UNIVERSITY OF KRAGUJEVAC
FACULTY OF MEDICAL SCIENCES

CLINICAL RADIOTHERAPY APPLICATION IN VULNERABLE PATIENTS GROUPS

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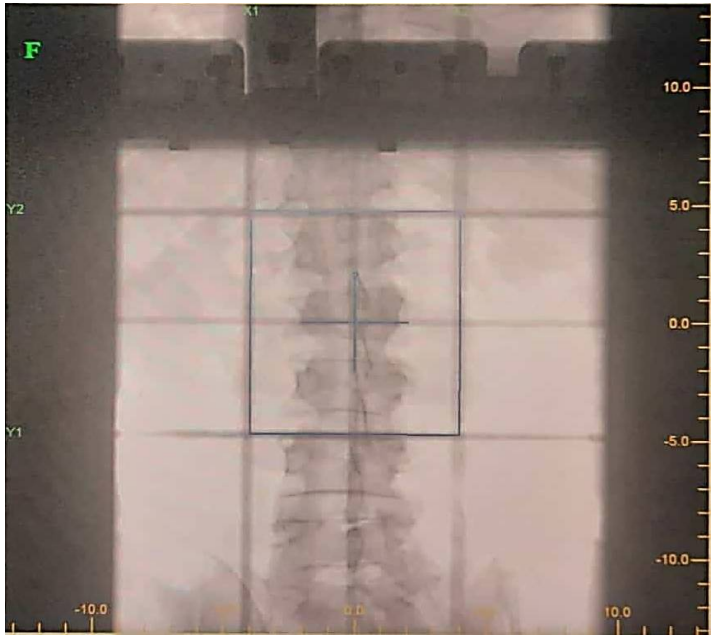
Kragujevac, 2023

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

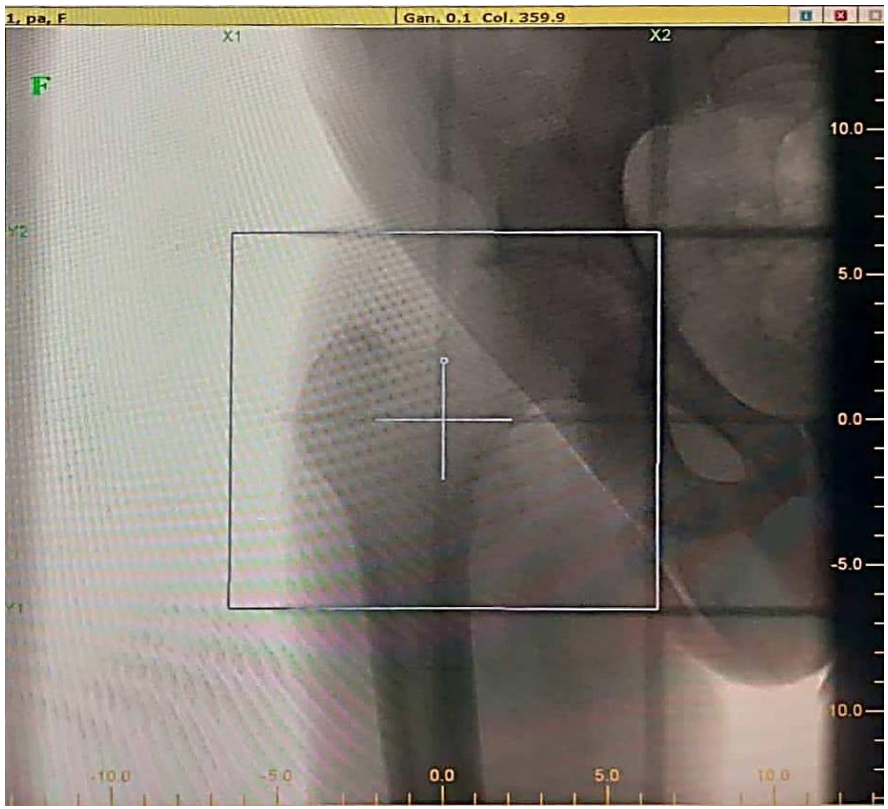
- Spine, sacrum
- Ribs, calvaria

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

Slika dostuona na: Researchers Analyze The Use of Adjuvant Radiotherapy in Elderly Patients With Early-Stage Breast Cancer. At: https://radiationtherapynews.com/2015/02/06/researchers-analyze-use-adjuvant-radiotherapy-elderly-patients-early-stage-breast-cancer/

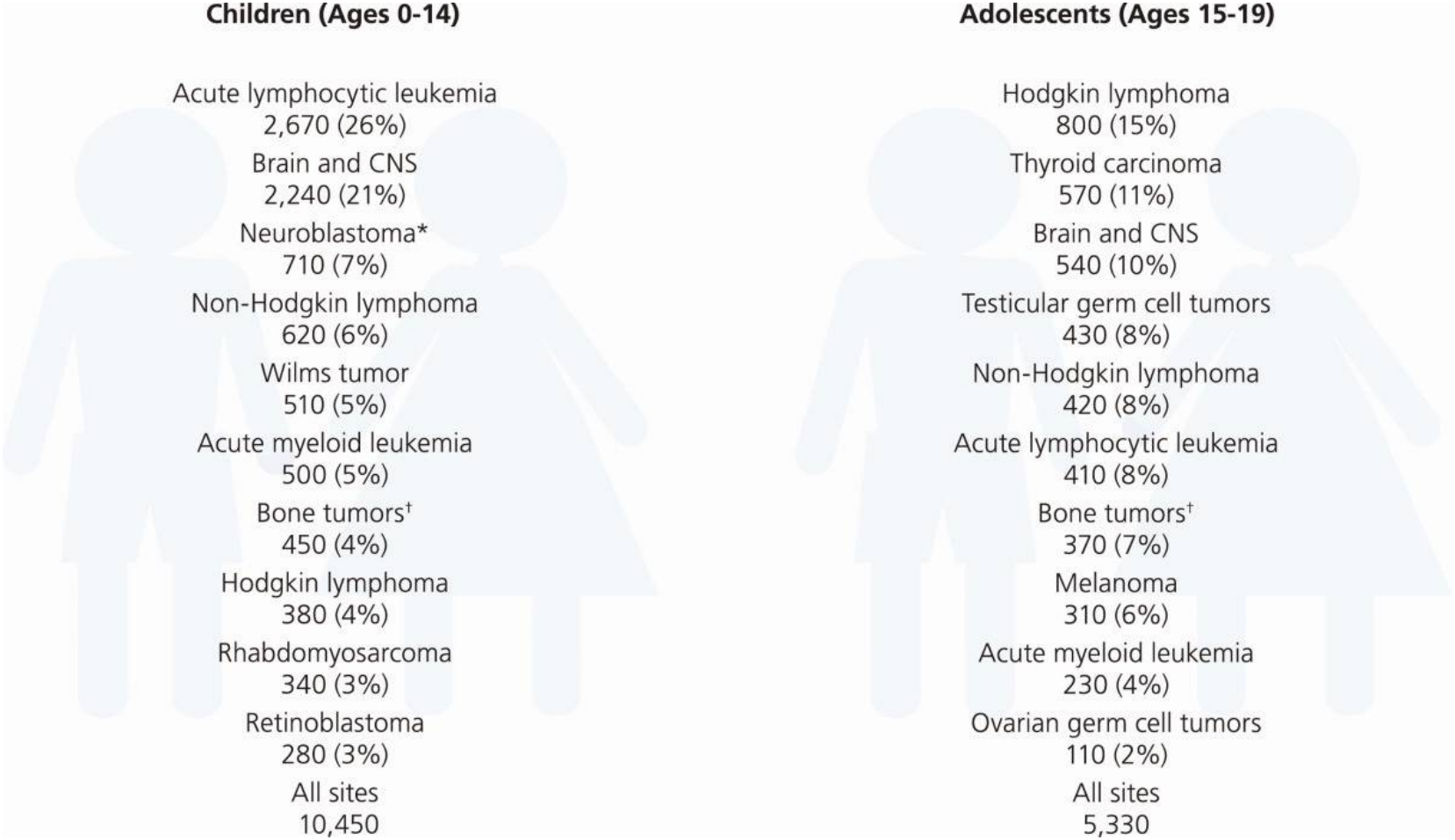
Radiotherapy specifics in the geriatric population

- 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

Vallard A, Guy JB, Espenel S, Langrand-Escure J, Trone JC, Méry B, Moriceau G, Rivoirard R, de Laroche G, Chargari C, Magné N. Personnes âgées et radiothérapie : une synthèse de la littérature [Elderly patients and radiotherapy: A short review]. Bull Cancer. 2015 Jun;102(6):539-49.

RADIOTHERAPY OF TUMORS IN PEDIATRIC POPULATION

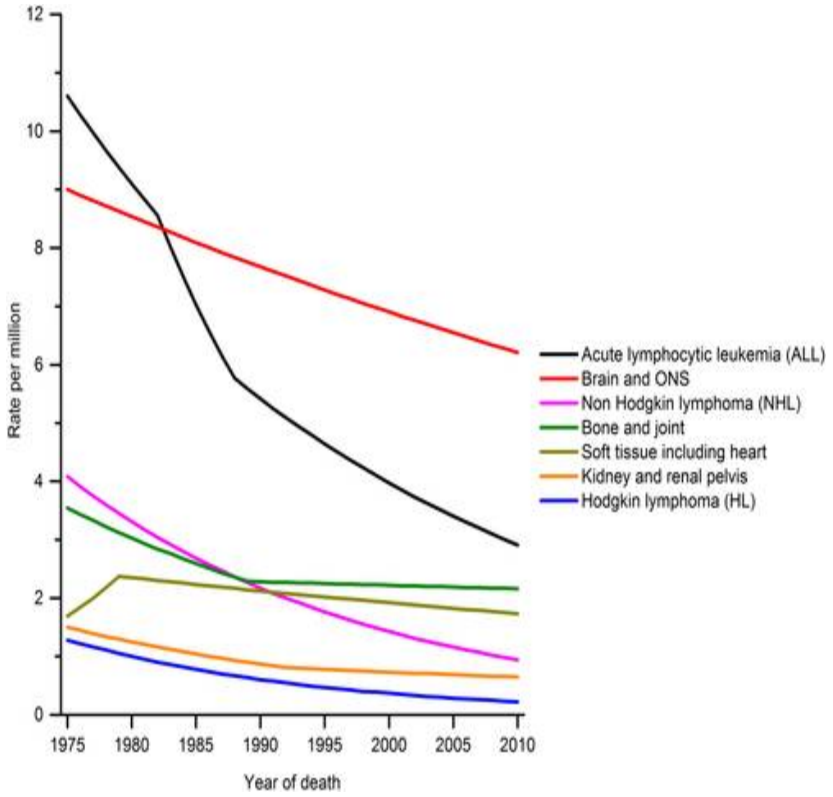
The most common tumors in children



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 annualy
- Approximately 1 child in 500 will develop cancer before the age of 15



Trend stope mortaliteta

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.

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.

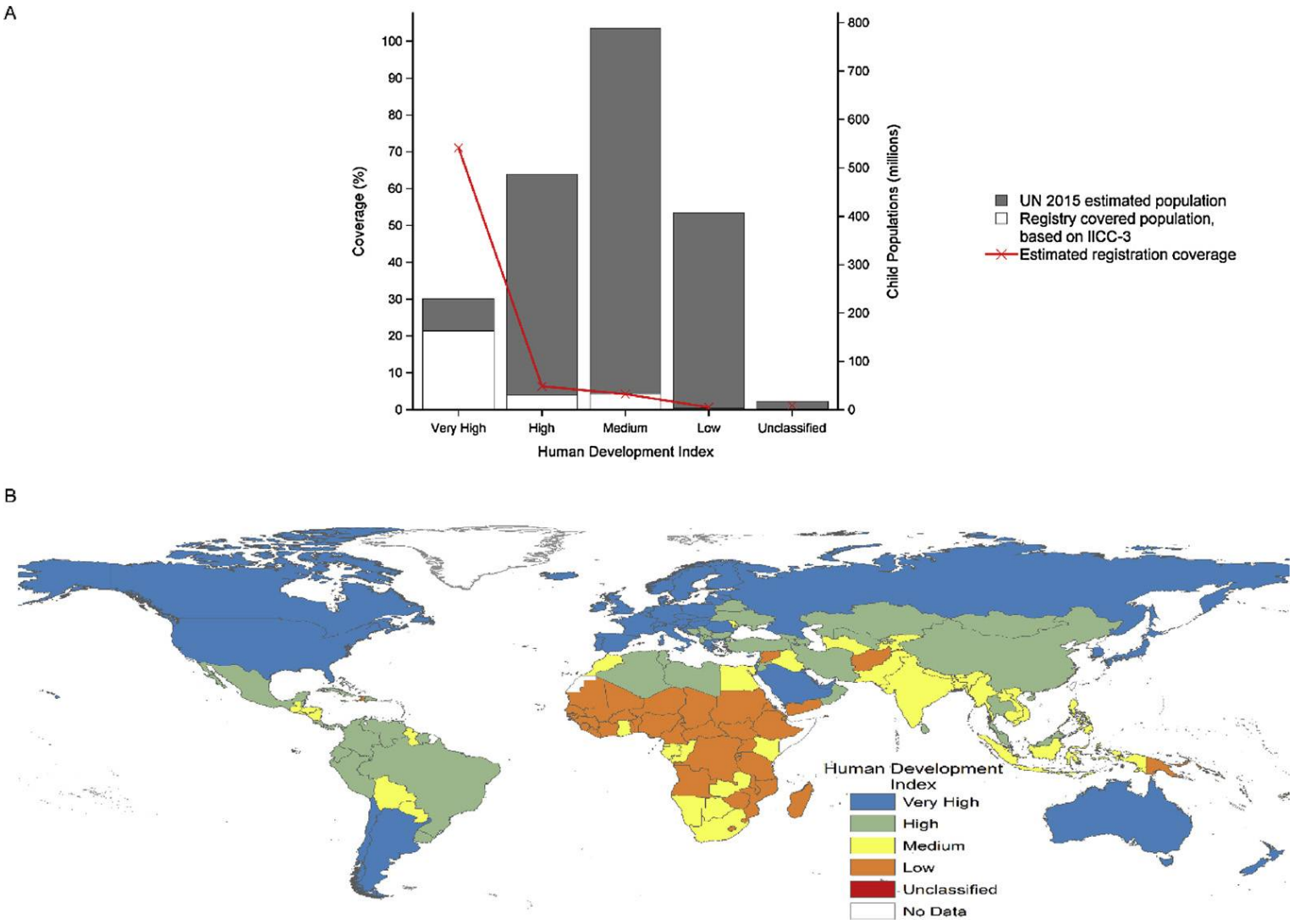
The estimated standardized rates ranged from

~178 cases per million in Europe and North America, to

~218 cases per million in West and Central Africa.

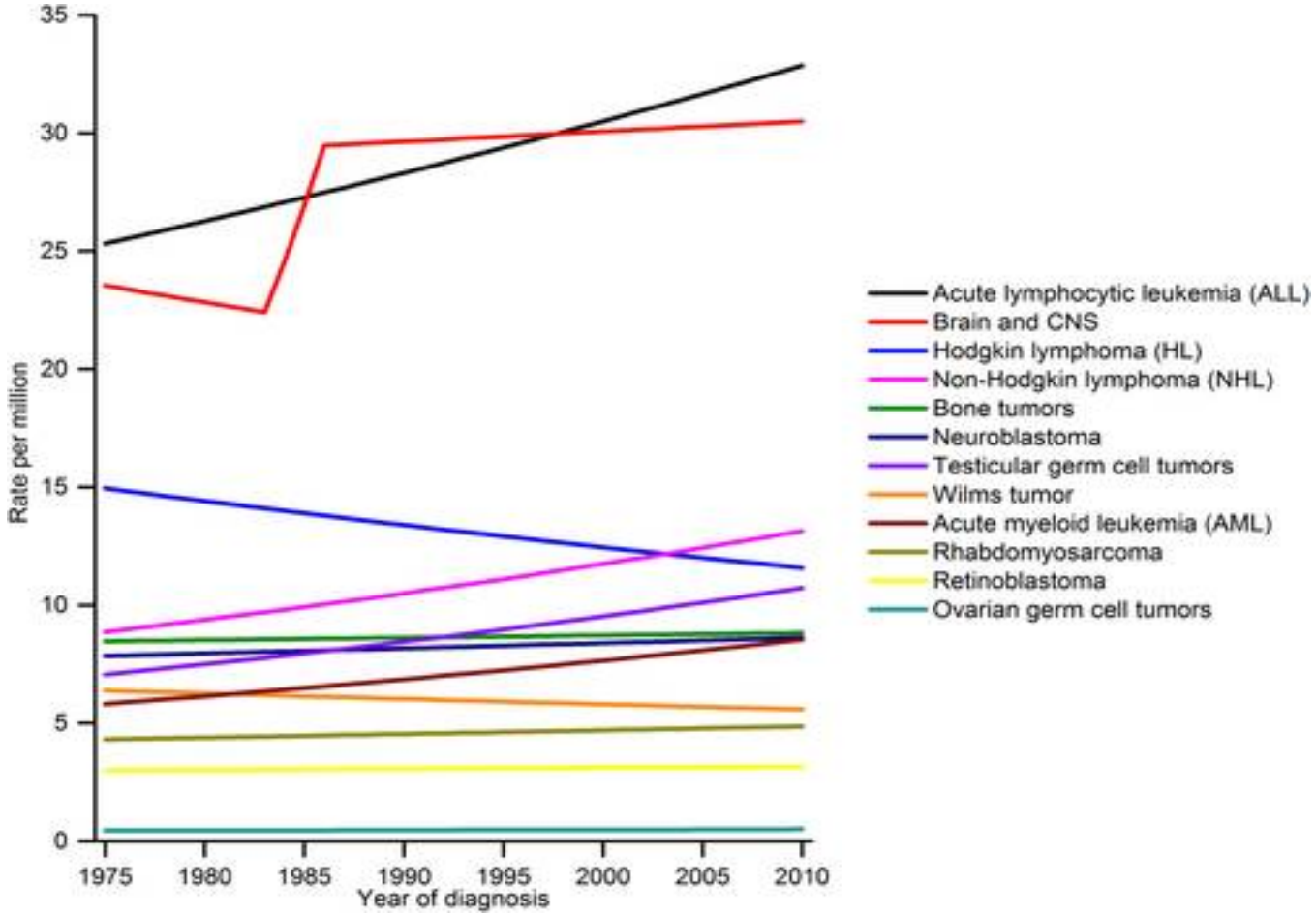
Johnston WT, Erdmann F, Newton R, Steliarova-Foucher E, Schüz J, Roman E. Childhood cancer: Estimating regional and global incidence. Cancer Epidemiol 2021 ;71(Pt B):101662.

Distribution of newly diagnosed tumors in children



Johnston WT, Erdmann F, Newton R, Steliarova-Foucher E, Schüz J, Roman E. Childhood cancer: Estimating regional and global incidence. Cancer Epidemiol 2021 ;71(Pt B):101662.

Incidence trends of pediatric tumors



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.

- 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.

IAEA Study Finds Global Gaps in Radiotherapy Services for Childhood Cancers, Sees Opportunity to Improve Clinical Practices. https://www.iaea.org/newscenter/pressreleases/iaea-study-finds-global-gaps-in-radiotherapy-services-for-childhood-cancers-sees-opportunity-to-improve-clinical-practices

- 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

Special superhero and cartoon masks bring joy to pediatric patients. At: https://healthier.stanfordchildrens.org/en/special-radiation-therapy-masks/

Published in final edited form as:
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

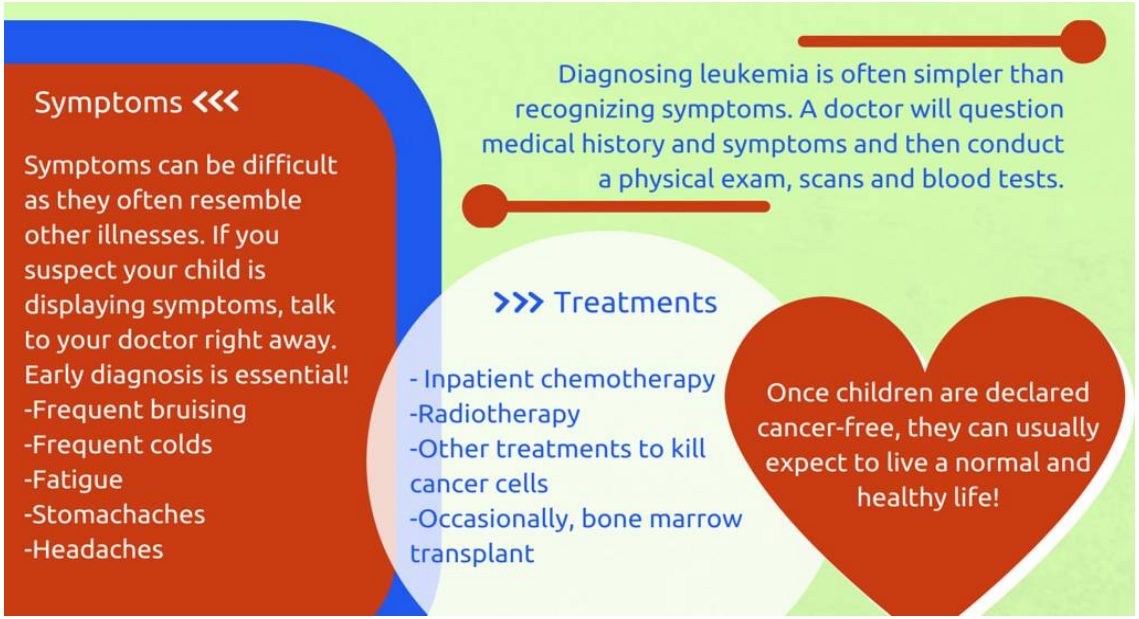
Louis S. Constine[a], **Cécile M. Ronckers**[b,c], **Chia-Ho Hua**[d], **Arthur Olch**[e], **Leontien C. M. Kremer**[b,c], **Andrew Jackson**[f], **Soren M. Bentzen**[g]

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

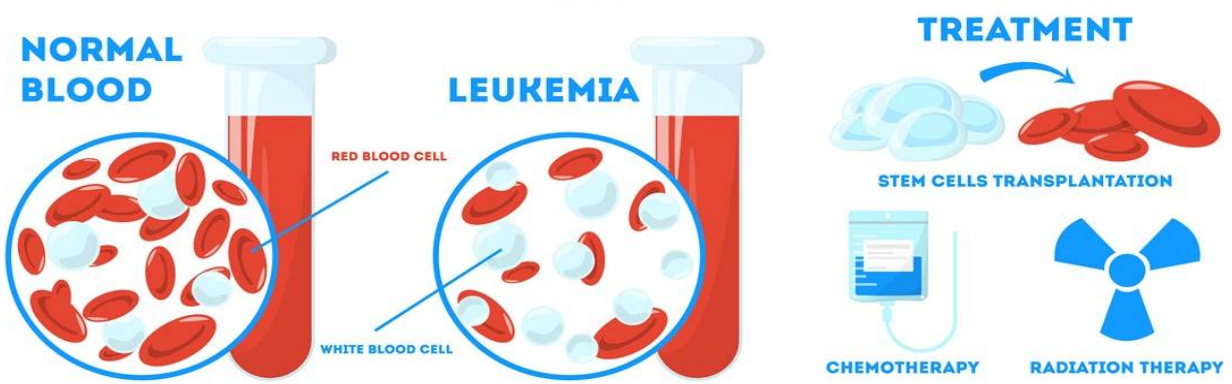
- The most common malignant disease in children (30% of childhood malignancies)
- 4000 new cases in the world annually
- ALL (80%), AML (15-20%), CML (5%)



Dostupno na:Leukemia in Children. At: https://iscc-charity.org/infographics/leukemia-in-children/

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

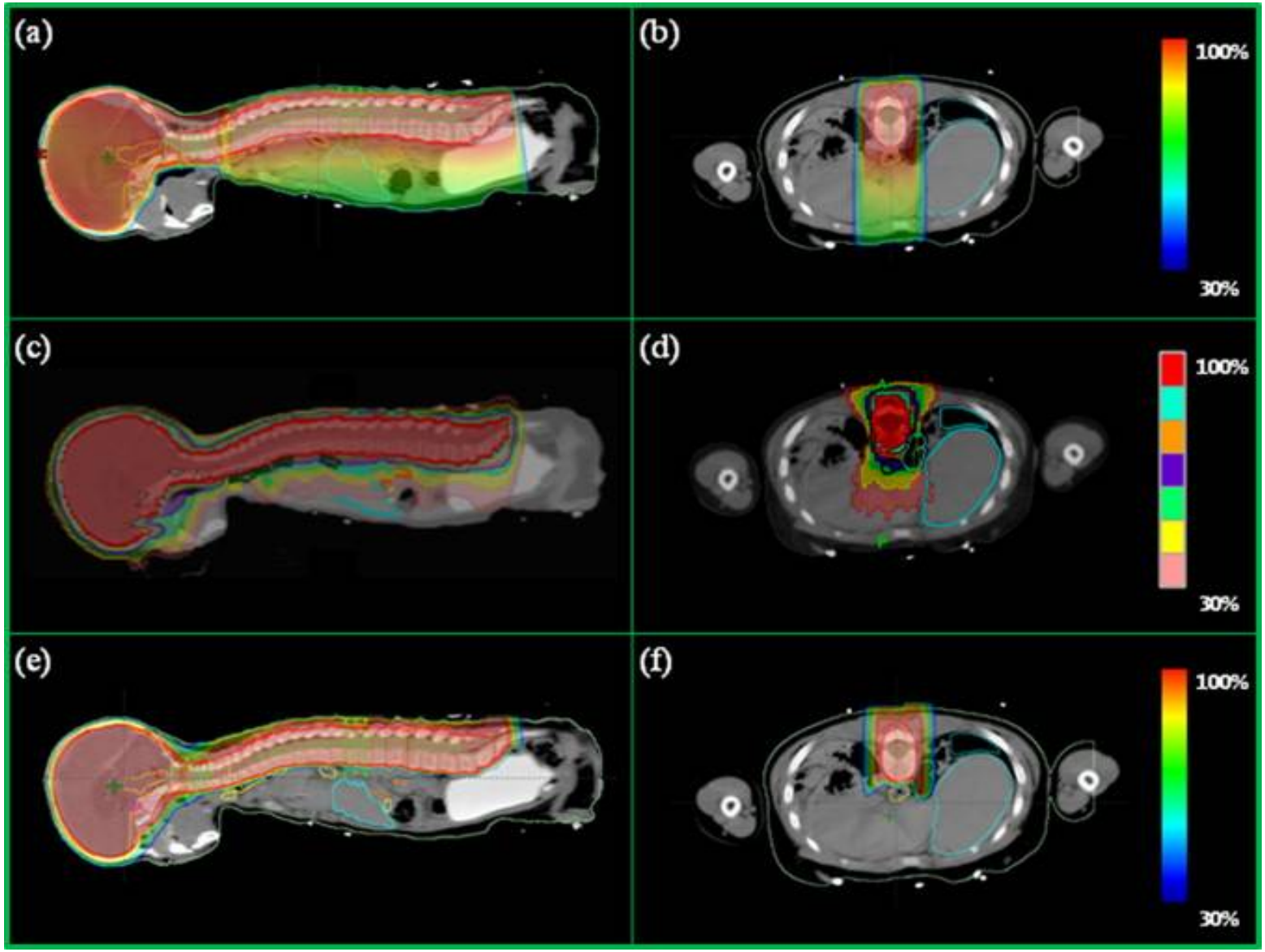


Dostupno na:Leukemia in Children. At: https://iscc-charity.org/infographics/leukemia-in-children/

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)

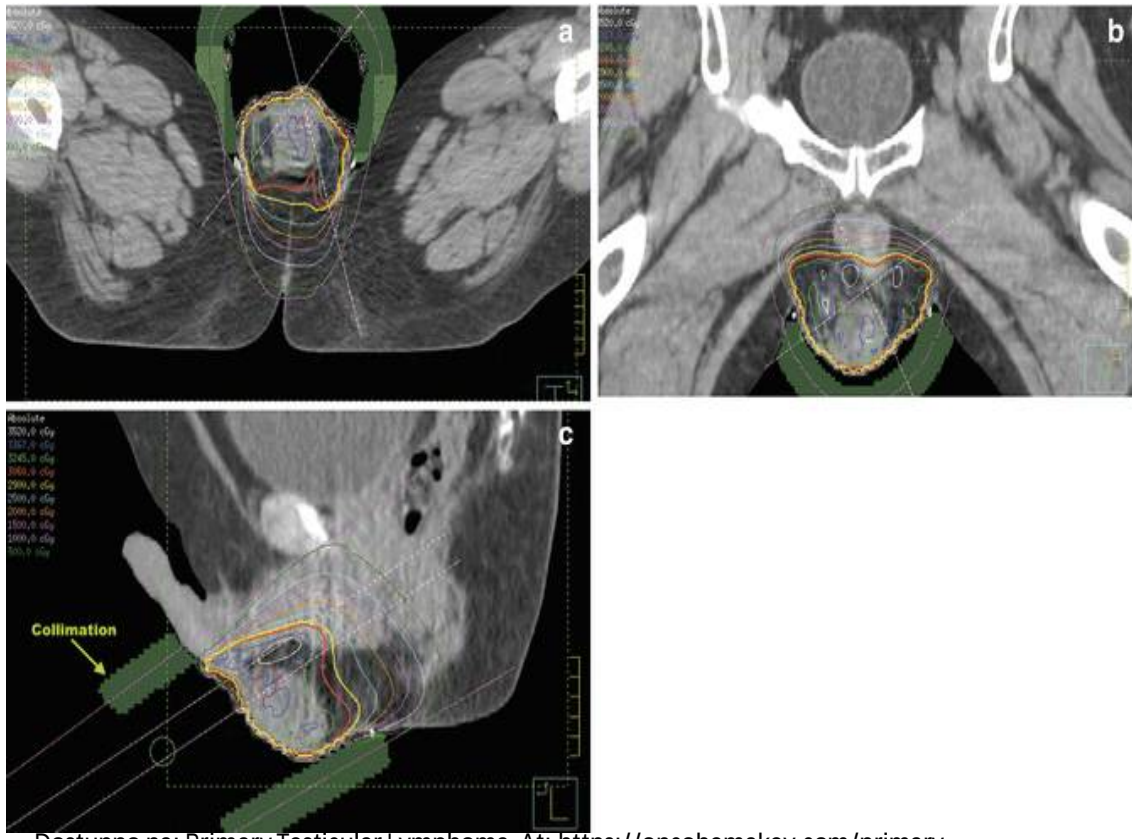


Yoon M, et al. Craniospinal irradiation techniques: a dosimetric comparison of proton beams with standard and advanced photon radiotherapy. Int J Radiat Oncol Biol Phys 2011;81(3):637-46.

Testicular radiotherapy in leukemia patients

- Indications:
- Residual testiculer disease persists after CHT
- Relapse of the testicles

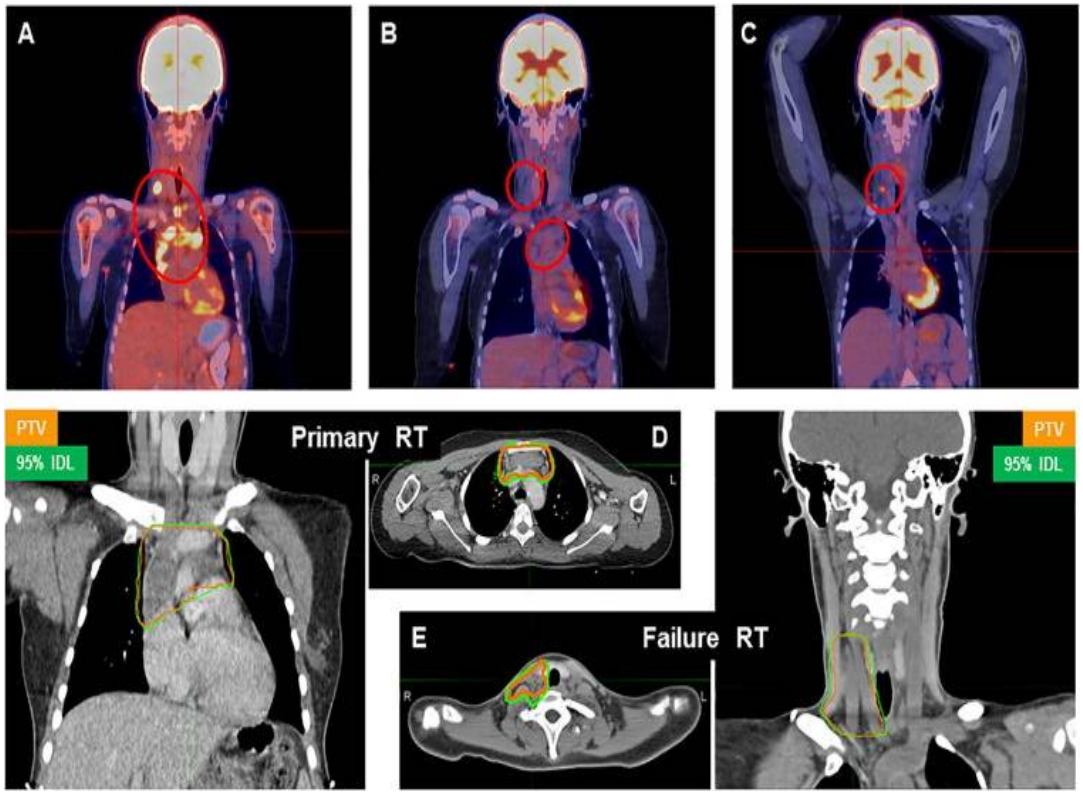
- TD 24 Gy (2Gy per fraction)



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

Hodgkin's lymphoma in childhood

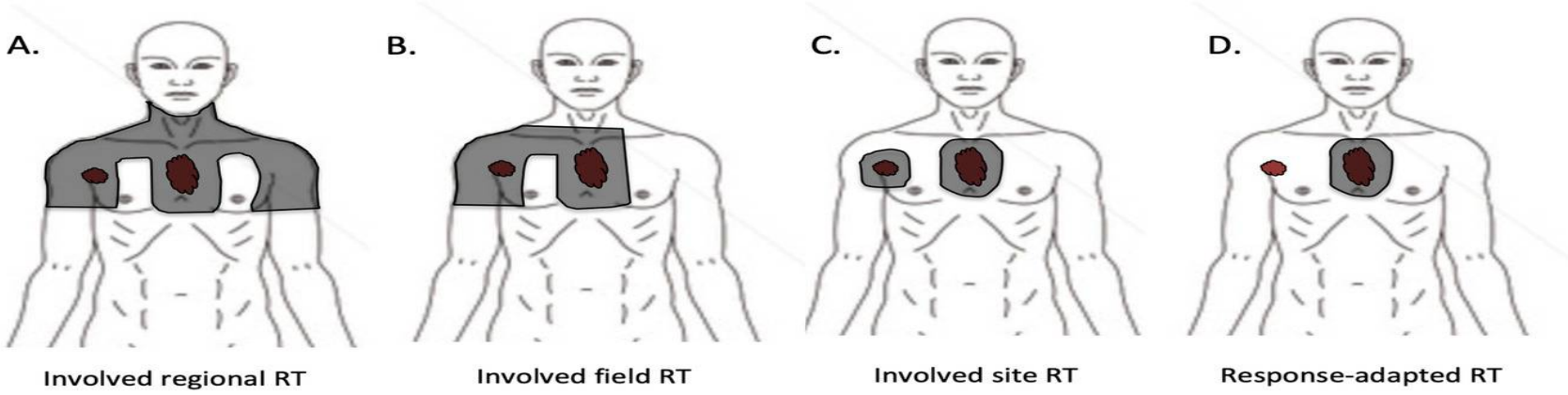
- Over 80% older than 10 years
- Enlargement of neck LN, mediastinum, supraclavicular LN
- 25-30% B symptomatology
- 10% diagnosed in the IV stage



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.



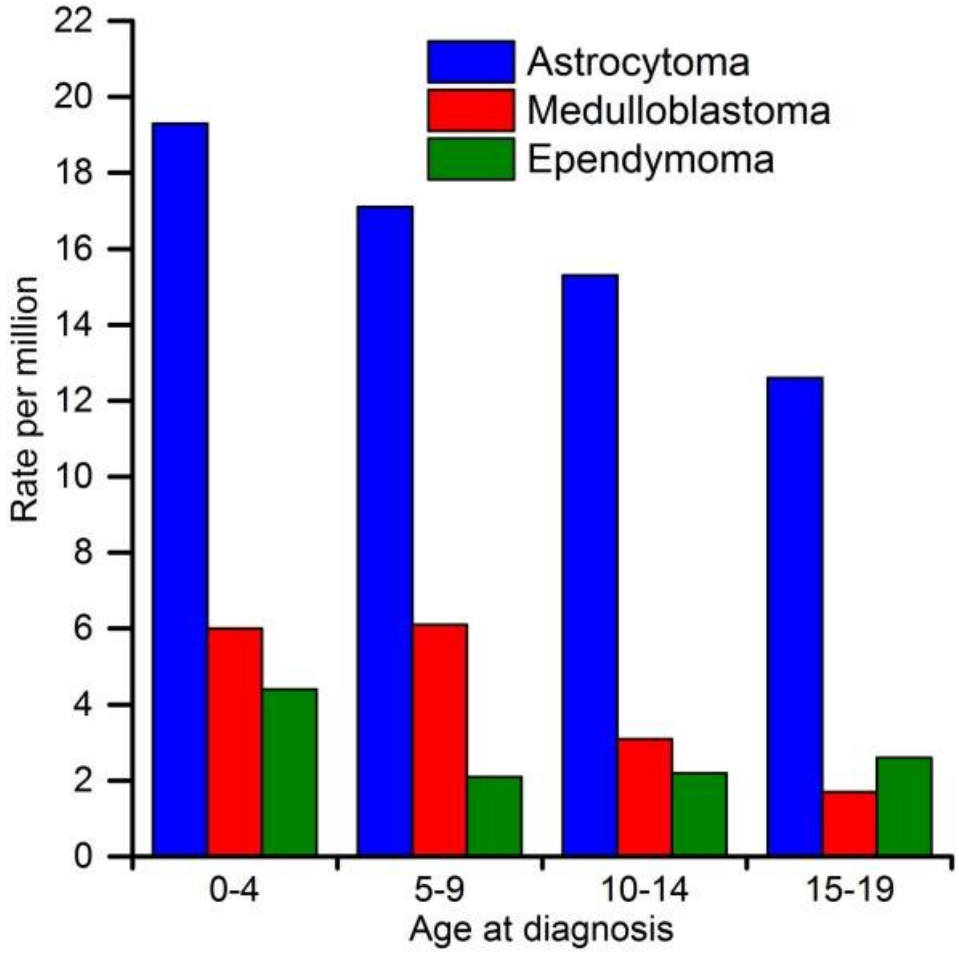
- **RT contraindications:** low risk patients, complete remission after HT
- **Indications for RT:**
- PR after HT = RT with TD 15-25 Gy (1.8 Gy per fraction)
- Intermediate and High risk patients = RT regardless of the achieved effect of CHT with TD 15-25 Gy

- 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

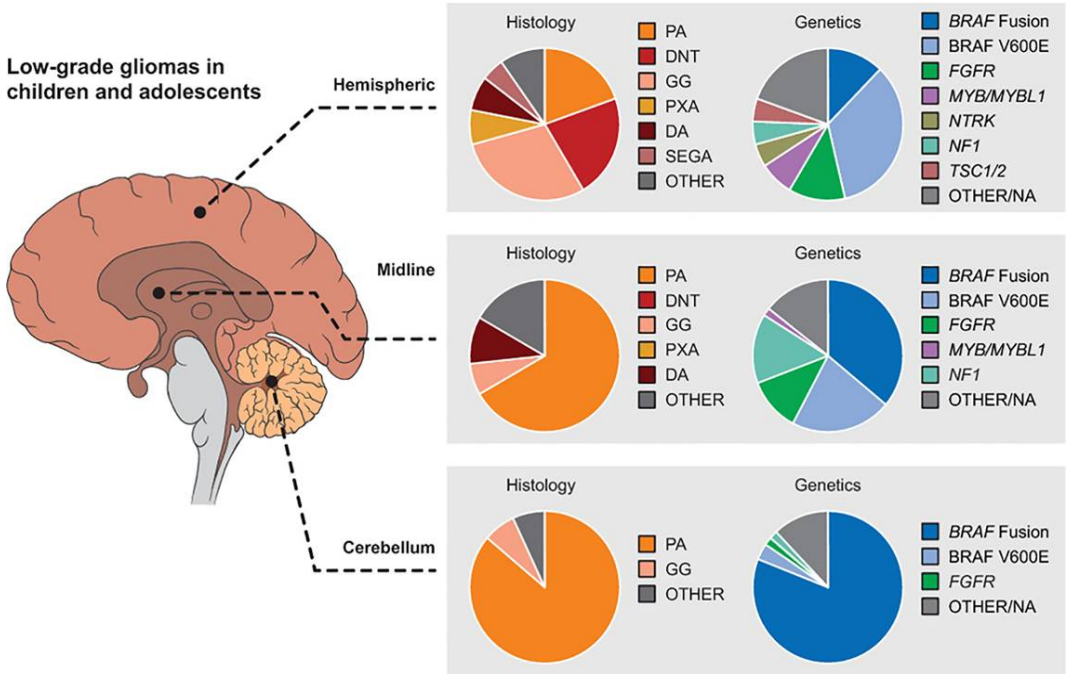
Frequency of certain tumors of the CNS in children



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



Shen CJ, Terezakis SA. The Evolving Role of Radiotherapy for Pediatric Cancers With Advancements in Molecular Tumor Characterization and Targeted Therapies. Front Oncol. 2021 Sep 16;11:679701.

Radiotherapy techniques for low-grade gliomas

Position and immobilization

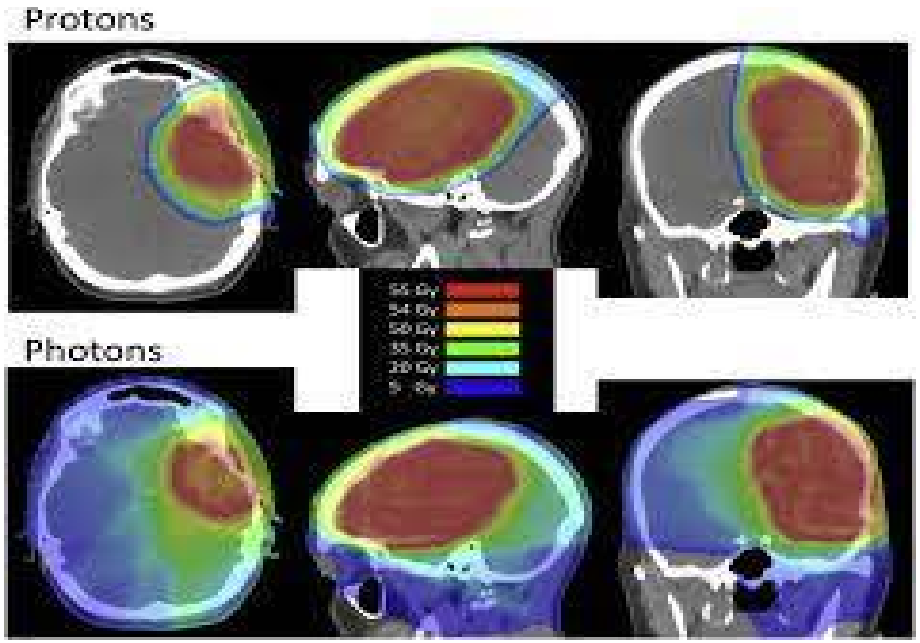
Supination or pronation depending on the anatomy, immobilization - head mask

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



Wang TJC, Mehta MP. Low-Grade Glioma Radiotherapy Treatment and Trials. Neurosurg Clin N Am 2019;30(1):111-118.

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

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

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7–17 years
	Desmoplastic / nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic / nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance

- 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

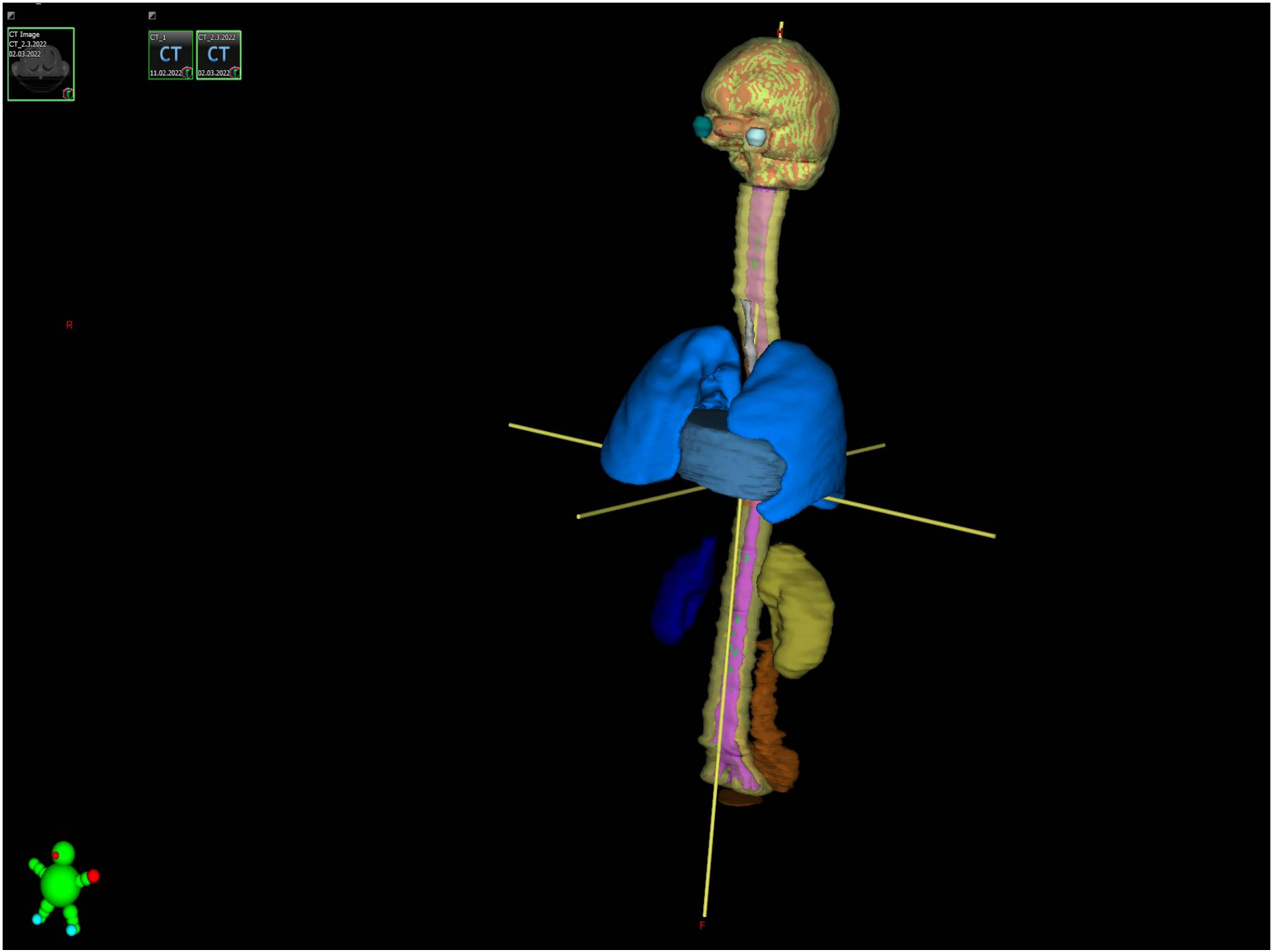
Standard risk group (age >3 years, postoperative residual tumor <1.5 cm^2, no signs of dissemination). The percentage of five-year disease free survival is 80%.

High-risk group (age < 3 years, postoperative residual tumor >1.5 cm^2, 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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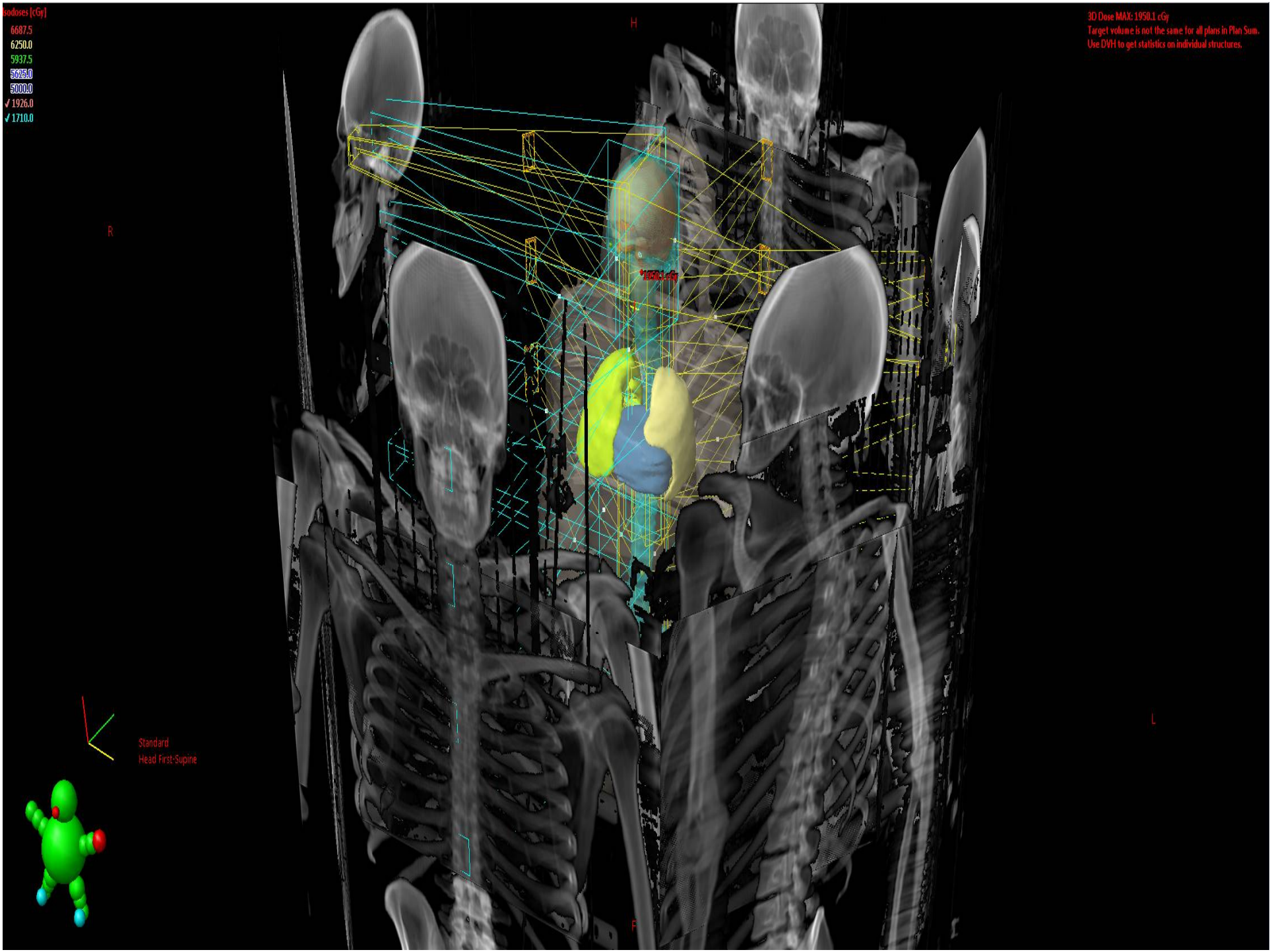
Isodoses [cGy]
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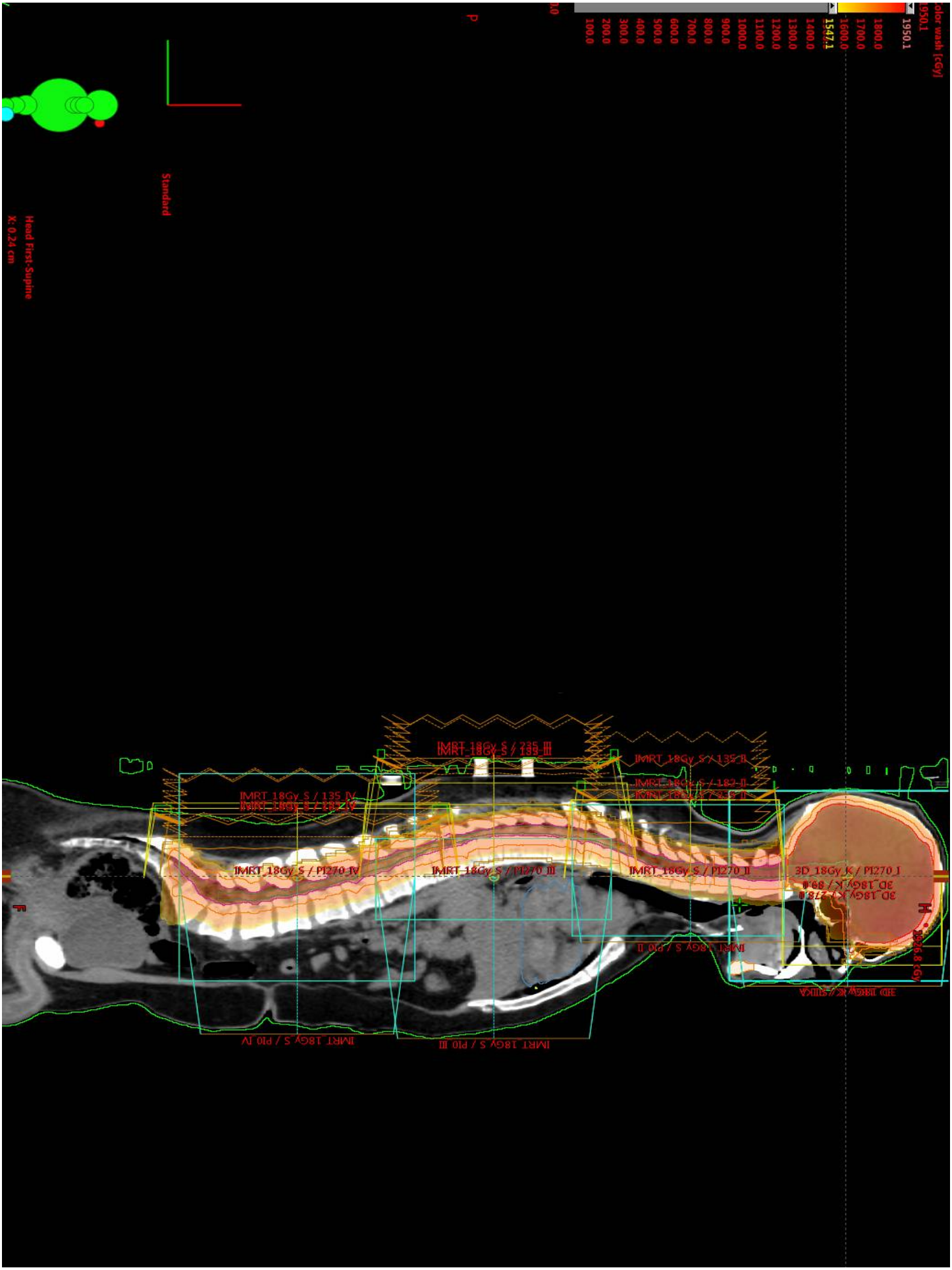
3D Dose MAX: 1950.1 cGy
Target volume is not the same for all plans in Plan Sum.
Use DVH to get statistics on individual structures.
1950.1 cGy
Standard
Head First-Supine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Standard
Head First-Supine
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IMRT_18Gy_S_/_135_II
IMRT_18Gy_S_/_135_IV
IMRT_18Gy_S_/_PI270_IV
IMRT_18Gy_S_/_PI270_III
IMRT_18Gy_S_/_PI270_II
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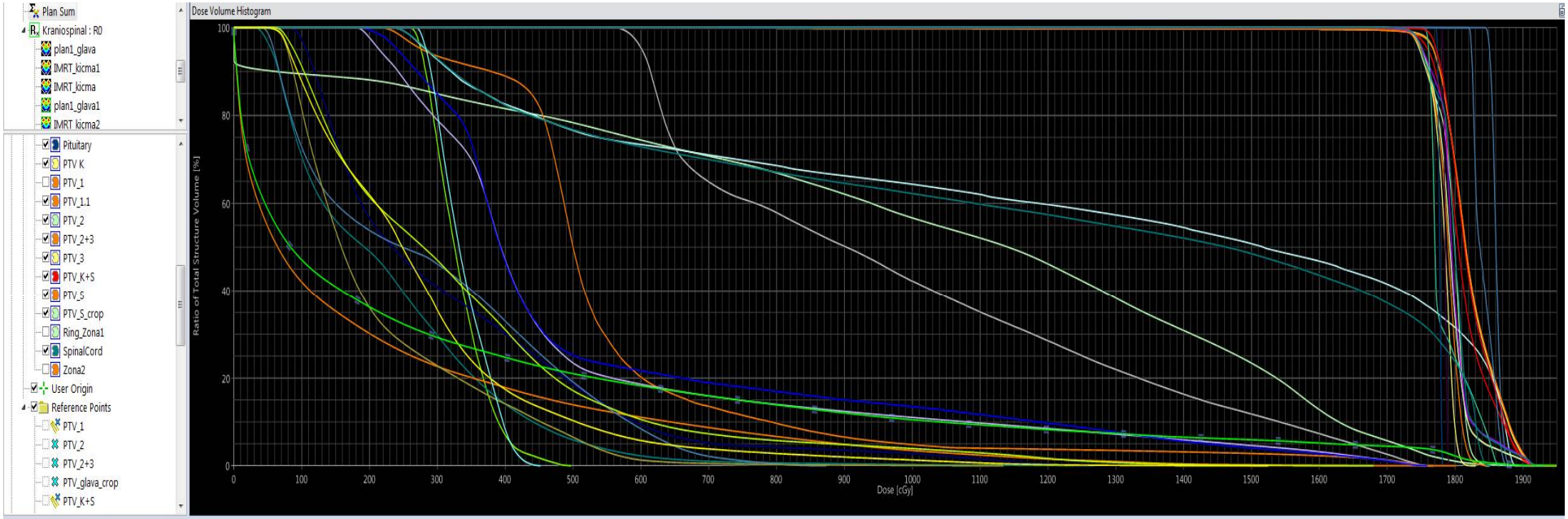
1976.8 cGy

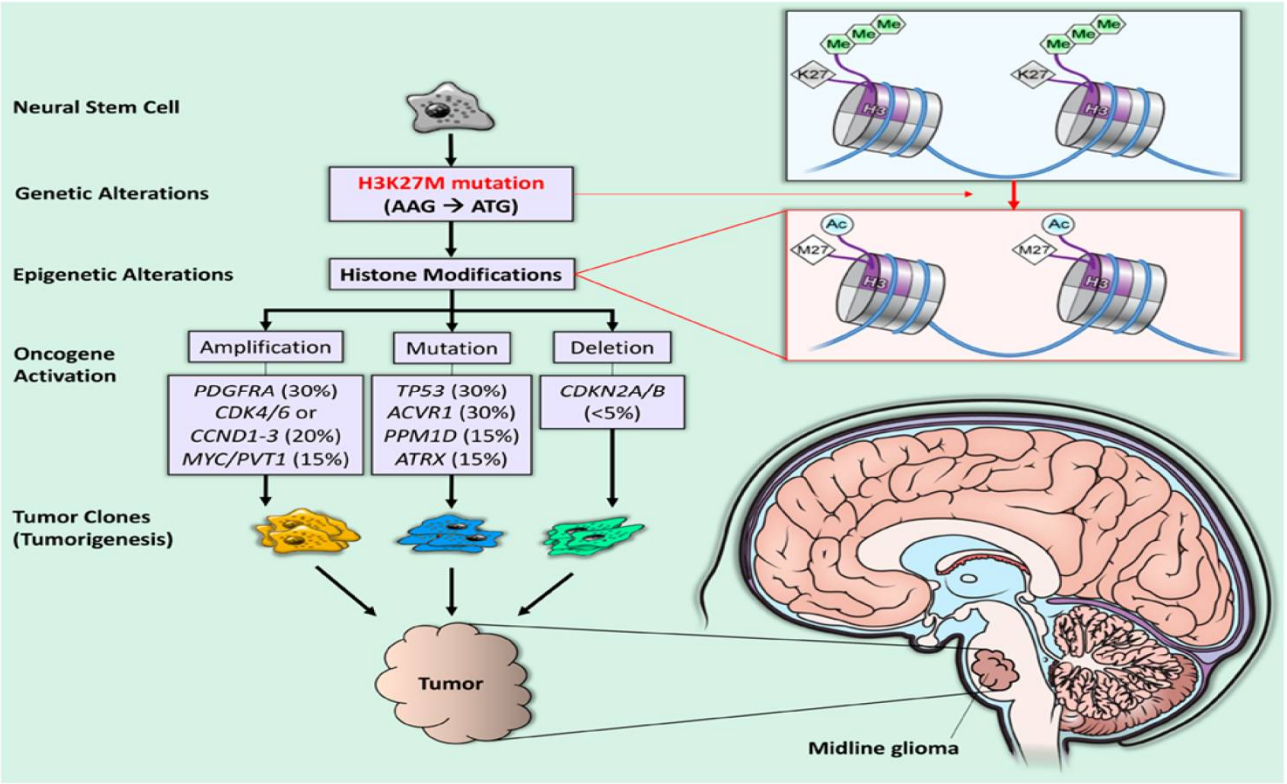


Dose | Reference Points | Dose Statistics

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

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.

Brainstem tumors

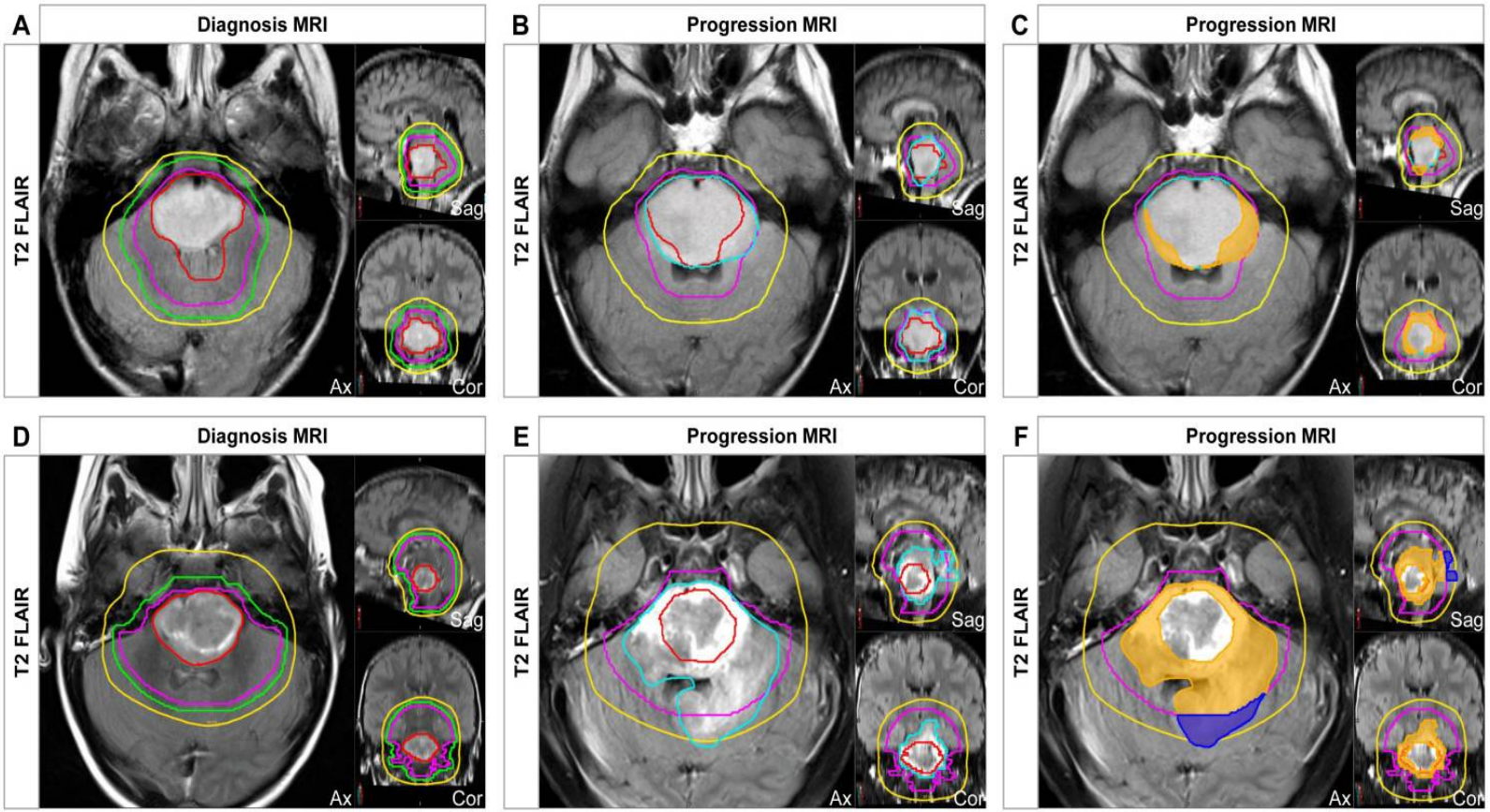
- Include tumors of the midbrain, pons and medulla.
- Focal (5-10%), dorsal exophytic (10-20%), cervicomedullary (5-10%) and diffuse tumors (75-85%).
- Focal, dorsal exophytic and cervicomedullary tumors are usually low grade astrocytomas.
- Treatment:
- **Surgical excision**
- **RT** reserved for inoperable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

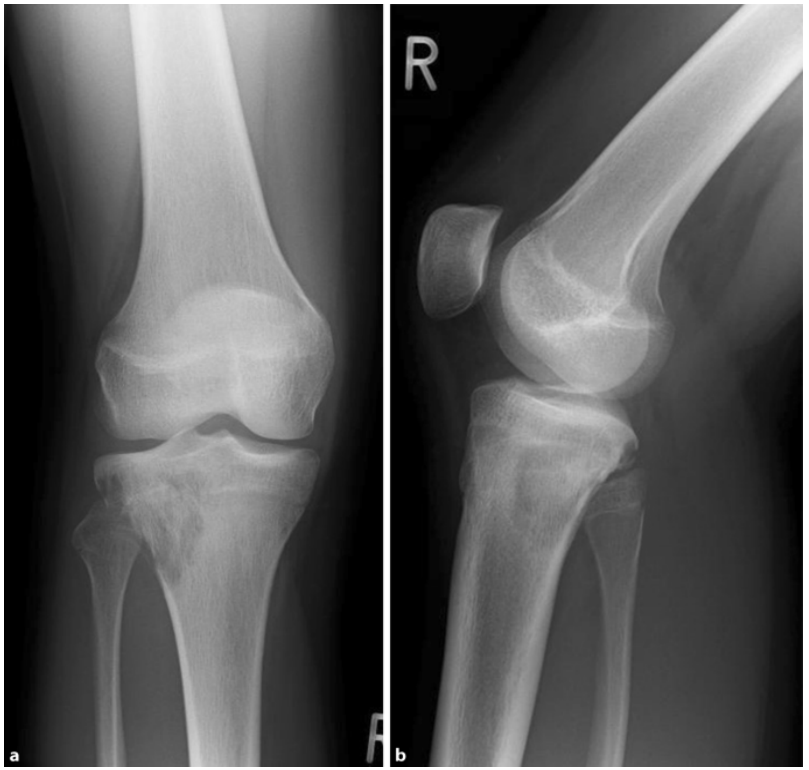
- GTV (Initial or residual tumor)
- CTV= GTV + margin 1-2cm
- PTV = CTV + margin 5-10 mm
- OAR (depending on localization)

- 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)

Kalapurakal 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

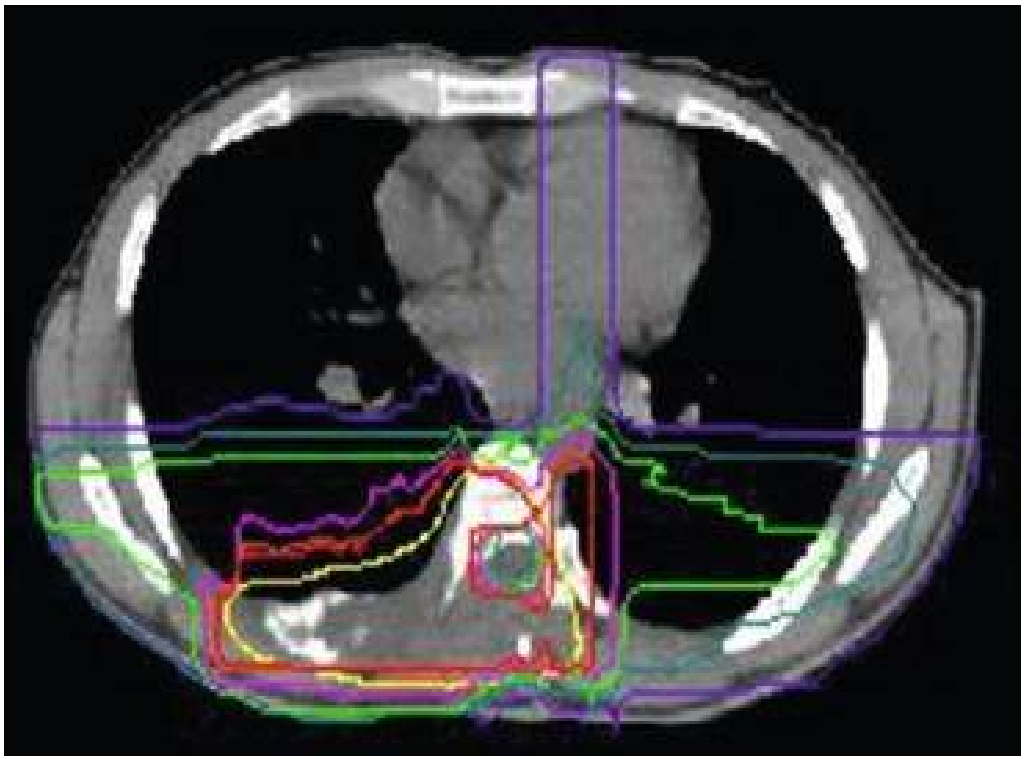
- The most common solid tumors in adolescents and young adults are second in incidence, behind malignant diseases of the hematopoietic system.
- Half of bone tumors in childhood are malignant.



- **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

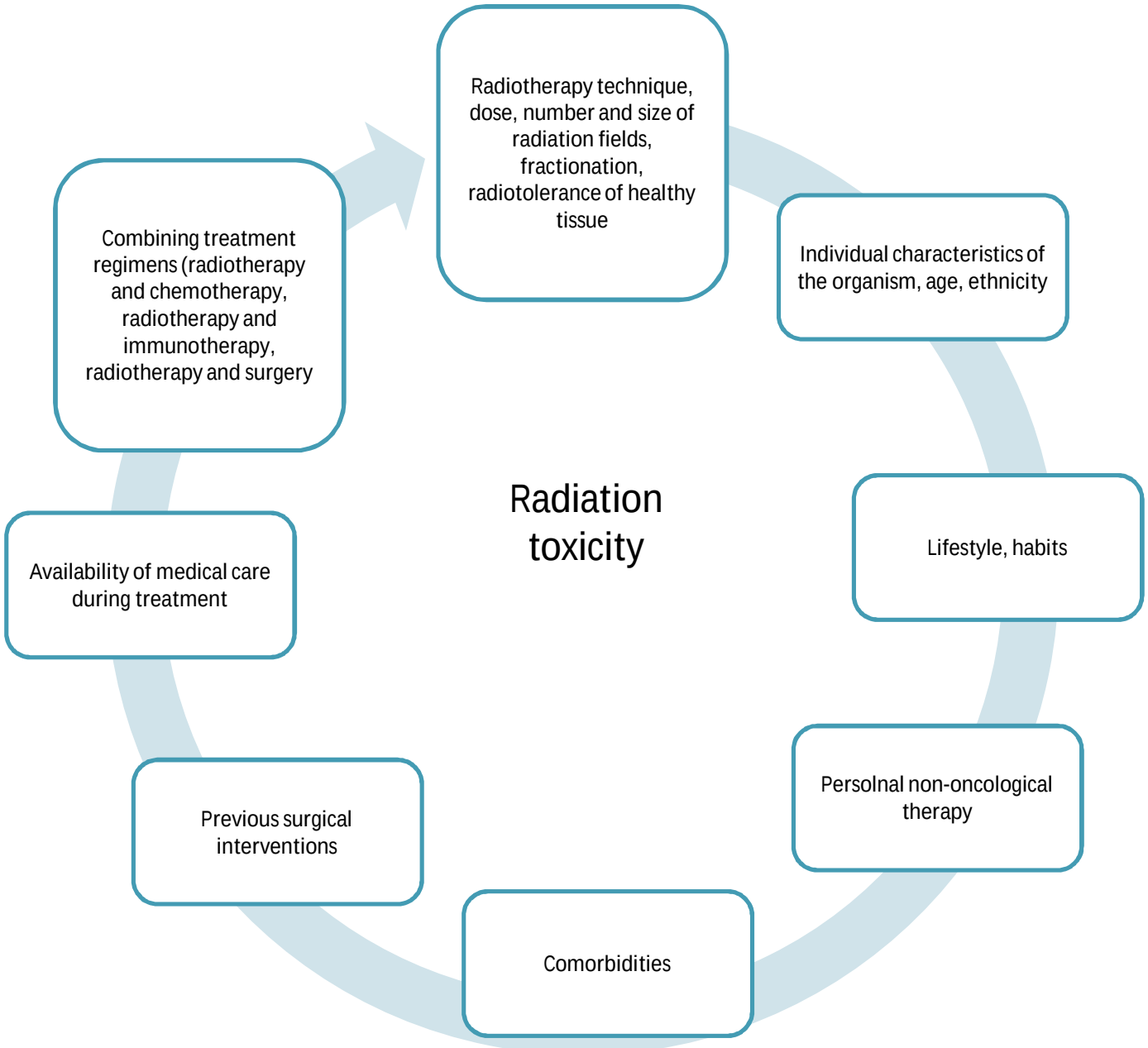
- The advantage of using protons over photons
- RT is carried out according to the same principles as in adults



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

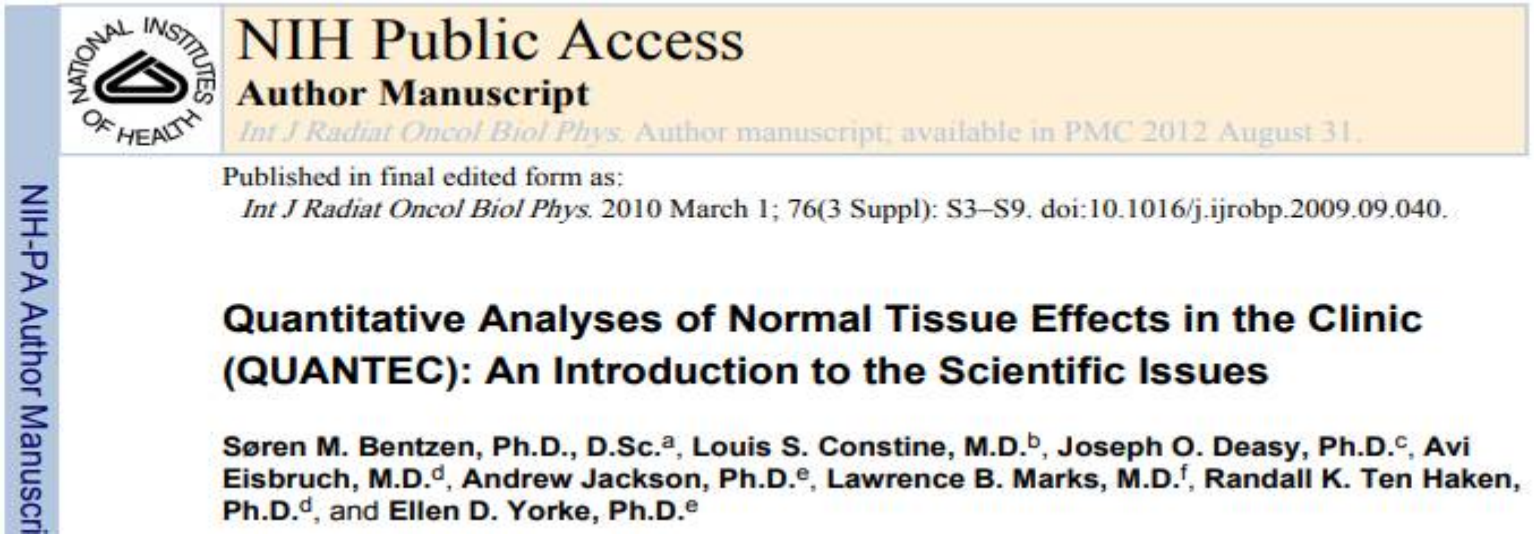
- Radiotolerance of organs at risk
- Therapeutic complications
- Dose-volume effects of healthy tissues

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



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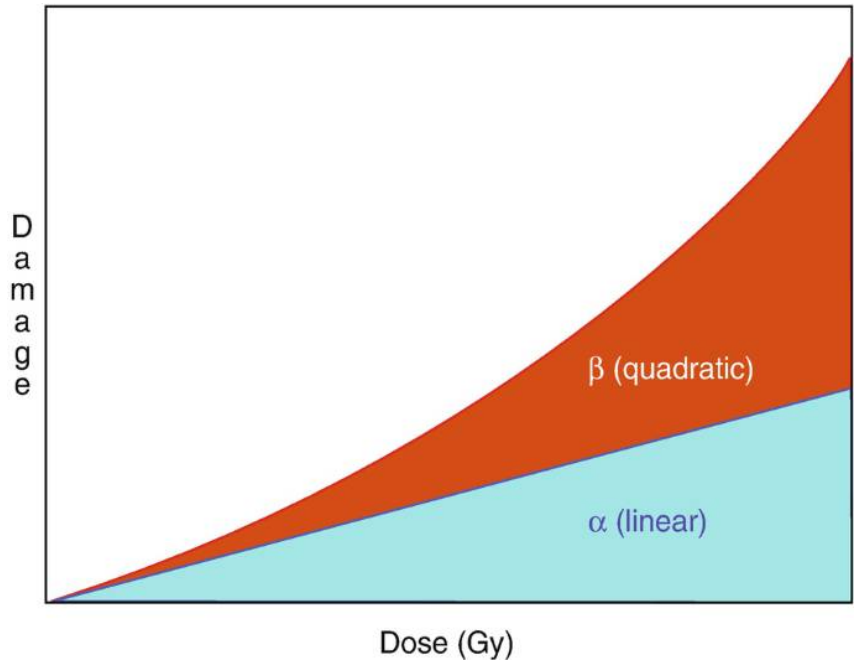
Int J Radiat Oncol Biol Phys. 2010 March 1; 76(3 Suppl): S3–S9. doi:10.1016/j.ijrobp.2009.09.040.

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



Chang, D.S., Lasley, F.D., Das, I.J., Mendonca, M.S., Dynlacht, J.R. (2021). Time Dose and Fractionation Effects. In: Basic Radiotherapy Physics and Biology. Springer, Cham. https://doi.org/10.1007/978-3-030-61899-5_29

Tabela 1. Vrijednosti tolerantnih doza zračenja za pojedine vrste tkiva i organa - konvencionalno frakcionisanje.

Organ pod rizikom	Dozna ograničenja	Izvor
Brahijalni pleksus	Maks. doza < 66 Gy; V_{60} < 5%	RTOG 0619
Moždano stablo	Maks. doza < 54 Gy; V_{60} < 1% V_{59} < 1–10 cm^3	RTOG 0225 QUANTEC
Temporalni režanj	Maks. doza < 60 Gy; V_{65} < 1%	RTOG 0225
Kičmena moždina	Maks. doza < 45 Gy Maks. doza < 50 Gy	RTOG 0623 QUANTEC
Kohlea	V_{55} < 5% Srednja doza < 45 Gy (uz cisplatin < 35 Gy)	RTOG 0615 QUANTEC
Unutrašnje i srednje uho	Srednja doza < 50 Gy	RTOG 0226
Optički nerv	Maks. doza < 54 Gy; V_{60} < 1% Maks. doza < 55 Gy	RTOG 0225 QUANTEC
Retina	Maks. doza < 50 Gy	RTOG 0539
Oči	Maks. doza < 50 Gy Srednja doza < 35 Gy	RTOG 0615, RTOG 0226
Očno sočivo	Maks. doza < 25 Gy Maks. doza < 7 Gy	RTOG 0615 RTOG 0539
Glotis	Srednja doza < 45 Gy	RTOG 0226
Faringealni konstriktori	Srednja doza < 54 Gy V_{50} < 51%; V_{52} < 60%	Caglar HB, Tishler RB, Othus M, et al. Dose to larynx predicts for swallowing complications after IMRT. Int J Radiat Oncol Biol Phys 2008;72(4):1110-8.
Usna šupljina	Srednja doza < 40 Gy	RTOG 0615
Jezik	Maks. doza < 55 Gy V_{65} < 1%	RTOG 0225
Mandibula	Maks. doza < 70 Gy V_{75} < 1cm^3	RTOG 0225, RTOG 0615
Temporomandibularni zglob	Maks. doza < 60 Gy V_{75} < 1cm^3	RTOG 0225, RTOG 0615
Parotidna žlijezda	Srednja doza < 26 Gy (jedna parotida); V_{30} < 50% (jedna parotida); V_{20} < 20 cm^3 (obje parotide) Srednja doza < 20 Gy (jedna parotida); srednja doza < 25Gy (obje parotide)	RTOG 0912 QUANTEC
Jednjak	Srednja doza < 35 Gy V_{54} < 15%; V_{45} < 33%	RTOG 0920
Srce	V_{60} < 33%; V_{45} < 67%; V_{40} < 100%	RTOG 0623
Pluća	Srednja doza < 20 Gy V_{20} < 37%	RTOG 0623
Bubreg	V_{50} < 33%; V_{30} < 67%; V_{23} < 100% Srednja doza < 18 Gy; V_{28} < 20%; V_{23} < 30%; V_{20} < 32%; V_{12} < 55%	RTOG 0436 QUANTEC
Jetra	V_{35} < 50%; V_{30} < 100% Srednja doza < 32 Gy (metastaze); Srednja doza < 28 Gy (primarni tumor jetre)	RTOG 0436 QUANTEC
Duodenum	Maks. doza < 60 Gy V_{45} < 33%	Spalding AC, Jee, KW, Vineberg K, et al. Potential for dose-escalation and reduction of risk in pancreatic cancer using IMRT optimization with lexicographic ordering and gEUD-based cost functions. Med Phys 2007;34(2):521-9.

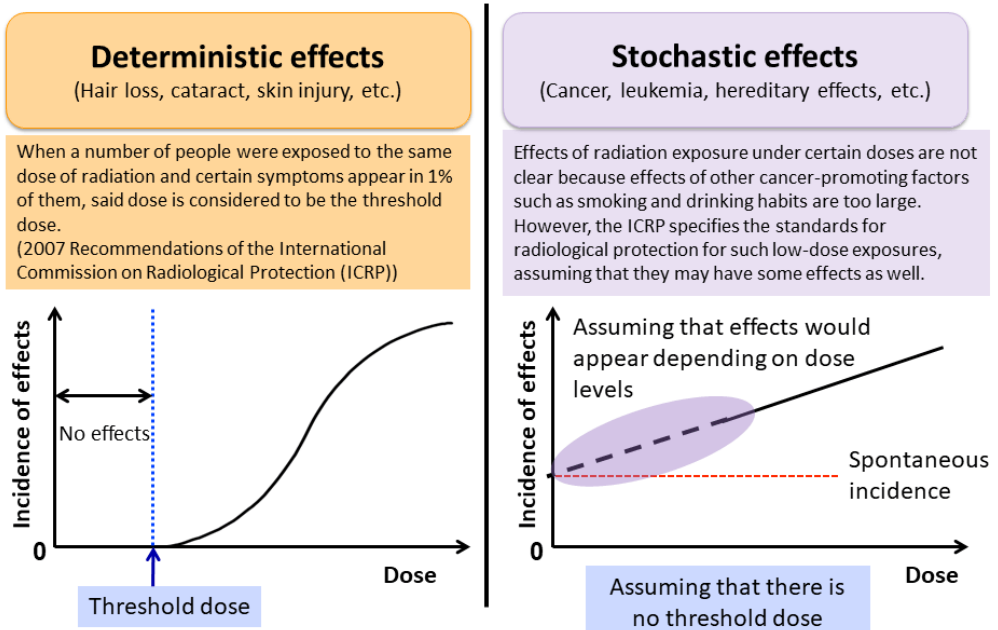
Radiotolerance of OAR with conventional fractionation regimen

Mileusnić D, et al. Radijaciona onkologija. Banja Luka, 2020.

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 (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) (vesion 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

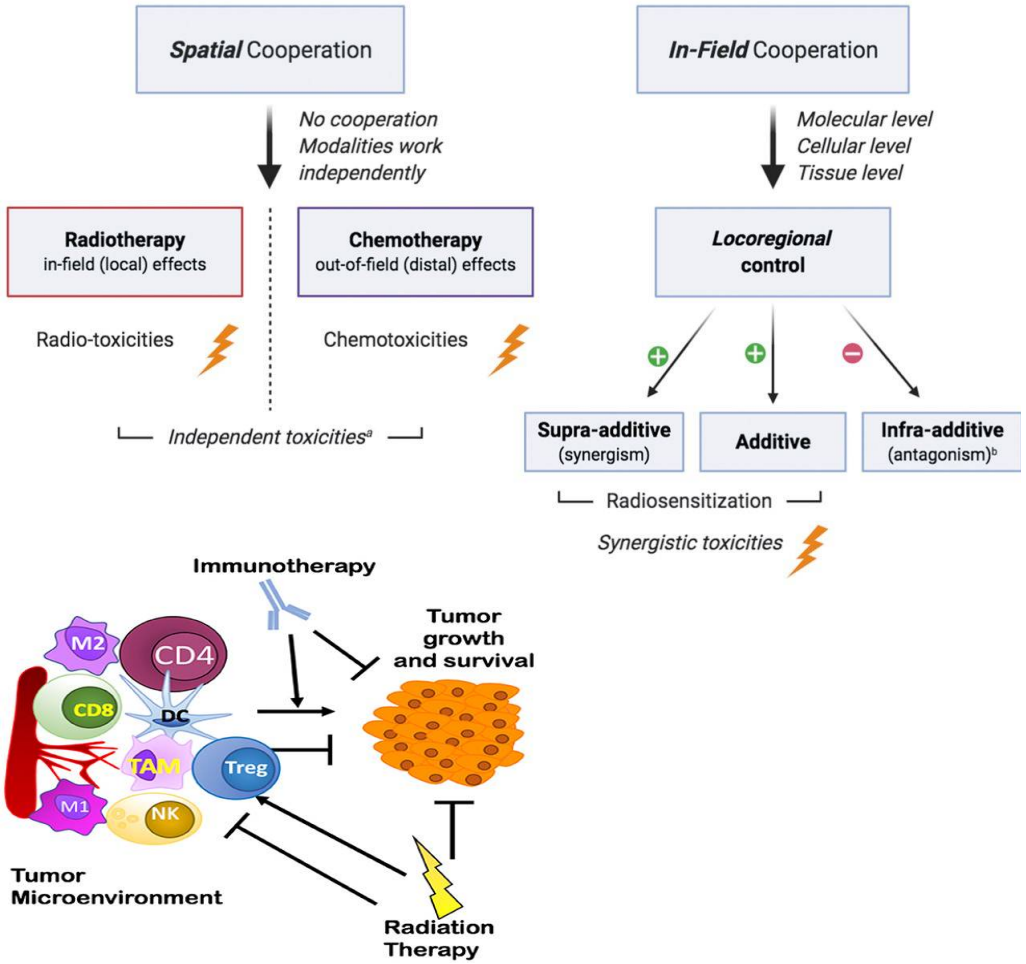
Combined treatment modalities and radiation toxicity

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

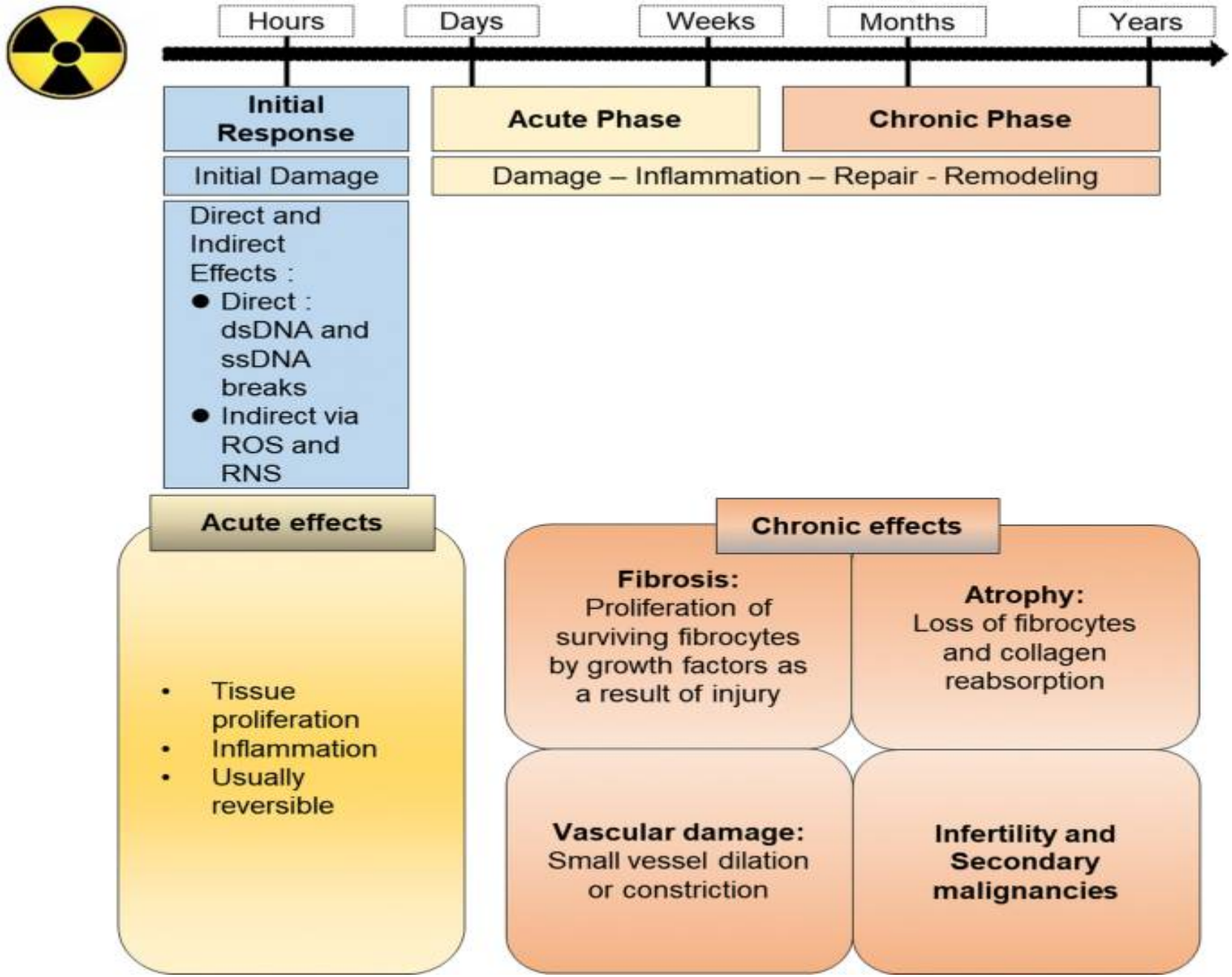
Chemotherapy: most often potentiates the desired and unwanted effects of radiotherapy and vice versa, increases the frequency and intensity of acute and late complications of radiotherapy

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

Hormonal therapy

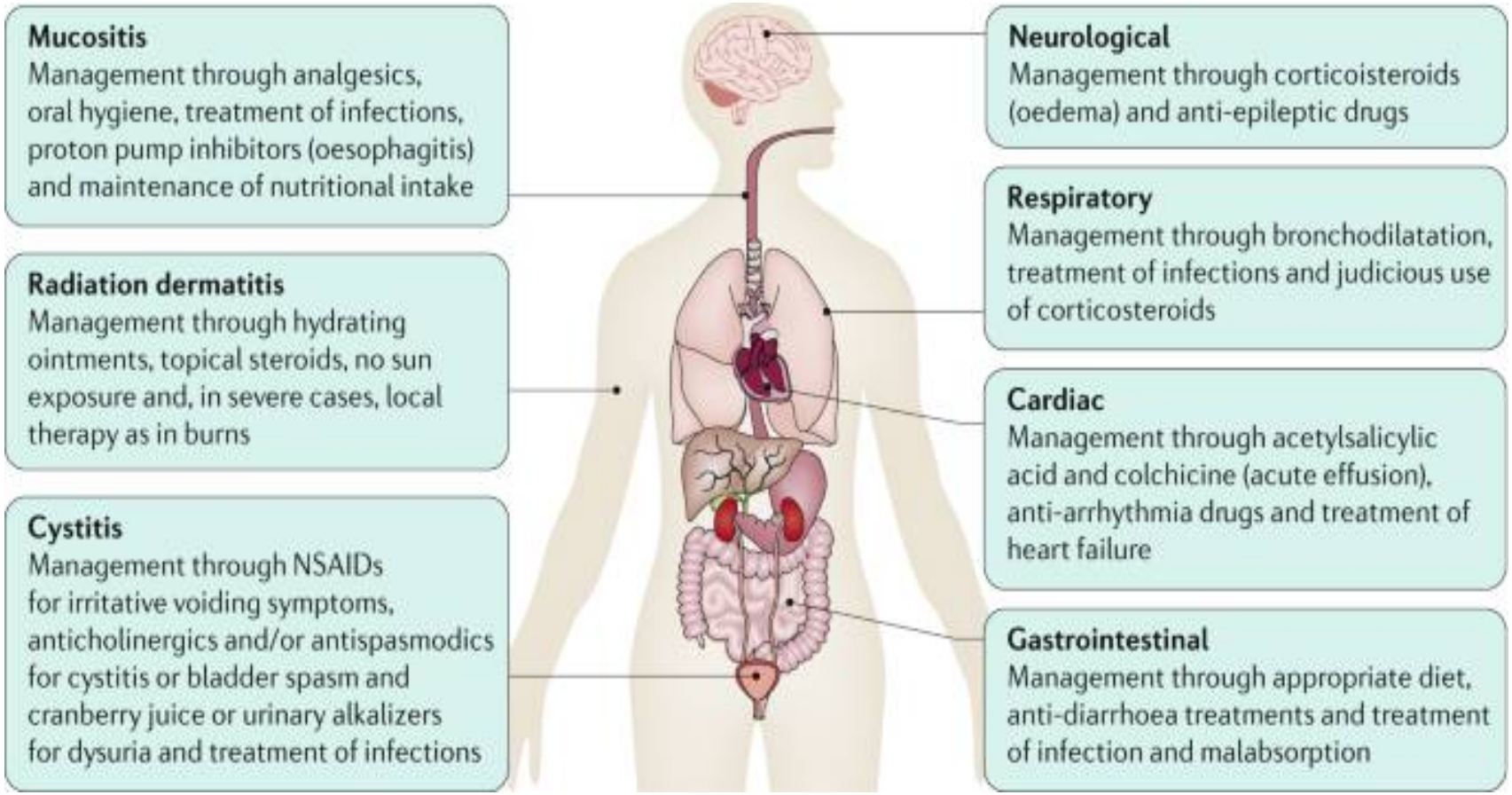


Rallis KS, Lai Yau TH, Sideris M. Chemoradiotherapy in Cancer Treatment: Rationale and Clinical Applications. Anticancer Res. 2021 Jan;41(1):1-7.
Darragh LB, Oweida AJ, Karam SD. Overcoming Resistance to Combination Radiation-Immunotherapy: A Focus on Contributing Pathways Within the Tumor Microenvironment. Front Immunol 2019;9:3154.



Mun, GI., Kim, S., Choi, E. et al. Pharmacology of natural radioprotectors. Arch. Pharm. Res. 41, 1033–1050 (2018).

Radiation toxicity



De Ruysscher, D., Niedermann, G., Burnet, N.G. et al. Radiotherapy toxicity. Nat Rev Dis Primers 5, 13 (2019).

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%)

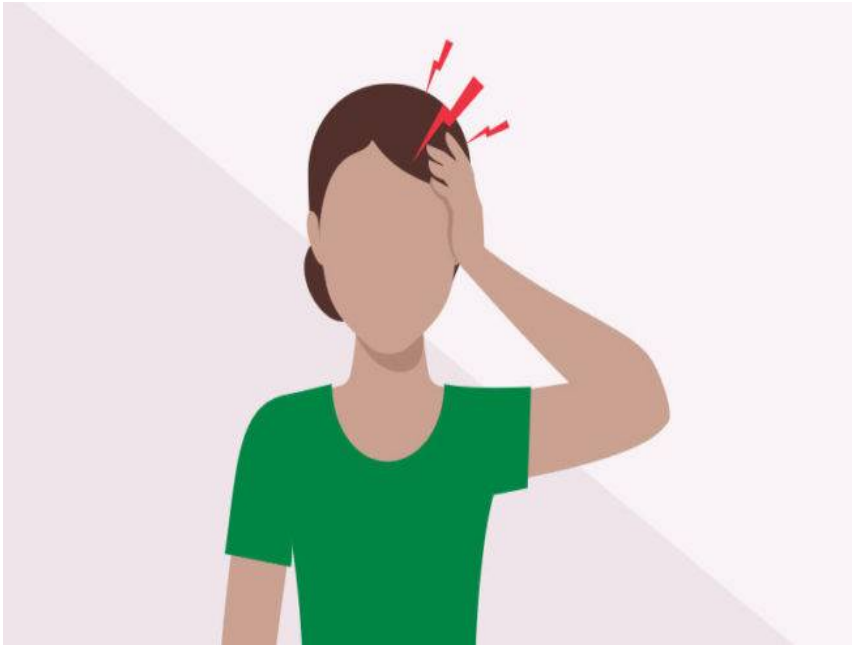
Diffuse leukoencephalopathy

Neurophysiological damage - impairment of intellectual functions, drop in IQ

Cerebrovascular complications

Secondary radiation-induced CNS tumors (< 3%)

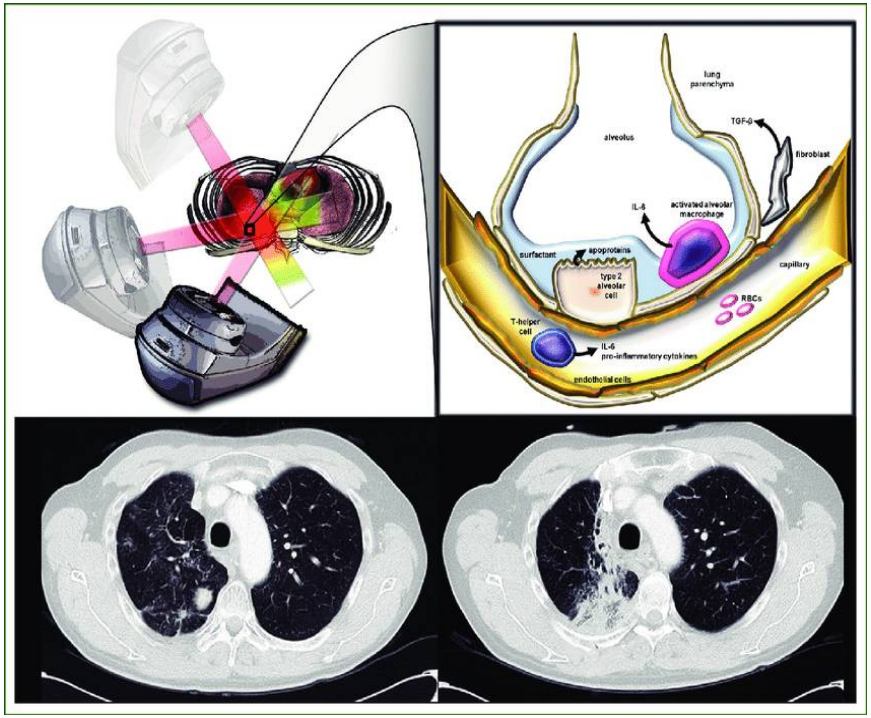
Radiation damage to the eye lens, retina and optic nerve



Slika dostupna na: Should I Worry About a Headache Only on One Side? At: https://health.clevelandclinic.org/when-should-i-worry-about-a-one-sided-headache/

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**



Palmer JD, Zaorsky NG, Witek M, Lu B. Molecular markers to predict clinical outcome and radiation induced toxicity in lung cancer. J Thorac Dis 2014;6(4):387-98.

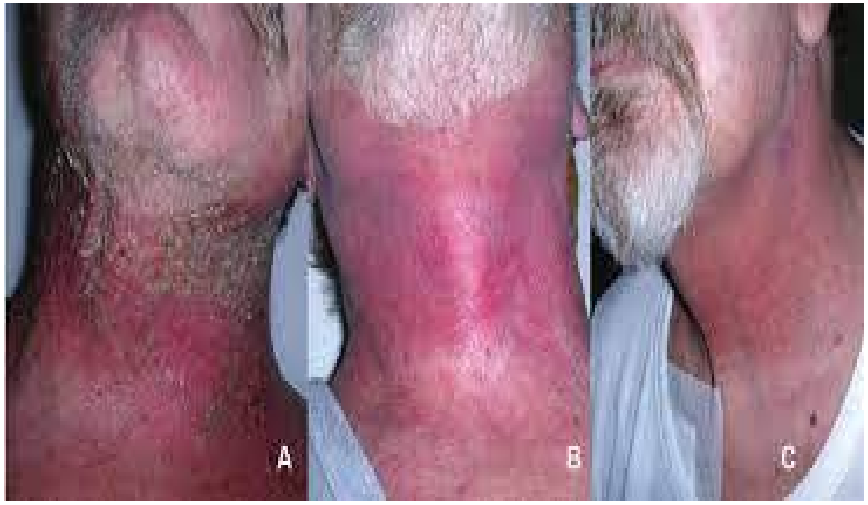
Radiodermatitis

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.

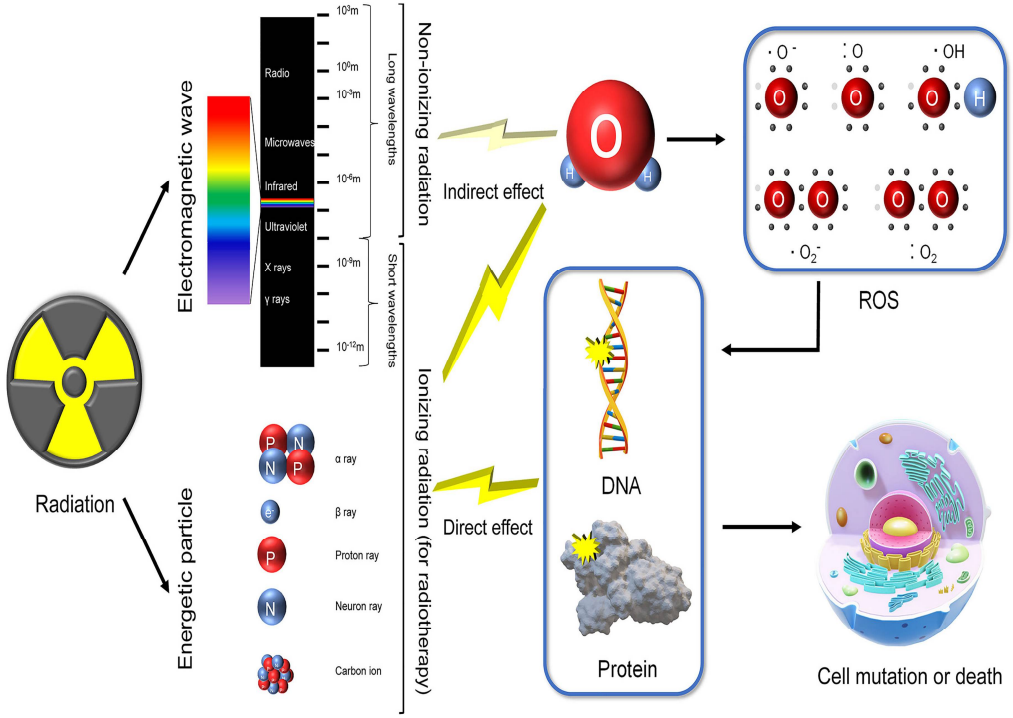
Gastrointestinal radiation toxicity

Acute

- Esophagitis
- Enterocolitis
- Radiation proctitis

Chronic

- Strictures
- Fibrosis
- Ulcerations
- Intestinal adhesions
- Fistula



Chen G, Han Y, Zhang H, Tu W, Zhang S. Radiotherapy-Induced Digestive Injury: Diagnosis, Treatment and Mechanisms. Front Oncol. 2021;11:757973.

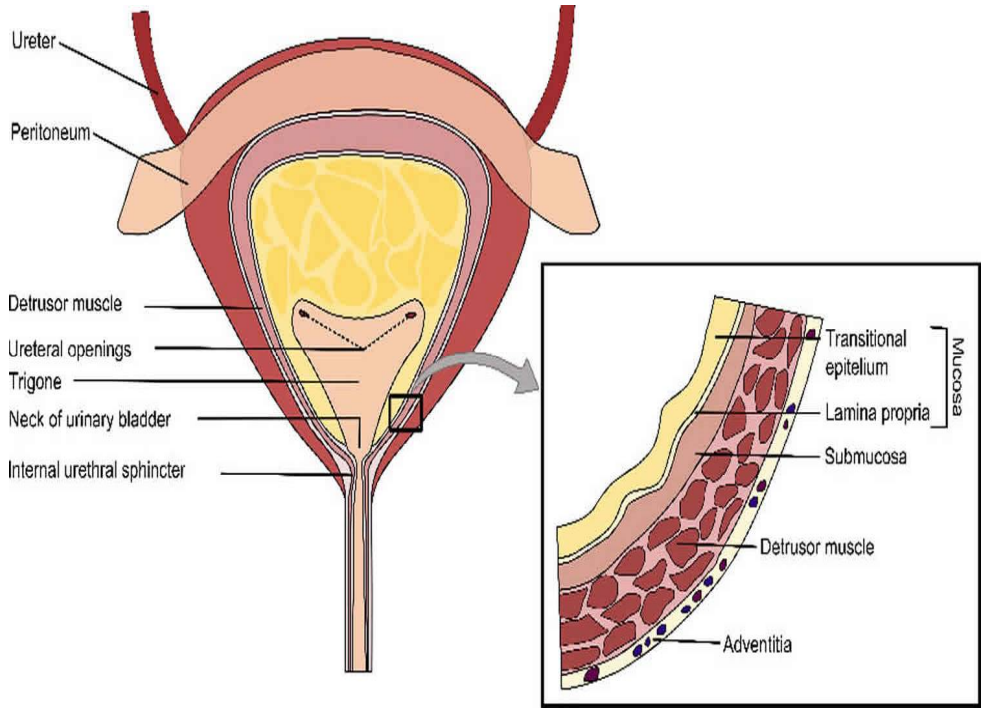
Genitourinary radiation toxicity

Acute

- Cystitis

Chronic

- Chronic radiation cystitis
- Fibrosis
- Ulcerations
- Fistula



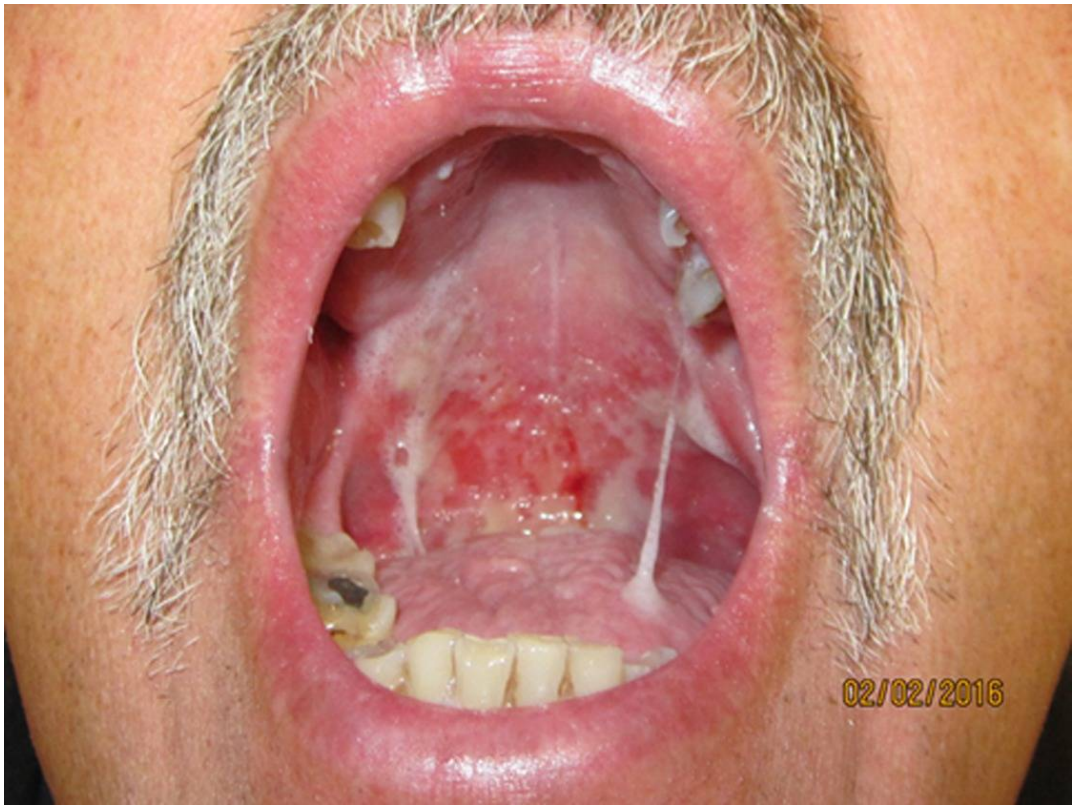
Slika: Radiation cystitis. At: https://healthjade.net/radiation-cystitis/

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

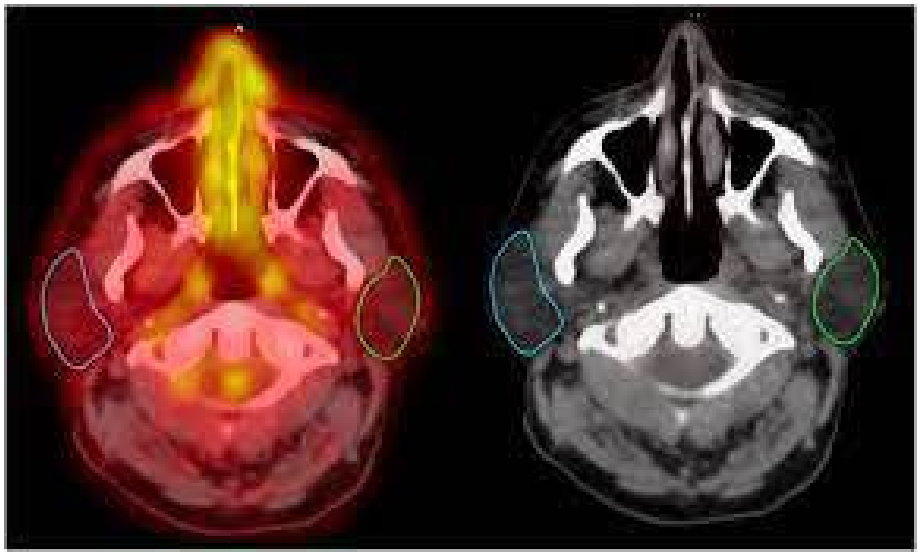
Xerostomia
Tooth/root caries
Oral mucositis
Loss of taste
Fungal/bacterial/viral infections
Increased phlegm
Trismus
Osteoradionecrosis



Cancer Medicine, Volume: 6, Issue: 12, Pages: 2918-2931, First published: 25 October 2017, DOI: (10.1002/cam4.1221)

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



Mouminah A, Borja AJ, Hancin EC, Chang YC, Werner TJ, Swisher-McClure S, Korostoff J, Alavi A, Revheim ME. 18F-FDG-PET/CT in radiation therapy-induced parotid gland inflammation. Eur J Hybrid Imaging. 2020 Dec 1;4(1):22.

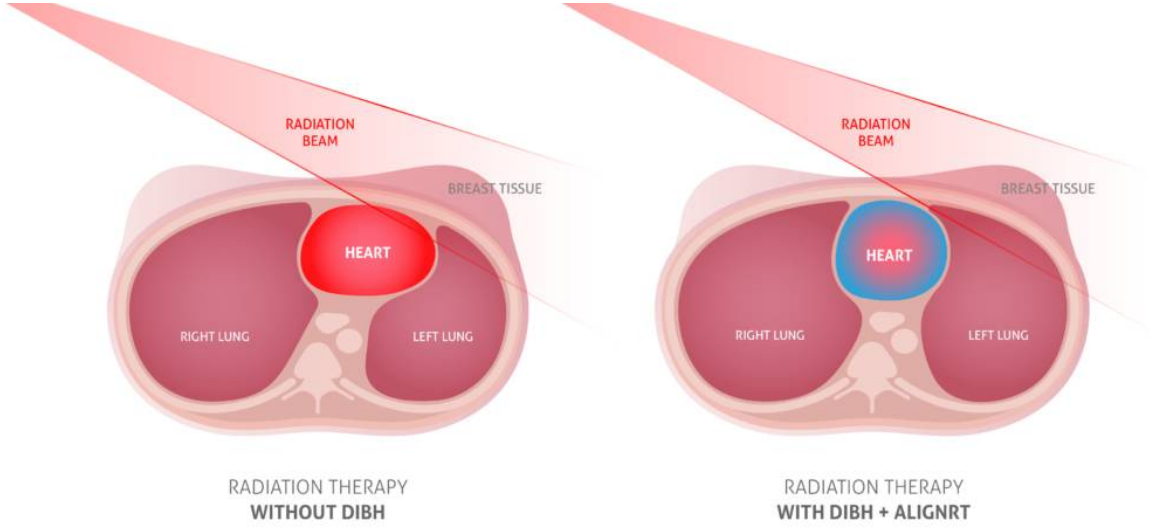
Radiation damage to the heart and pericardium

Acute exudative pericarditis

Late pericardial effusion (cardiac tamponade)

Constrictive pericarditis

Pancarditis = cardiomyofibrosis (cardiomyopathy + pericardial constriction)



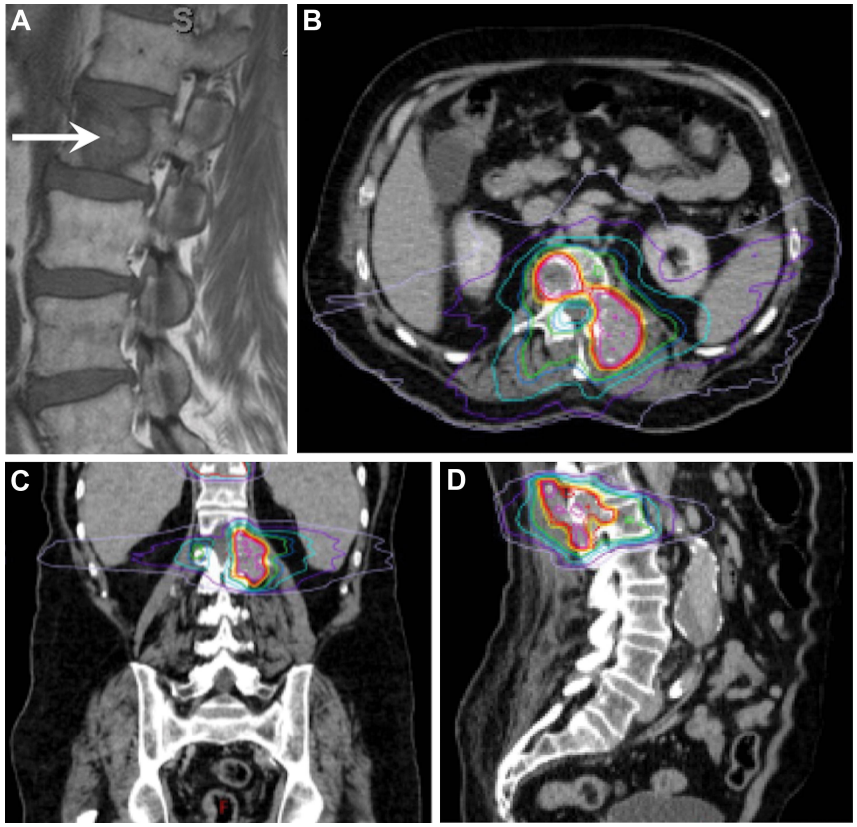
Left-Breast Cancer Patient's Side Effect Risks. Dostupno na https://www.saferradiationtherapy.com/27-of-left-breast-cancer-patients-are-at-risk-of-having-heart-damage/

Radiation myelopathy

<u>Acute radiation myelopathy</u> - up to 3 months after RT

Demyelination of the spinal cord

<u>Late radiation myelopathy</u> - months and years after RT, most often after a latent period

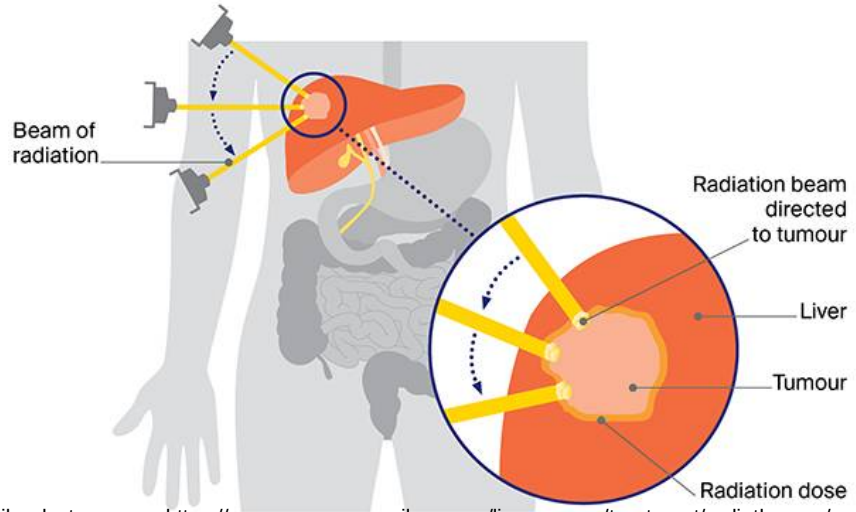


Gottumukkala S, Srivastava U, Brocklehurst S, Mendel JT, Kumar K, Yu FF, Agarwal A, Shah BR, Vira S, Raj KM. Fundamentals of Radiation Oncology for Treatment of Vertebral Metastases. Radiographics. 2021 Nov-Dec;41(7):2136-2156.

Liver radiation toxicity

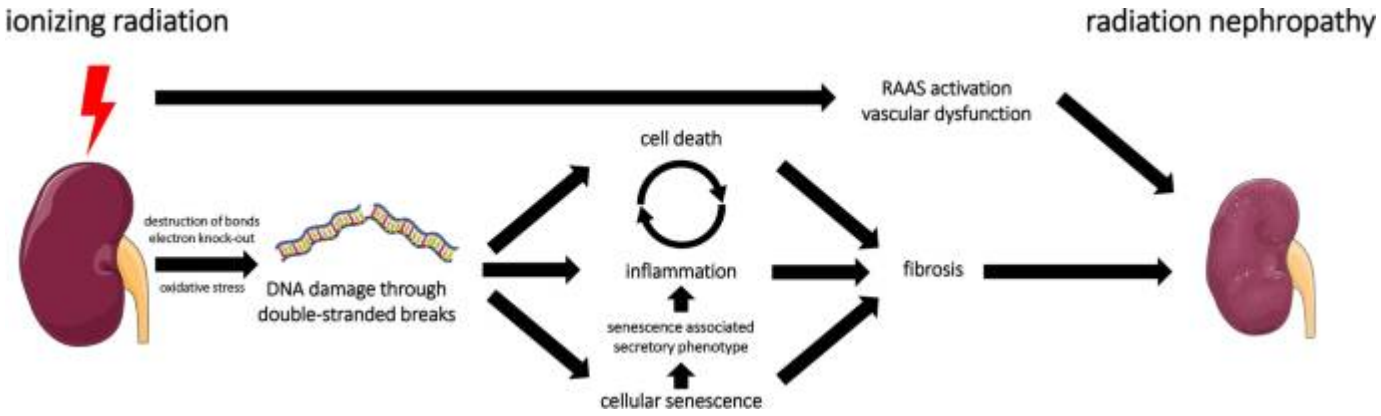
- SBRT or conventional treatment regimens
- Damage caused by irradiation of primary or secondary tumors
- Liver damage as a risk organ
- Veno-occlusive disorder is the basis of the swelling
- Symptoms 4-8 weeks after RT (hepatomegaly, ascites, increase in trasaminases, icterus, encephalopathy, pain in 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



Slika dostupna na: https://www.cancercouncil.com.au/liver-cancer/treatment/radiotherapy/

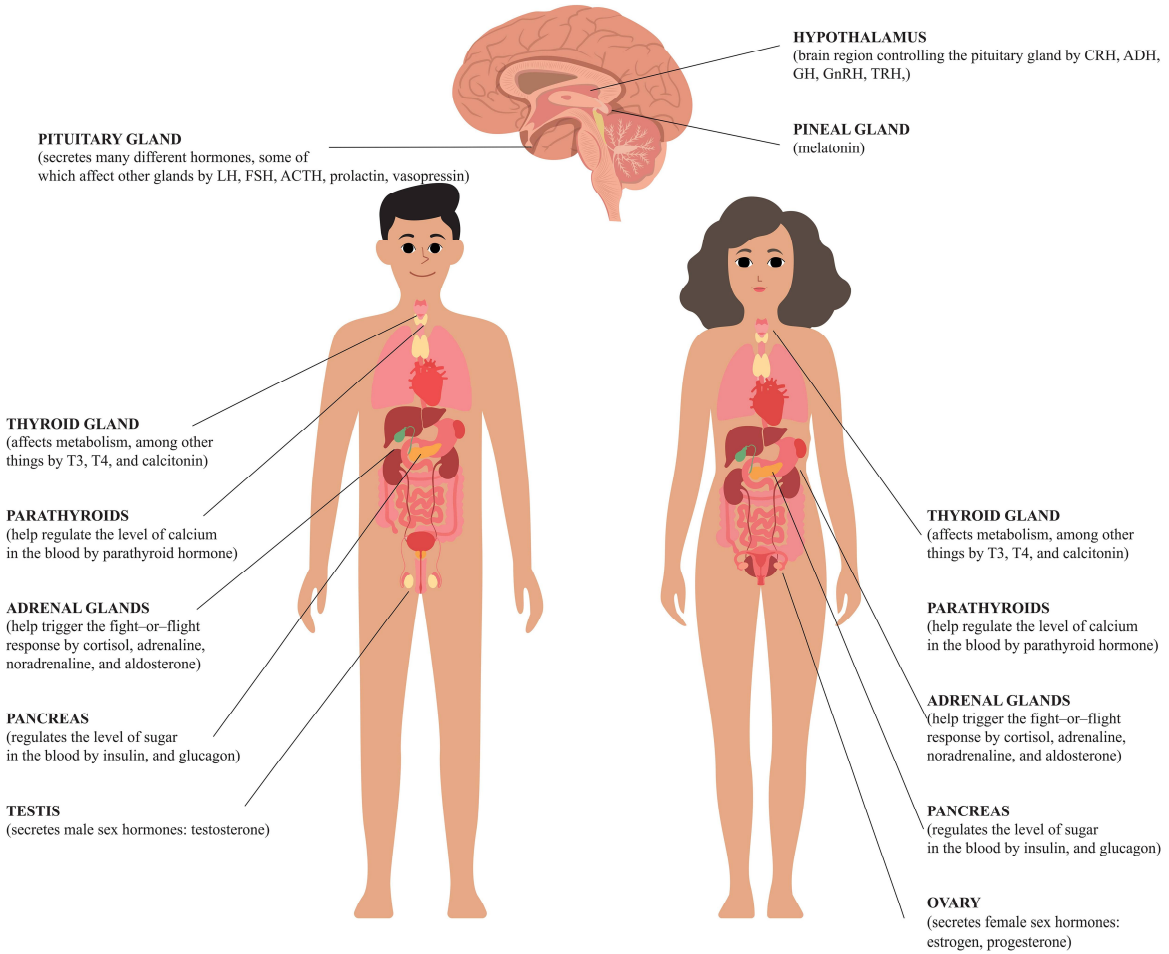
Renal radiation toxicity



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

Klaus R, Niyazi M, Lange-Sperandio B. Radiation-induced kidney toxicity: molecular and cellular pathogenesis. Radiat Oncol 2021;16(1):43.

Endocrine system radiation toxicity



Bendarska-Czerwińska A, Zmarzły N, Morawiec E, Panfil A, Bryś K, Czarniecka J, Ostenda A, Dziobek K, Sagan D, Boroń D, Michalski P, Pallazo-Michalska V, Grabarek BO. Endocrine disorders and fertility and pregnancy: An update. Front Endocrinol (Lausanne). 2023;13:970439.

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

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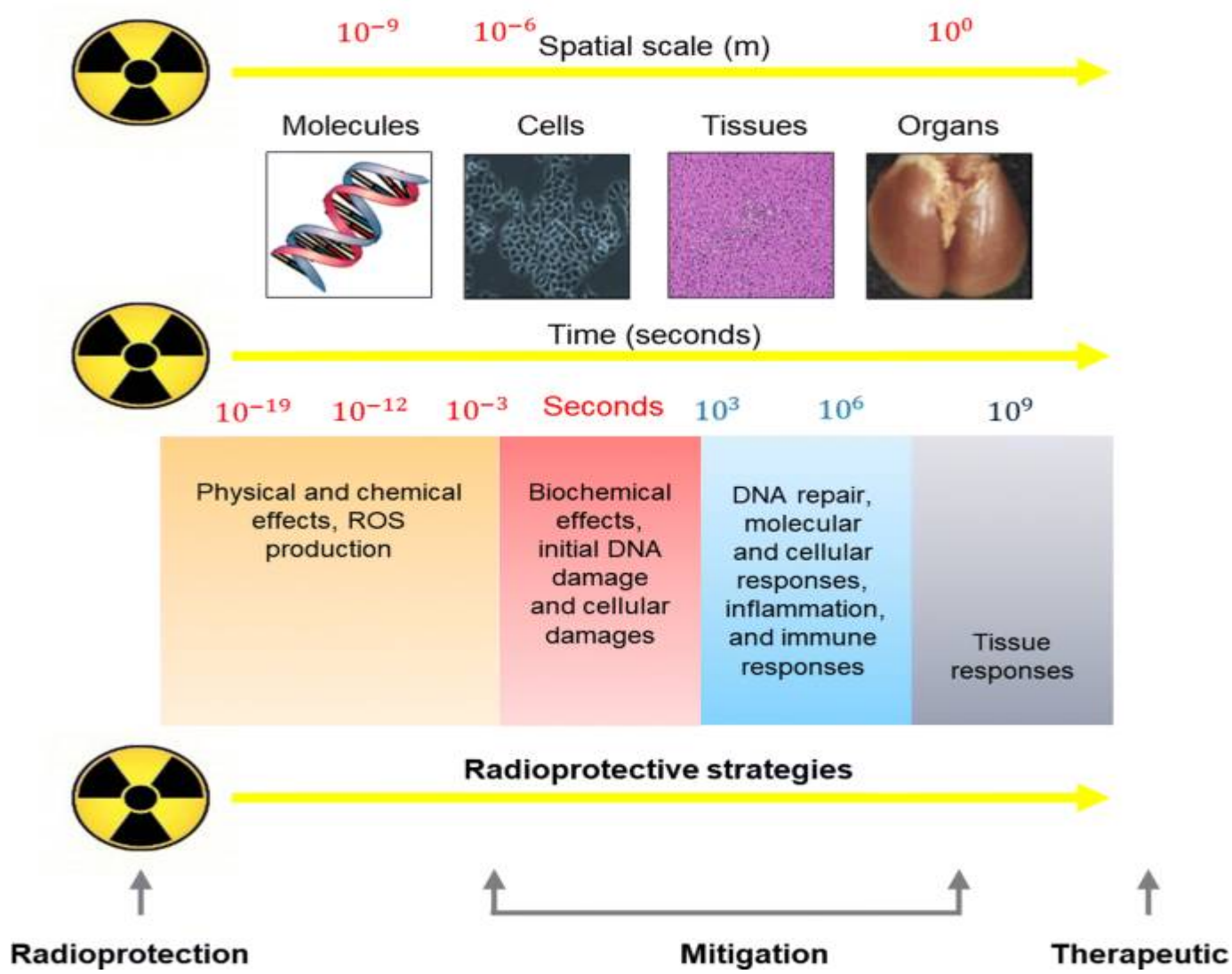
Highlights

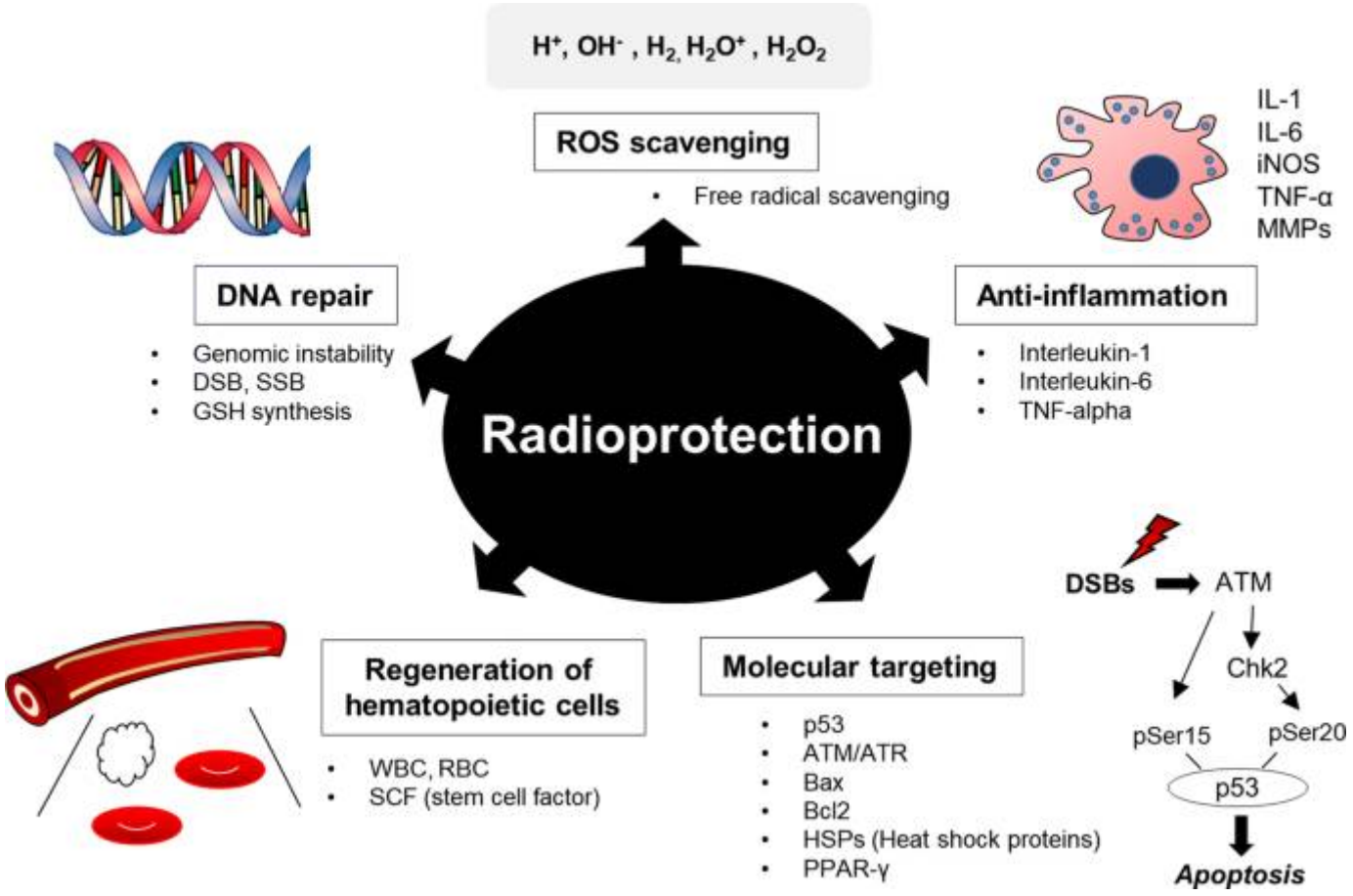
- RT for pediatric cancer can cause long-term adverse normal tissue effects
- Radiation damage depends on the radiation dose and volume, and developmental status
- For some organs, chemotherapy can exacerbate the effects of radiation
- PENTEC seeks to increase knowledge about pediatric RT dose constraints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

Radioprotectors, mitigators and radiation toxicity therapy



Mun, GI., Kim, S., Choi, E. et al. Pharmacology of natural radioprotectors. Arch. Pharm. Res. 41, 1033–1050 (2018).

Radioprotectors and mitigators



Mun, GI., Kim, S., Choi, E. et al. Pharmacology of natural radioprotectors. Arch. Pharm. Res. 41, 1033–1050 (2018).

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!