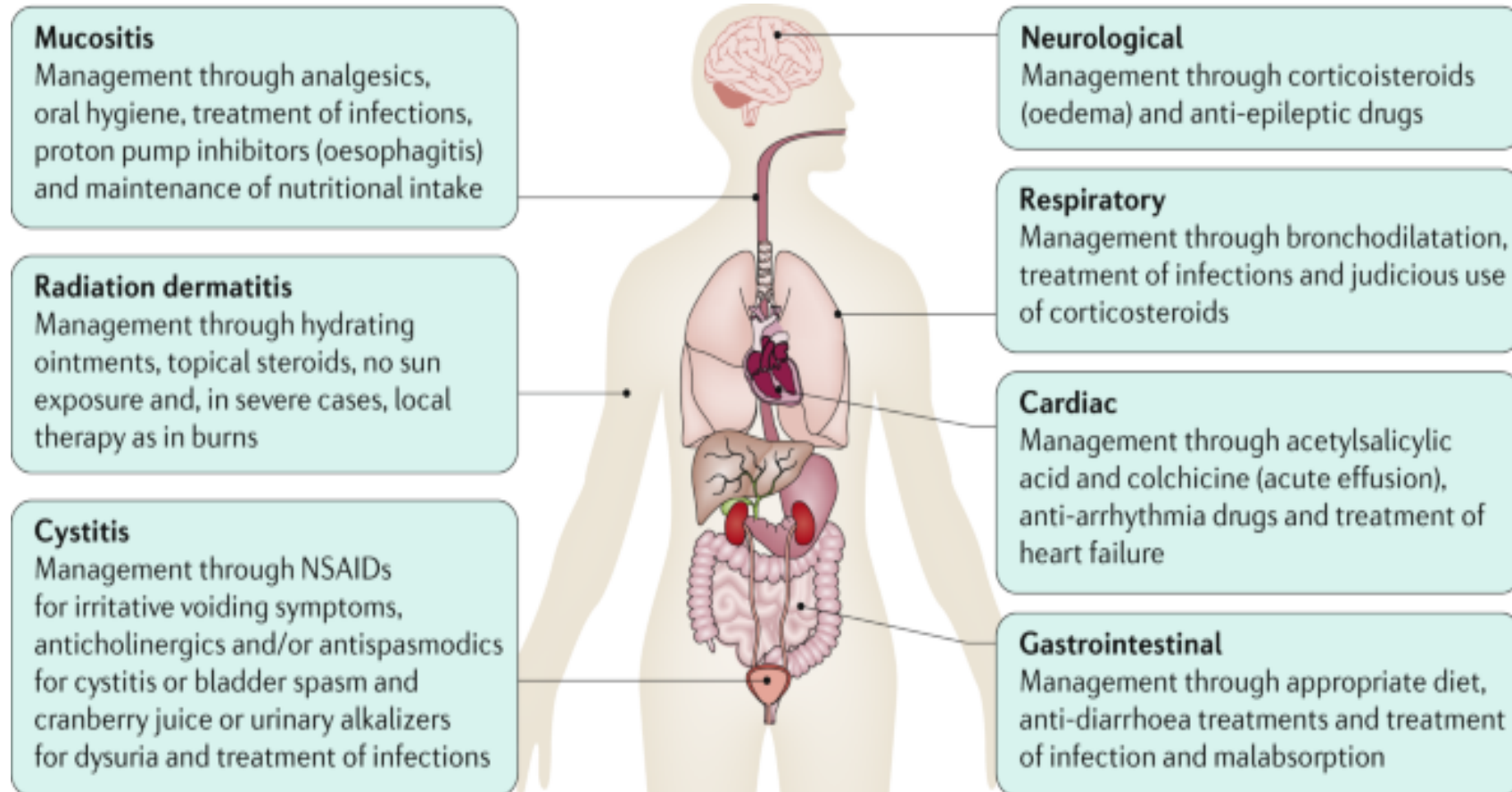
Immunotherapy: there are numerous mechanisms of interaction between these two treatment modalities

Hormonal therapy





Radiation toxicity

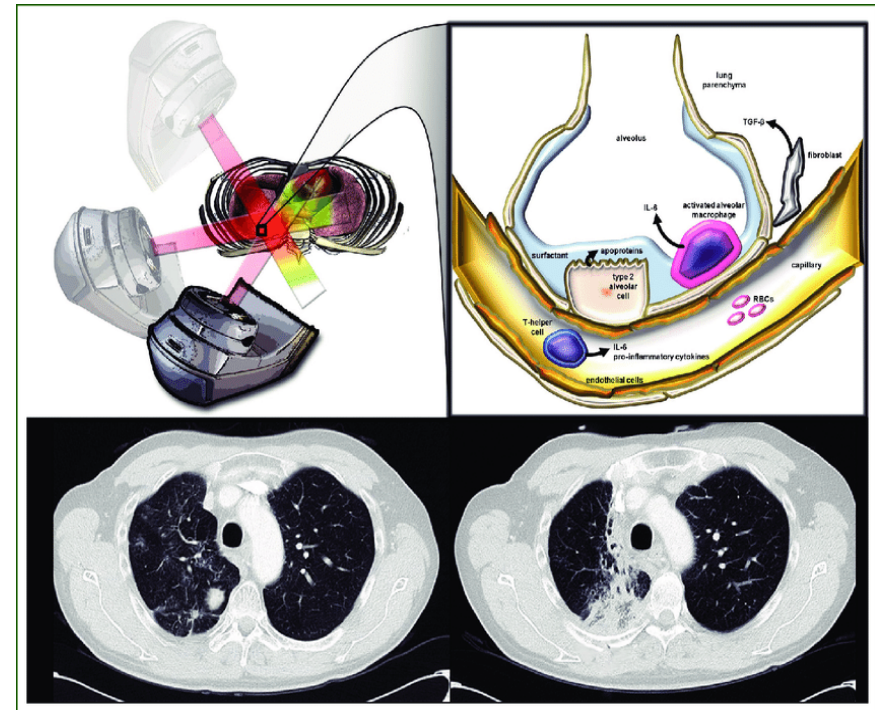


Adverse effects of CNS radiotherapy

- **Acute complications** (caused by induced edema, altered mental status, headache, nausea, epileptic attacks or signs of focal neurological disorders)
- **Subacute complications** (somnolence syndrome)
- **Late complications:**
 - Focal radionecrosis (<10%)
 - Diffuse leukoencephalopathy
 - Neurophysiological damage - impairment of intellectual functions, drop in IQ
 - Cerebrovascular complications
 - Secondary radiation-induced CNS tumors (< 3%)
 - Radiation damage to the eye lens, retina and optic nerve

Radiation toxicity after chest radiotherapy

- **Radiation pneumonitis** 1 to 3 months after RT with a dose that exceeds the radiotolerance of healthy lung tissue (about 20 Gy applied to the entire lung volume)
- **Fibrosis** of the lung parenchyma occurs 1-2 years after RT
- **Radiation pericarditis**
- **Radiation esophagitis**
- **Myelopathy**
- **Radiation brachial plexopathy**



Radiodermatitis

Acute skin reactions are dose-dependent:

- erythema
- pigmentation
- epilation
- dry desquamation
- wet desquamation

Late complications:

- atrophy of the skin, sebaceous and sweat glands
- telangiectasia
- subcutaneous fibrosis
- induration, thickening of the dermis and subcutis
- radionecrosis



Bernier J, Russi EG, Homey B, et al. Management of radiation dermatitis in patients receiving cetuximab and radiotherapy for locally advanced squamous cell carcinoma of the head and neck: proposals for a revised grading system and consensus management guidelines. *Ann Oncol* 2011;22(10):2191-200.

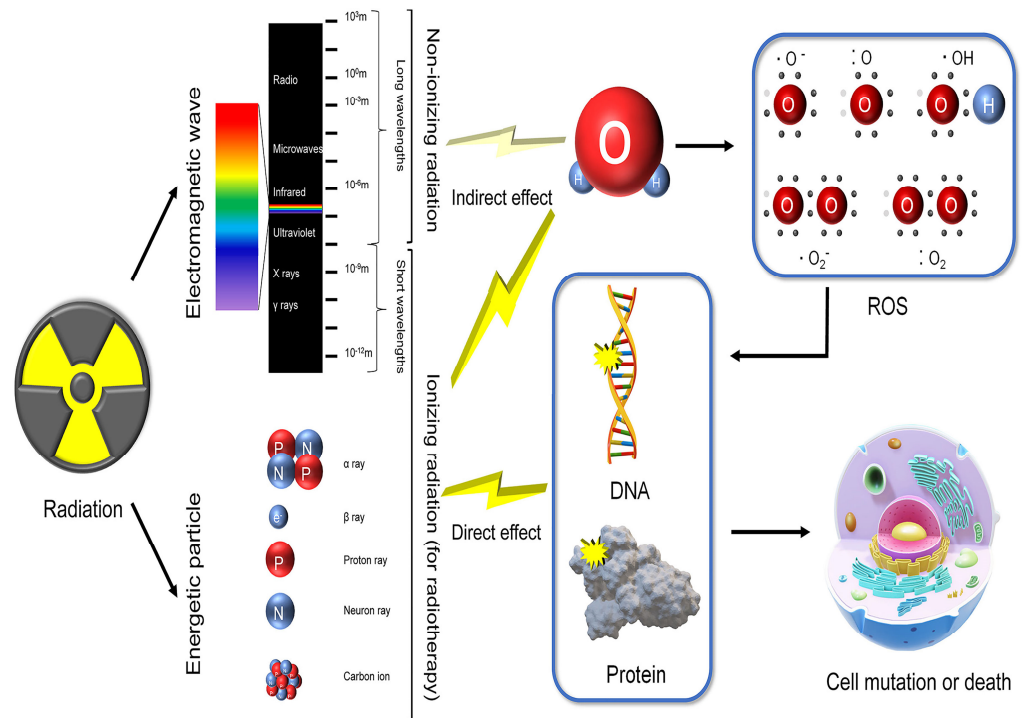
Gastrointestinal radiation toxicity

Acute

- Esophagitis
- Enterocolitis
- Radiation proctitis

Chronic

- Strictures
- Fibrosis
- Ulcerations
- Intestinal adhesions
- Fistula



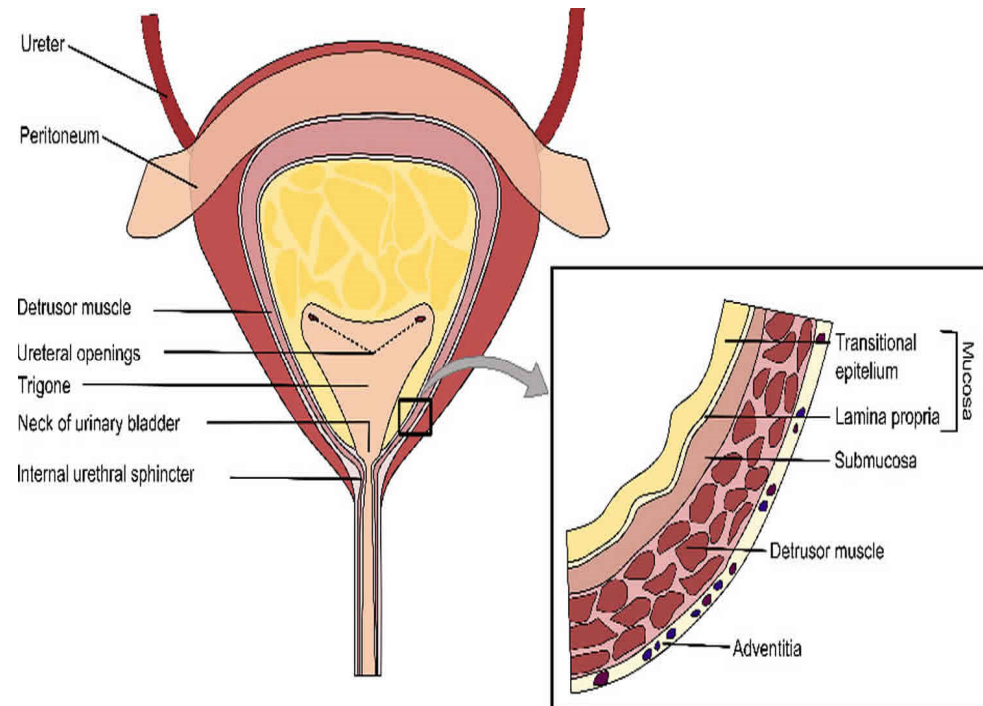
Genitourinary radiation toxicity

Acute

- Cystitis

Chronic

- Chronic radiation cystitis
- Fibrosis
- Ulcerations
- Fistula



Slika: Radiation cystitis. At: <https://healthjade.net/radiation-cystitis/>

Radiation mucositis during radiotherapy of respiratory and gastrointestinal tracts

- **Active radiation mucositis** - usually manifests itself after 10 fractions
- The result is a radiation-induced lethal effect on the basal cells of the mucosal epithelium
- The reactions are reversible, they are remedied after the application of symptomatic therapy.
- Depending on the intensity of toxicity, a break in RT treatment is planned.
- **Late radiation mucositis** (atrophy, reduced elasticity, loss of taste, sclerosis, ulceration, dysphagia)

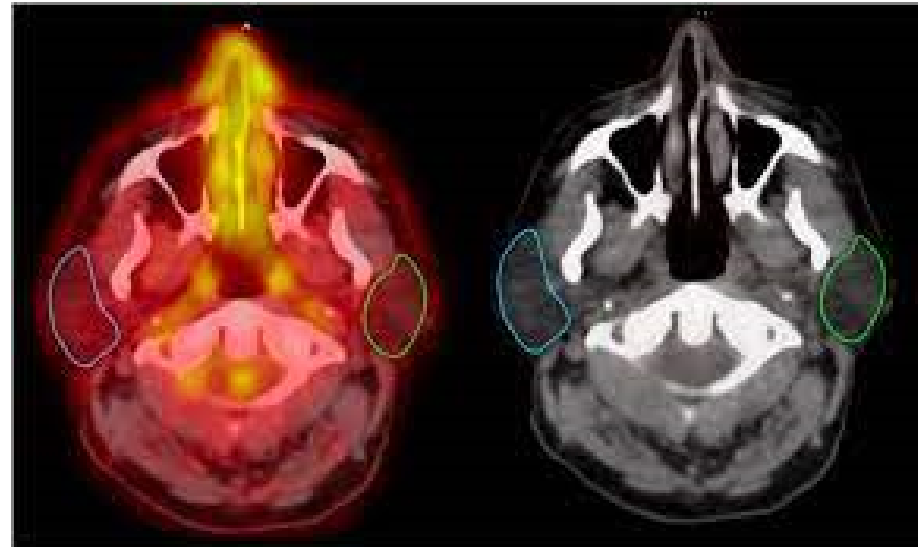
Radiotherapy side effects of head and neck tumors

Xerostomia
Tooth/root caries
Oral mucositis
Loss of taste
Fungal/bacterial/viral infections
Increased phlegm
Trismus
Osteoradionecrosis



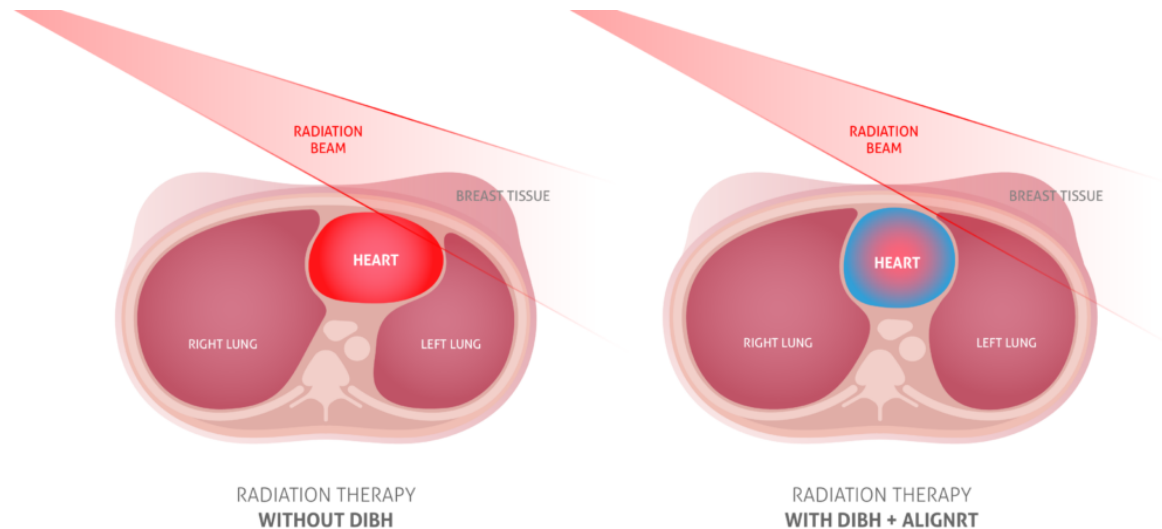
Acute radiation parotitis

- Occurs during radiotherapy of the head and neck cancer
- Due to the radiosensitivity of the parotid gland, symptoms of xerostomia appear shortly after the start of radiotherapy



Radiation damage to the heart and pericardium

Acute exudative pericarditis
Late pericardial effusion (cardiac tamponade)
Constrictive pericarditis
Pancarditis = cardiomyofibrosis
(cardiomyopathy + pericardial constriction)



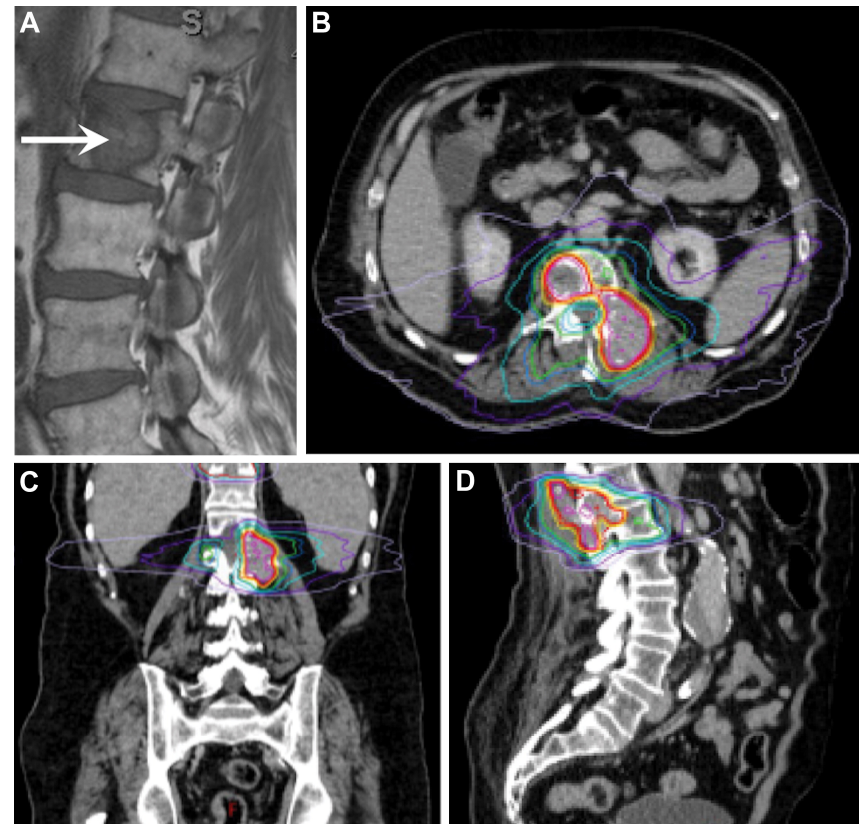
Left-Breast Cancer Patient's Side Effect Risks. Dostupno na <https://www.saferradiationtherapy.com/27-of-left-breast-cancer-patients-are-at-risk-of-having-heart-damage/>

Radiation myelopathy

Acute radiation myelopathy - up to 3 months after RT

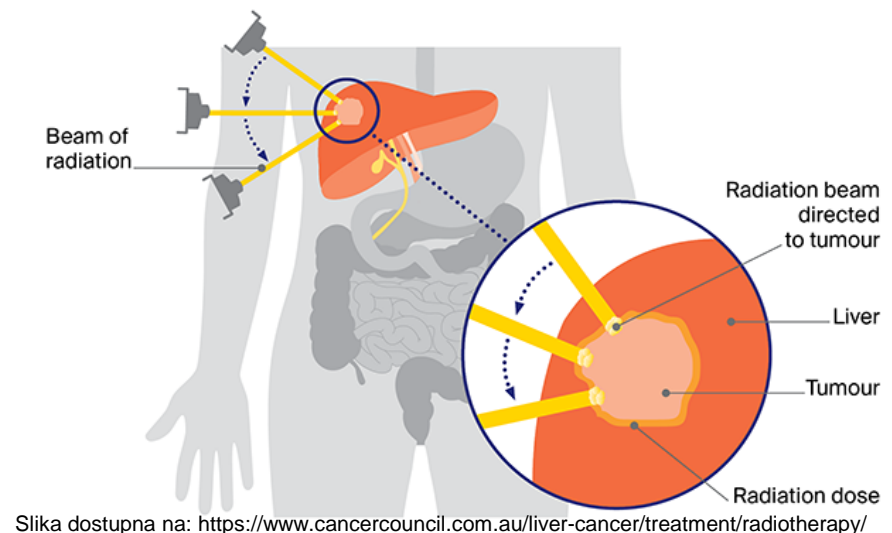
Demyelination of the spinal cord

Late radiation myelopathy - months and years after RT, most often after a latent period

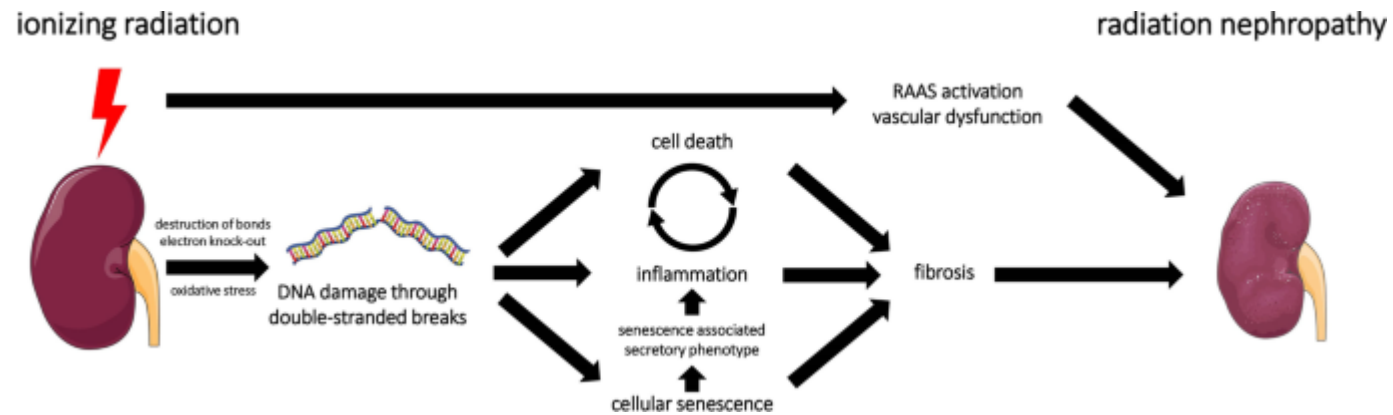


Liver radiation toxicity

- SBRT or conventional treatment regimens
- Damage caused by irradiation of primary or secondary tumors
- Liver damage as a risk organ
- Veno-occlusive disorder is the basis of the swelling
- Symptoms 4-8 weeks after RT (hepatomegaly, ascites, increase in trasaminases, icterus, encephalopathy, pain in the area of the right rib cage)
- Radiation-induced liver disease (RILD)
- Liver damage after combined treatment (Combined modality induced liver disease - CMILD)
- Post-radiation fibrosis

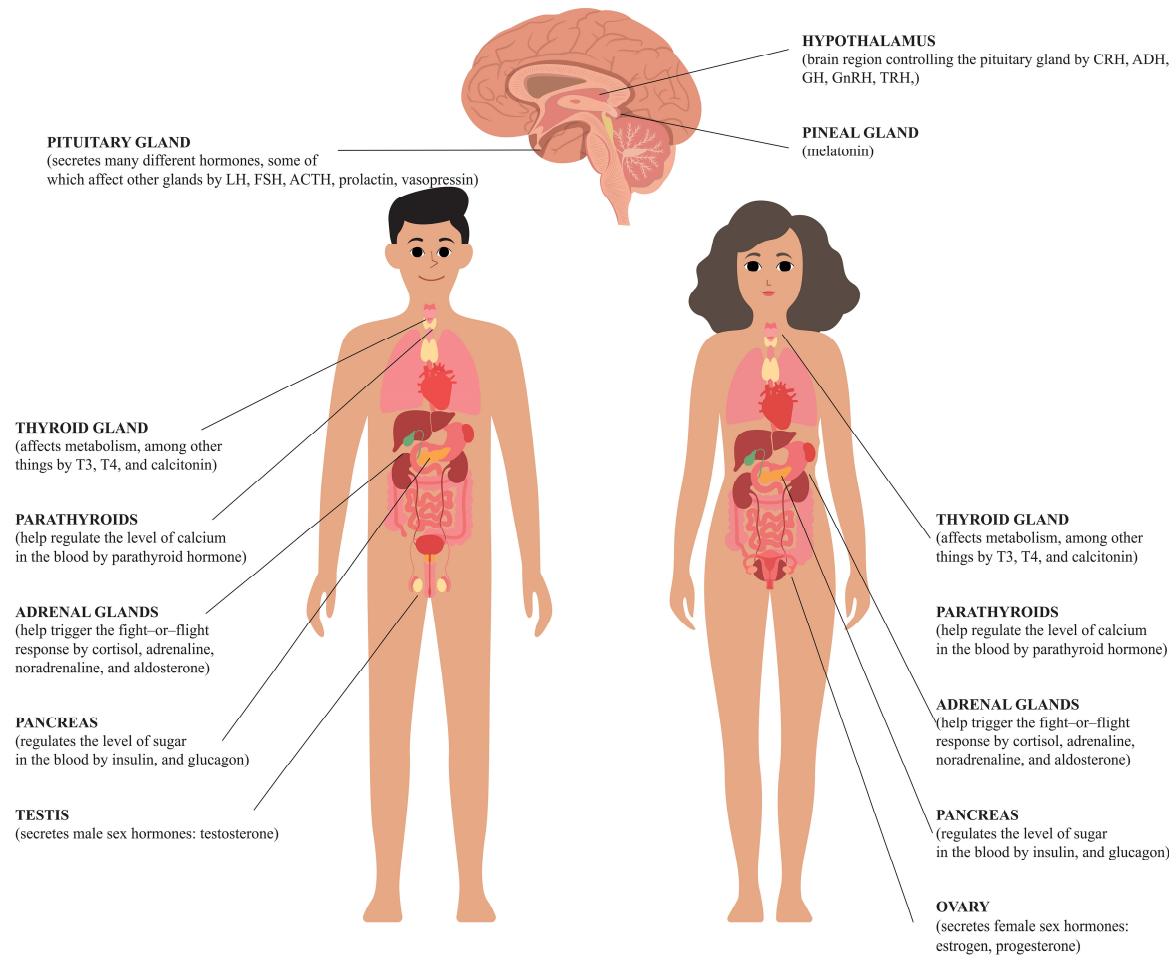


Renal radiation toxicity



Acute or chronic radiation damage to the kidneys
Reversible or irreversible damage

Endocrine system radiation toxicity





HHS Public Access

Author manuscript

Clin Oncol (R Coll Radiol). Author manuscript; available in PMC 2020 October 14.

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Clin Oncol (R Coll Radiol). 2019 March ; 31(3): 199–207. doi:10.1016/j.clon.2019.01.002.

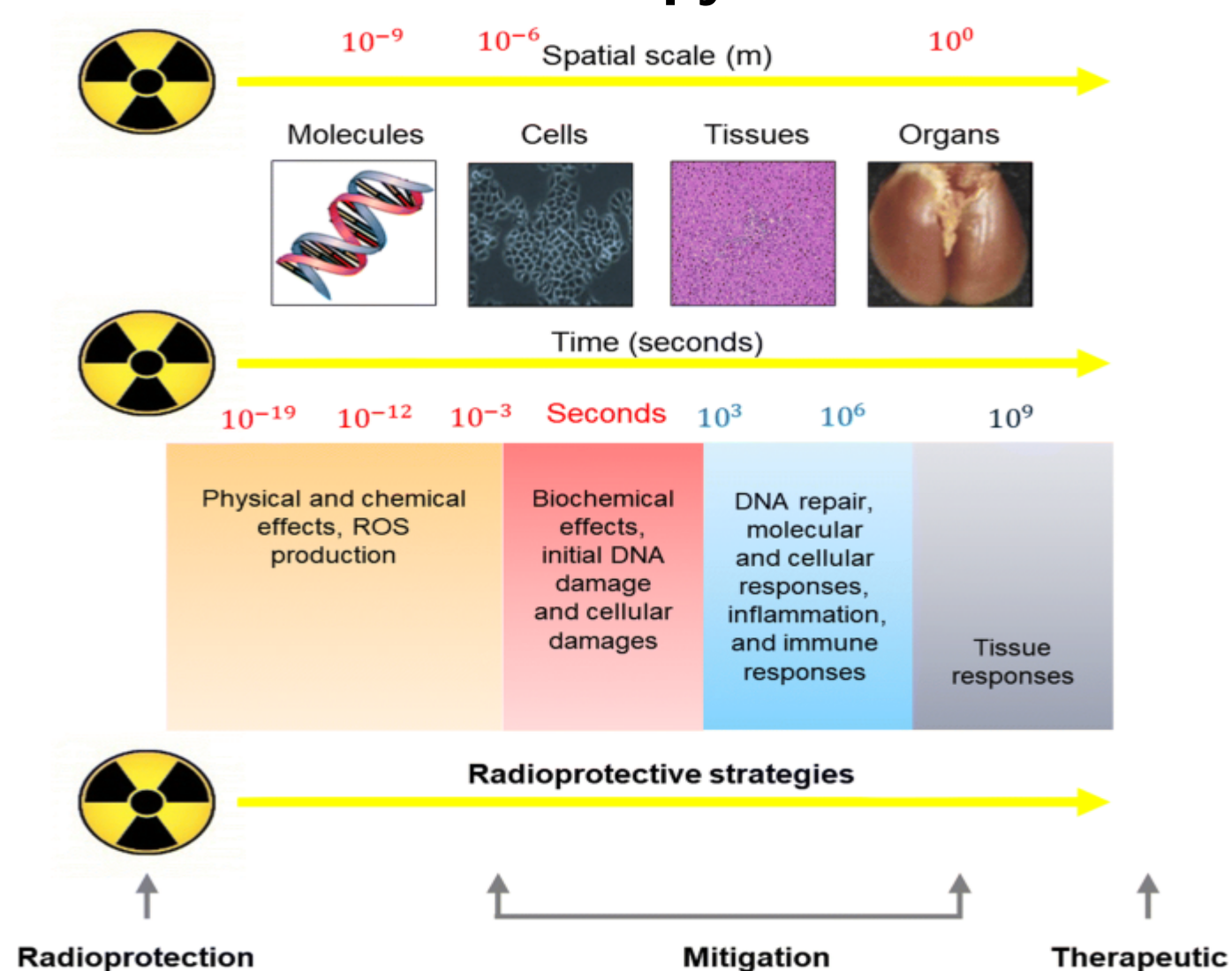
Pediatric Normal Tissue Effects in the Clinic (PENTEC): an international collaboration to analyze normal tissue radiation dose-volume-response relationships for pediatric cancer patients

Louis S. Constine^a, Cécile M. Ronckers^{b,c}, Chia-Ho Hua^d, Arthur Olch^e, Leontien C. M. Kremer^{b,c}, Andrew Jackson^f, Soren M. Bentzen^g

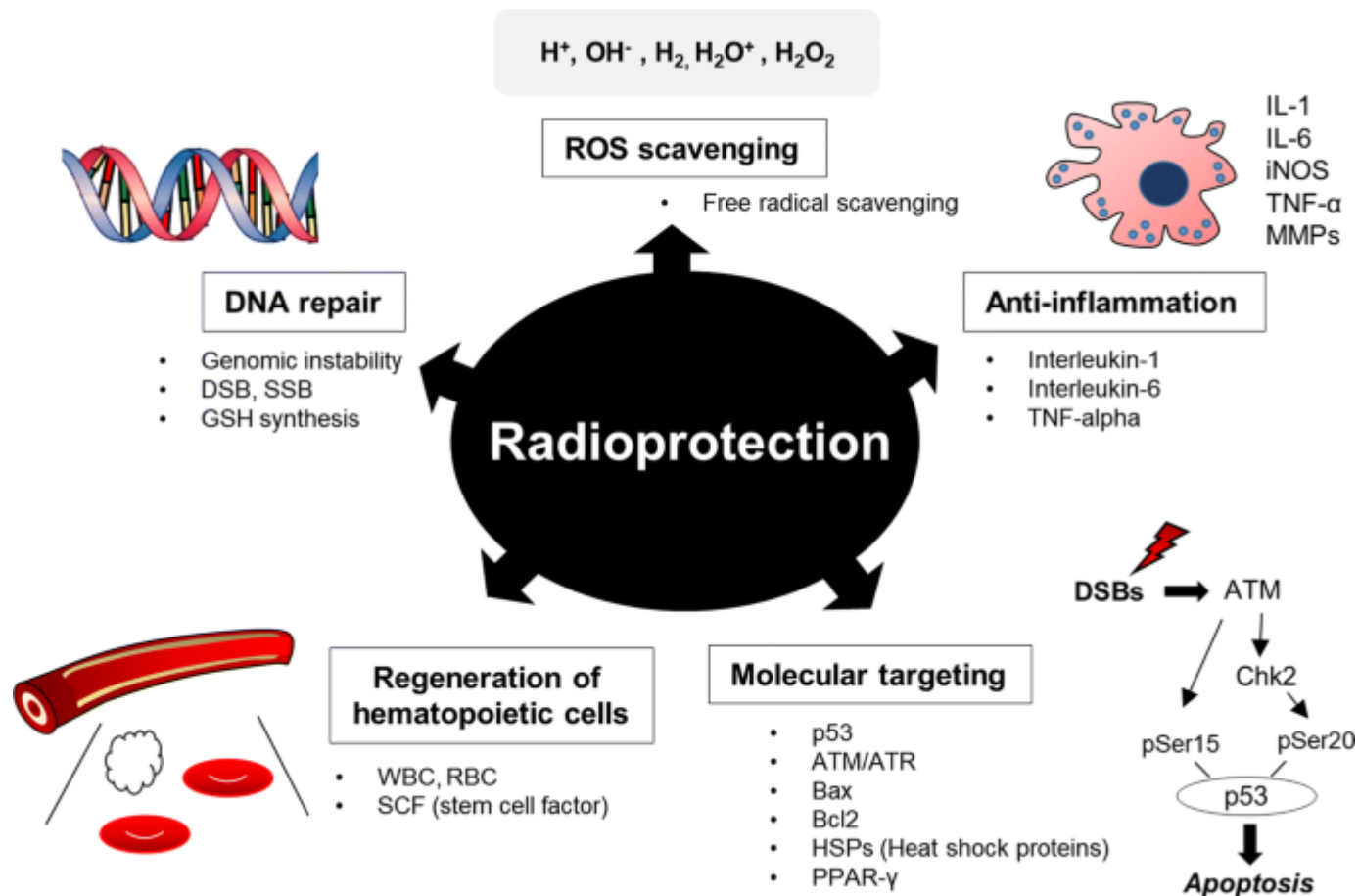
Highlights

- RT for pediatric cancer can cause long-term adverse normal tissue effects
- Radiation damage depends on the radiation dose and volume, and developmental status
- For some organs, chemotherapy can exacerbate the effects of radiation
- PENTEC seeks to increase knowledge about pediatric RT dose constraints for organs
- Radiation dosimetric data should be precisely reported in pediatric RT studies

Radioprotectors, mitigators and radiation toxicity therapy



Radioprotectors and mitigators



Treatment of manifestations of radiation toxicity

- Assessment of the presence and intensity of toxicity (definition of toxicity grade)
- Defining the type of toxicity (acute or chronic)
- Analysis of interaction with other therapeutic treatment modalities
- Procedure depending on the toxicity grade (follow-up under increased patient supervision, symptomatic treatment and continuation of RT, pause in RT treatment, hospital treatment of complications)

Reduction of toxicity intensity

- Preventive measures
- National and institutional protocols for the treatment of radiation toxicity
- European and world protocols for the treatment of radiation toxicity

THANK YOU FOR YOUR ATTENTION!

