



**UNIVERSITY OF KRAGUJEVAC
FACULTY OF MEDICAL SCIENCES**



Radiotherapy of bone, soft tissue and skin malignancies

**Assist. Professor Marija Živković Radojević, MD, PhD
Center for Radiation Oncology, University Clinical Center Kragujevac
Assist. Professor Neda Milosavljević, MD, PhD
Center for Radiation Oncology, University Clinical Center Kragujevac**

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Radiotherapy of soft tissue tumors

- Fibrous tissue
 - Fat tissue
 - Blood vessels
 - Smooth and striated muscles
 - Tendons and cartilage
 - Tumors of peripheral glands
-
- 40% occur on the extremities
 - 70% in this group is above the knee
 - 10% in the retroperitoneum
 - 20% chest and abdominal wall
-
- Treatment:
 - Surgery
 - Radiotherapy
 - Chemotherapy

Histological subtypes

Adipocytic tumours

Fibroblastic and myofibroblastic tumours

Fibrohistiocytic tumours

Vascular tumours

Pericytic (perivascular) tumours

Smooth muscle tumours

Skeletal muscle tumours

Gastrointestinal stromal tumours

Chondro-osseous tumours

Peripheral nerve sheath tumours

Tumours of uncertain differentiation

Undifferentiated small round cell sarcomas

Review

The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives

Marta Sbaraglia¹, Elena Bellan¹, Angelo P. Dei Tos^{1,2}

Major changes in the 2020 WHO classification.

TUMOUR CATEGORY	MAJOR CHANGES	Age & Distribution of new entities
Adipocytic	Addition of atypical spindle cell/pleomorphic lipomatous tumour in benign tumours Addition of myxoid pleomorphic liposarcoma in malignant tumours Recognition of adverse prognostic features in dedifferentiated liposarcoma	Limbs Children and young adults, Mediastinum
Fibroblastic and myofibroblastic tumours	Locally aggressive and malignant variety of solitary fibrous tumour introduced Pathognomic genetic mutations of SFT identified and predictors of recurrence and metastases enumerated Angiofibroma of soft tissues introduced as a benign tumour Superficial CD34 positive fibroblastic tumour added in rarely metastasizing category Ewsr1- Smad3 Positive Fibroblastic Tumour	Lower extremity, middle-age females Lower extremities, middle-aged adults Females, superficial location in hands and feet
Vascular	Epithelioid Hemangioendothelioma with YAP1- TFE3 fusion in malignant category	Young adults, head and neck
Smooth muscle tumour	Smooth muscle tumour of uncertain malignant potential added Inflammatory leiomyosarcoma designated as a separate entity	Young adults, Extremities and trunk
Skeletal muscle tumour	Ectomesenchymoma reclassified as skeletal muscle tumour	
Peripheral nerve sheath tumour	Melanotic schwannoma reclassified as Melanotic malignant peripheral nerve sheath tumour Ectomesenchymoma reclassified as skeletal muscle tumour Addition of malignant perineurioma and removal of malignant triton tumour	Adults, spinal or autonomic nerve
Chondro-osseous tumours	Removal of mesenchymal chondrosarcoma which has been classified as bone tumour	
Tumours of uncertain differentiation	Acral fibromyxoma reclassified as fibroblastic tumour and removal of ectopic hamartomatous thymoma Addition of angiomyolipoma in benign and epithelioid angiomyolipoma in locally aggressive category Phosphaturic mesenchymal tumours reclassified from rarely metastasizing group into benign and malignant varieties Addition of NTRK rearranged spindle cell neoplasm in malignant category Merging of undifferentiated/unclassified sarcomas	Children, extremities or trunk

Histological grading according to FNCLCC	
Tumour differentiation	
Score 1	Closely resembling normal tissue
Score 2	Histological typing is certain
Score 3	Embryonal or undifferentiated sarcomas
Mitotic count (per 1.7 mm ²)	
Score 1	0-9 mitoses per 1.7 mm ²
Score 2	10-19 mitoses per 1.7 mm ²
Score 3	>19 mitoses per 1.7 mm ²
Tumour necrosis	
Score 0	No necrosis
Score 1	<50% tumour necrosis
Score 2	≥50% tumour necrosis
Histological grade	Grade 1: total score 2, 3 Grade 2: total score 4, 5 Grade 3: total score 6, 7, 8

Fig. 1.7

A) Appendicular skeleton, trunk, skull and facial bones (4)

Definition of primary tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 8 cm in greatest dimension
T2	Tumor > 8 cm in greatest dimension
T3	Discontinuous tumors in the primary bone site

Definition of regional lymph node (N)

N Category	N Criteria
NX	Regional lymph node cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph nodes metastasis

Definition of distant metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Bone or other distant sites

Histologic Grade (G)

G	G Definition
GX	Grade cannot be assessed
G1	Well differentiated, low grade

B) Spine (4)

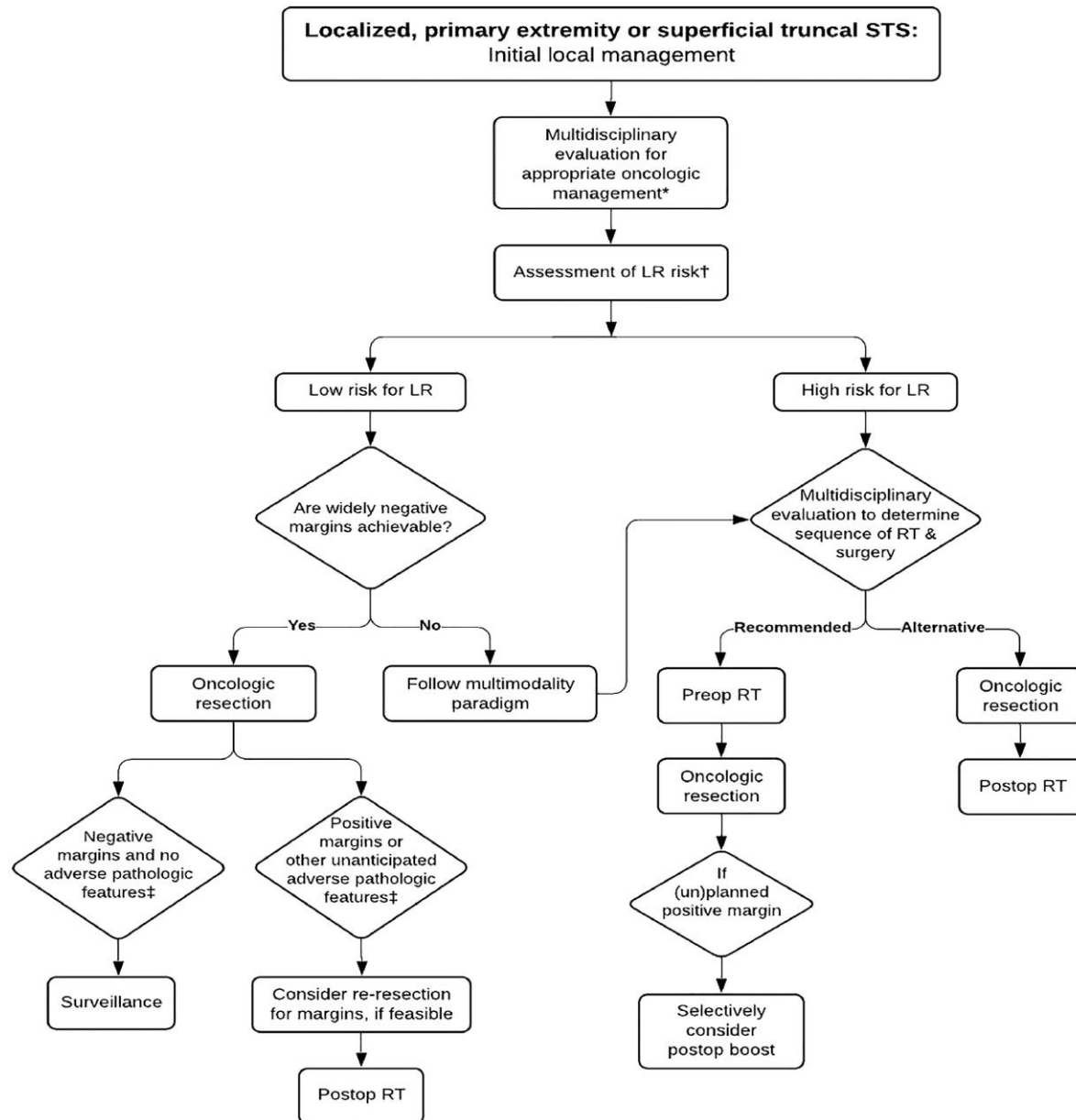
Definition of primary tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one vertebral segment or two adjacent vertebral segments
T2	Tumor confined to three adjacent vertebral segments
T3	Tumor confined to four or more adjacent vertebral segments, or any nonadjacent vertebral segments
T4	Extension into the spinal canal or great vessels
T4a	Extension into the spinal canal
T4b	Extension of gross vascular invasion or tumor thrombus in the great vessels

C) Pelvis (4)

Definition of primary tumor (T)

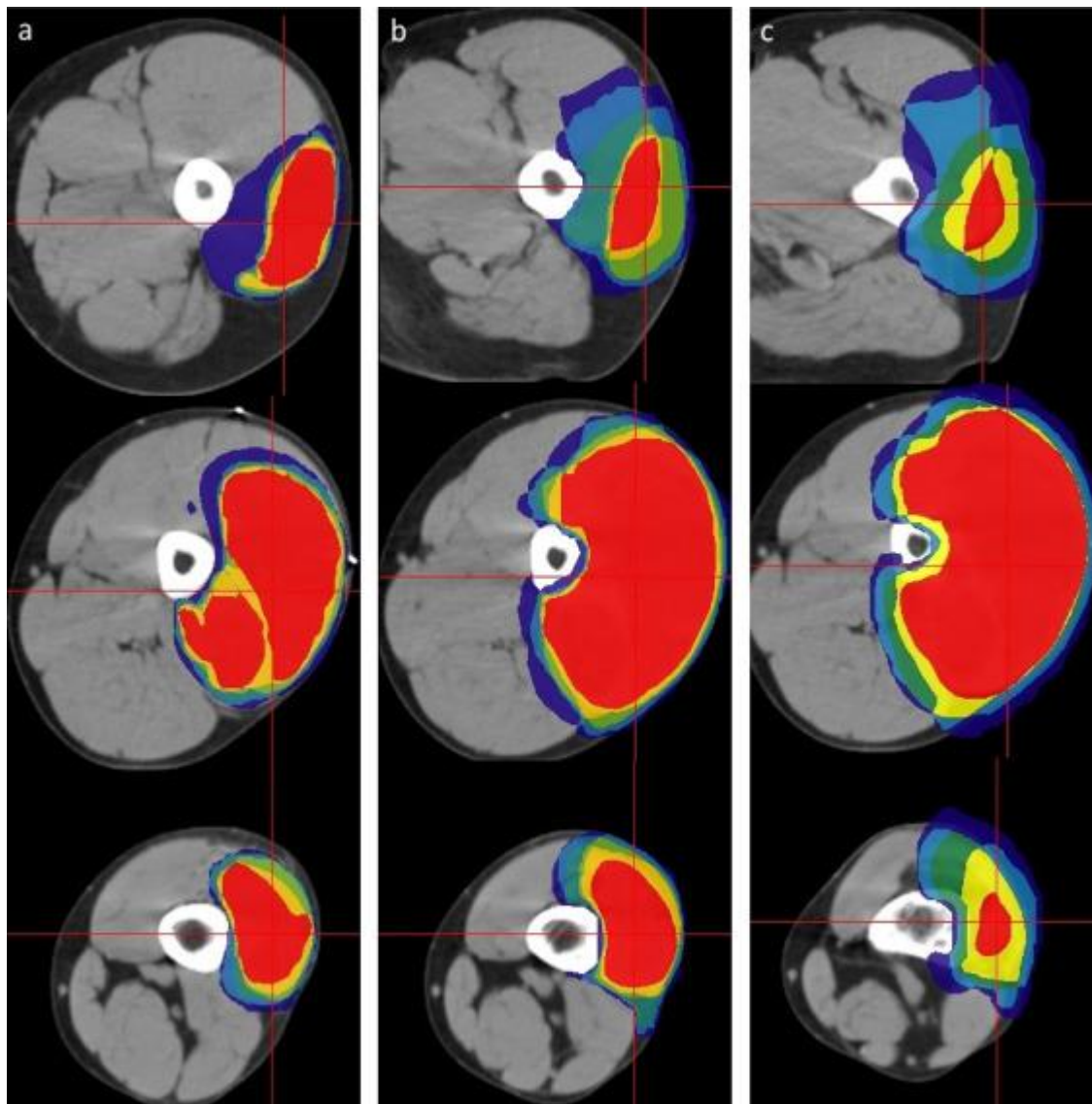
T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one pelvic segment with no extraosseous extension
T1a	Tumor ≤ 8 cm in greatest dimension
T1b	Tumor > 8 cm in greatest dimension
T2	Tumor confined to one pelvic segment with extraosseous extension or two segments without extraosseous extension
T2a	Tumor ≤ 8 cm in greatest dimension
T2b	Tumor > 8 cm in greatest dimension
T3	Tumor spanning two pelvic segments with extraosseous extension
T3a	Tumor ≤ 8 cm in greatest dimension
T3b	Tumor > 8 cm in greatest dimension
T4	Tumor spanning three pelvic segments or crossing the sacroiliac joint
T4a	Tumor involves sacroiliac joint and extends medial to the sacral neuroforamen
T4b	Tumor encasement of external iliac vessels or pres-



Salerno KE, et al. Radiation Therapy for Treatment of Soft Tissue Sarcoma in Adults: Executive Summary of an ASTRO Clinical Practice Guideline. *Pract Radiat Oncol* 2021 ;11(5):339-51.

Grade FNCLCC G1-3	Margin	Depth	Radiotherapy
G1	Wide	sc/deep	No
G1	Marginal	sc	No
G1	Marginal	deep	Consider RT
G2-3	Wide	sc	Consider RT
G2-3	Wide	deep	RT 50 Gy/25 fractions
G2-3	Marginal	sc/deep	RT 50 Gy/25 fractions
G1-3	Intralesional: micro/macro positive	sc/deep	RT 60 -70 Gy (2 Gy fractions)
G1-G3	Inoperable	sc/deep	64-70 (74) Gy (2 Gy fractions)

Table 6. Recommendation for adjuvant radiotherapy in patients with extremity and trunk wall soft tissue sarcoma.



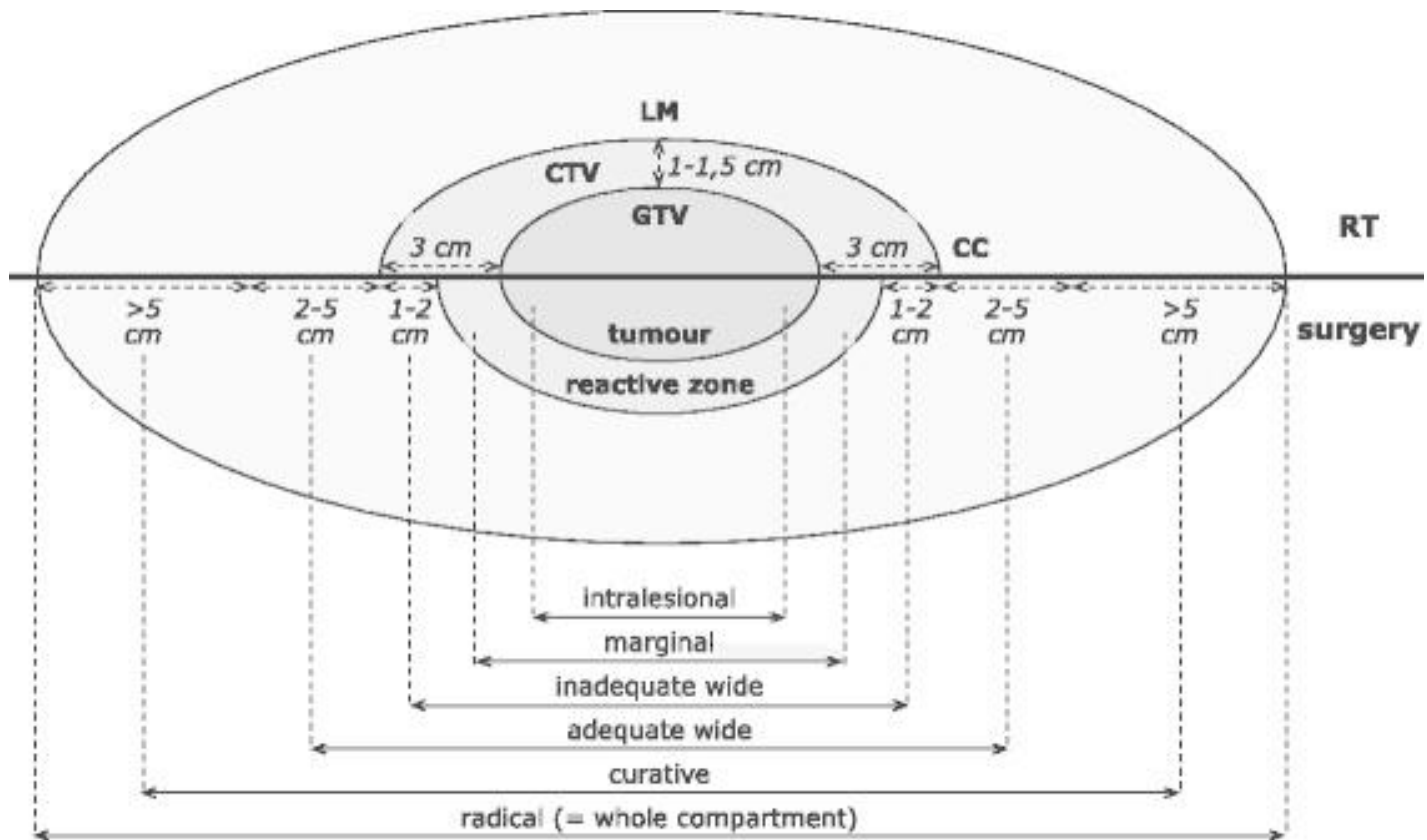
Sargos P, et al. Pre- and postoperative radiotherapy for extremity soft tissue sarcoma: Evaluation of inter-observer target volume contouring variability among French sarcoma group radiation oncologists. *Cancer Radiother* 2018;22(2):131-9.

Postoperative radiotherapy

- After limb-concerning surgery (removal of the tumor mass with a narrow excision margin $<1\text{cm}$) or due to microscopic residual disease (R1)
- Macroscopic residual disease (R2)
- Grade 2 or 3 histology
- Tumor size $\geq 5\text{cm}$
- All tumors of the head and neck region (due to the impossibility of adequate excision)
- Applying a dose $> 64\text{ Gy}$

Shrinking field

- **In the first phase**, a dose of about 45 Gy is applied to the expanded target volume (PTV1).
- **In the second phase**, an additional 10 to 15 Gy is applied to the reduced target volume (PTV2).
- **In the third phase**, the tumor bed (PTV3) is irradiated with a boost dose of 6 to 10 Gy



Radical (definitive) radiotherapy

- Surgery is contraindicated
- Unresectable tumors
- The patient refuses surgery
- Inaccessible localization
- With or without HT

I Wide volume 50 Gy

II Boost volume 10-16 Gy

Intraoperative radiotherapy

- An essential device in the operating room
- Educated radiation oncologist and surgeon
- Irradiation of the tumor bed in one fraction
- A dose of 10 to 15 Gy is applied to the tumor bed with electrons

Dose prescription and fractionation regimens

Radical or adjuvant RT: Phase 1 (25 x 1.8-2 Gy)

- GTV1 - Tumor / tumor bed on pre-therapy CT/MRI/PET imaging
- CTV1 - GTV + 50 mm (low and moderate grade SMT) or GTV + 70 mm (high grade SMT)
- PTV1 - CTV + 5-10 mm (depending on the IGRT method and tumor localization)

Radical or adjuvant RT: Phase 2 (R1: 16-18 Gy; R2: 20-26 Gy)

- GTV2 - Tumor / tumor bed on pre-therapy CT/MRI/PET imaging
- CTV2 - GTV + 20 mm
- PTV2 - CTV2 + 5-10 mm (depending on the IGRT method)

Radical or adjuvant RT (optional): Phase 3 (boost: 6-10 Gy)

- PTV3 - GTV2 + 5-10 mm (depending on the IGRT method)

Preoperative radiotherapy

- Downsizing
- Reduction of the risk of dissemination of tumor cells during surgery
- Formation of a thick acellular capsule
- The tumor is well oxygenated and intact
- A smaller radiation field can be used
- Lower radiation dose without reducing local control
- Final limb function better
- Postponing surgery 3-6 weeks after RT

Preoperative radiotherapy

- Neoadjuvant RT (25 x 1.8-2 Gy)
 - GTV - Tumor on pre-therapy CT/MRI/PET imaging
 - CTV - GTV + 20 mm
 - PTV - CTV + 5-10 mm (depending on the IGRT method and tumor localization)
-
- R1 – boost dose to the tumor bed of 16 to 18 Gy
 - R2 - boost dose from 20 to 26 Gy

Interstitial brachytherapy

- Monotherapy or in combination with surgery
- Intraoperative or perioperative (HDR interstitial brachytherapy, 36 Gy in 10 fractions)
- Postoperative interstitial brachytherapy with TD 14-24 Gy + EBRT with TD 50 Gy

Palliative radiotherapy

- Reduction of symptoms
- Improving the quality of life
- Local control of oligometastatic lung disease (SBRT)

Challenges in radiotherapy planning

- Different localizations
- Demanding positioning
- Immobilization
- Knowledge of the anatomy of muscles, their attachments, muscle lodges and fascia

Extremities

- Large volume
- 50Gy in 25 daily fractions during
- Boost volume
- 10-16Gy in 5-8 daily fractions
- Groos residual disease 66Gy in 33 daily fractions or up to 70Gy in 35 fractions

Retroperitoneum - 45Gy in 22 daily fractions

Shoulder area, superficial trunk tumors

Tangential fields to reduce doses to the lungs, that is, the small intestine

Gluteal region

Direct rear field and two lateral oblique fields with filters

Head and neck - 66Gy in 33 daily fractions

Rhabdomyosarcoma

- STSs account for 7% of all childhood malignancies
- It is the most common soft tissue sarcoma in the first decade of life
- Multimodal therapies indicated on the basis of assessed risk factors - improvement of long-term survival
- 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

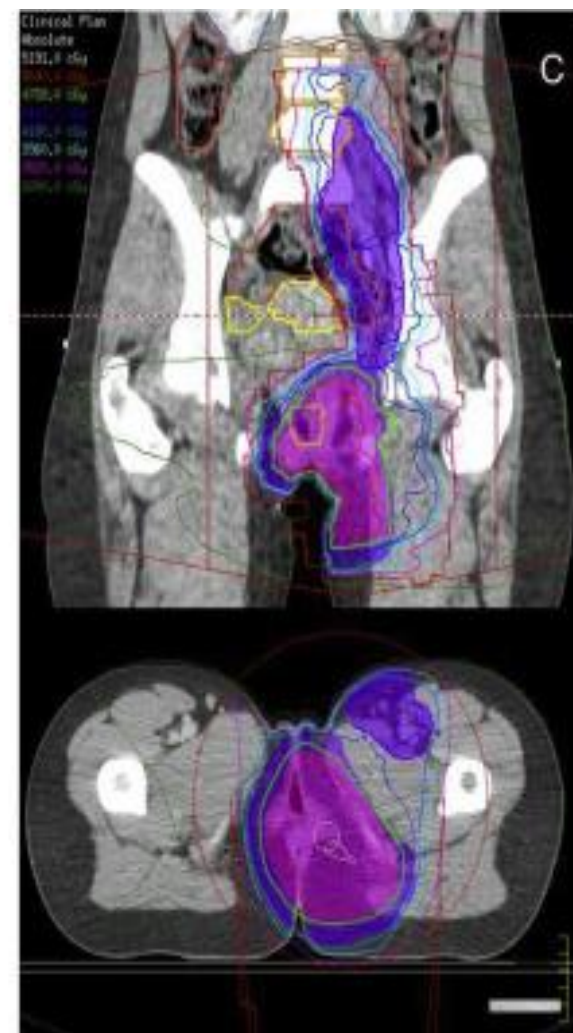
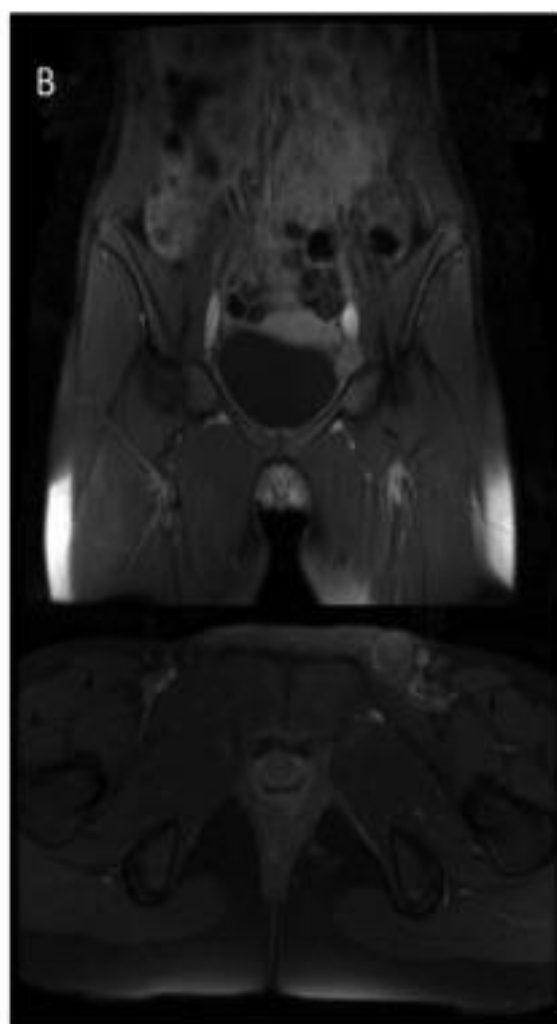
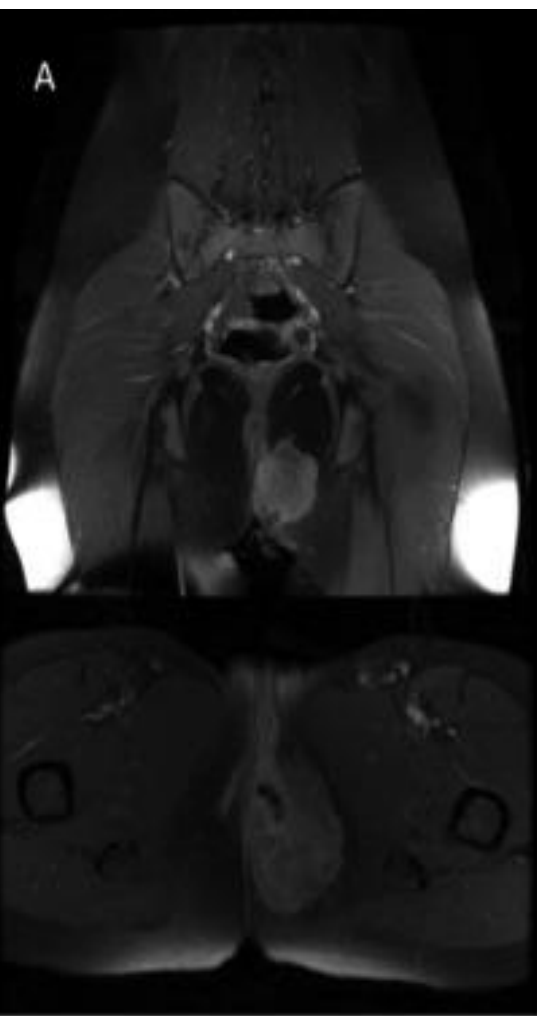
Surgery

CHT

RT (The target volume is defined in accordance with the recommendations of IGRU 50 and IGRU 62)

- The radiation dose prescribed for the target volume 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)

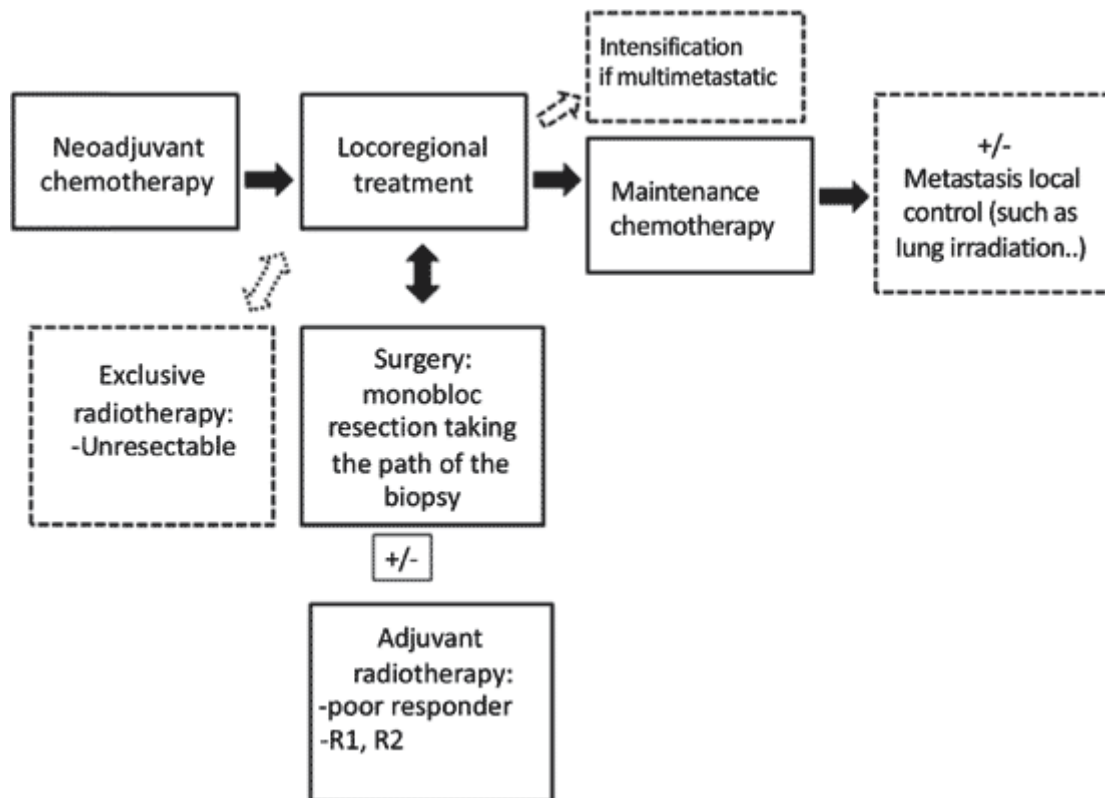


Bone tumors

- 0.2% of all malignant diseases.
- Osteosarcomas (0.2-0.3/100,000), chondrosarcomas (0.2/100,000), then Ewing sarcomas (0.3/100,000)
- 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 limb: 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)

Ewing sarkom

Treatment of Ewing sarcoma



Kridis WB, et al. A Review of Ewing Sarcoma Treatment: Is it Still a Subject of Debate? Rev Recent Clin Trials 2017;12(1):19-23.

Radiotherapy of Ewing sarcoma

CHT – chemosensitive

RT – radiosensitive

Radical ("shrinking field" approach)

- Phase I (40Gy in 22 fractions)
- Primary tumor + 5 cm margin in long bones
- A narrow strip of tissue for lymphatic drainage
- Protection of the growth pineal gland
- II phase (15-20Gy in 8-10 fractions)
- Volume reduction
- Primary tumor + 2 cm margin
- Preoperative (54.4Gy)

Postoperative

- Intralesional surgery 54.4Gy
- Marginal surgery with poor histological response ($\geq 10\%$ residual tumor cells) 54.4Gy
- Marginal surgery with good histological response ($< 10\%$ residual tumor cells) 44.8Gy
- Wide resection with poor histological response ($\geq 10\%$ residual tumor cells) 44.8Gy

Palliative RT

Lungs

- Whole lung irradiation
- 15Gy – patients < 14 years
- 18Gy – patients ≥ 14 years
- 1.5Gy daily dose

Bone metastases

- Small volume irradiation
- 45Gy / 22 fractions
- 36Gy / 12 fractions

Cerebral metastases

- Whole brain irradiation
- 30Gy (5x2Gy / week)
- Boost (1-2 lesions, max. 2-3 cm)
- 20 Gy

Surgery

- Lung metastases:
- WLI – TD 15 or 18 Gy, 1.5 Gy per day
- WLI – TD 12 Gy in 8 fractions (in children up to 6 years old)

Osteosarcoma

- Bimodal distribution
- Metaphyses of the lower extremities (in 75%), in old age it occurs more often in other locations
- Secondary osteosarcomas

Conventional osteosarcoma
Intramedullary osteosarcoma
Parasosseous osteosarcoma
Perioseal osteosarcoma
Superficial osteosarcoma

Radiotherapy of osteosarcoma

- Neoadjuvant CHT
- Surgery
- RT

In the first phase - 55 Gy (1.8 to 2 Gy per day) on PTV1 which includes GTV1 (tumor shown on preoperative imaging) and CTV1 (GTV1 + margin width 10-15 mm) with CTV1/PTV1 margin width 5-10 mm

In the second phase - a boost dose of 9 Gy (up to a total of 64 Gy) is applied to the reduced target volume of PTV2, which includes CTV2 (tumor bed shown on RT simulation imaging) with a CTV2/PTV2 margin of 5-10 mm width

Secondary bone tumors

Single fields

- Spine, sacrum
- Ribs, calvaria

Parallel - opposite fields

- Pelvis, long bones
- Base of skull

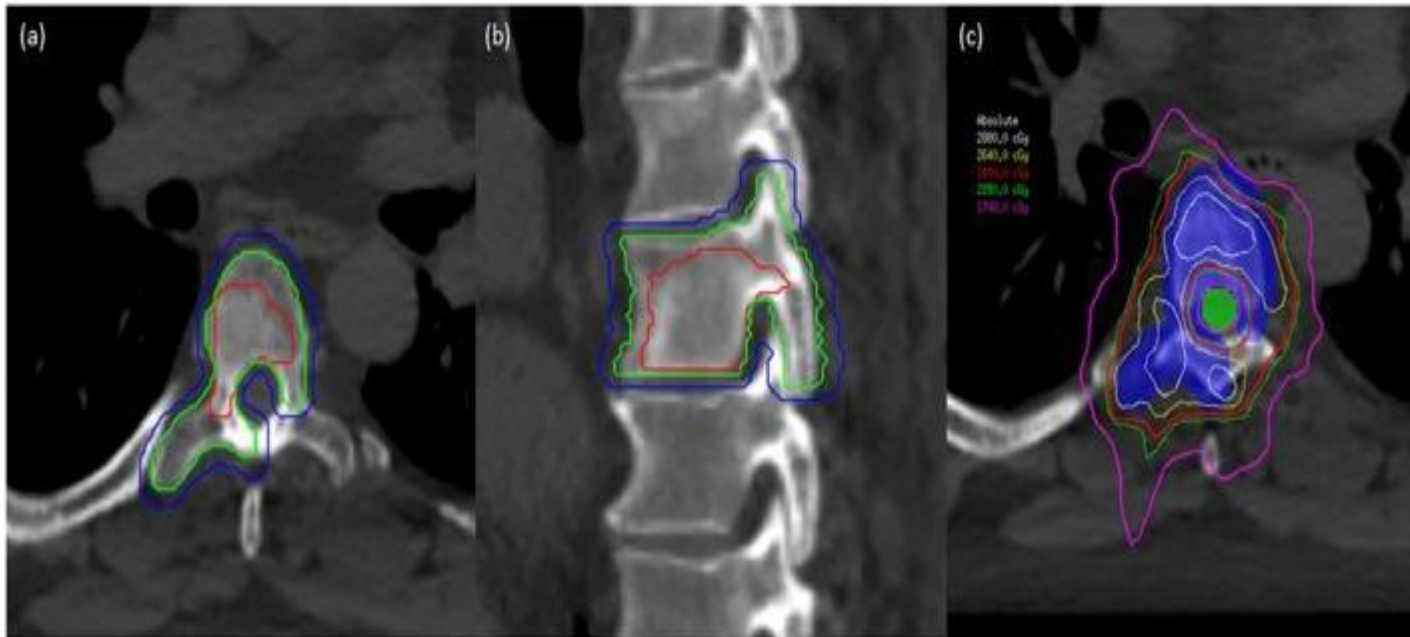
Dose and fractionation

- 30Gy / 10 fractions
- 20Gy / 5 fractions
- 8Gy / 1 fraction

Hemibody irradiation

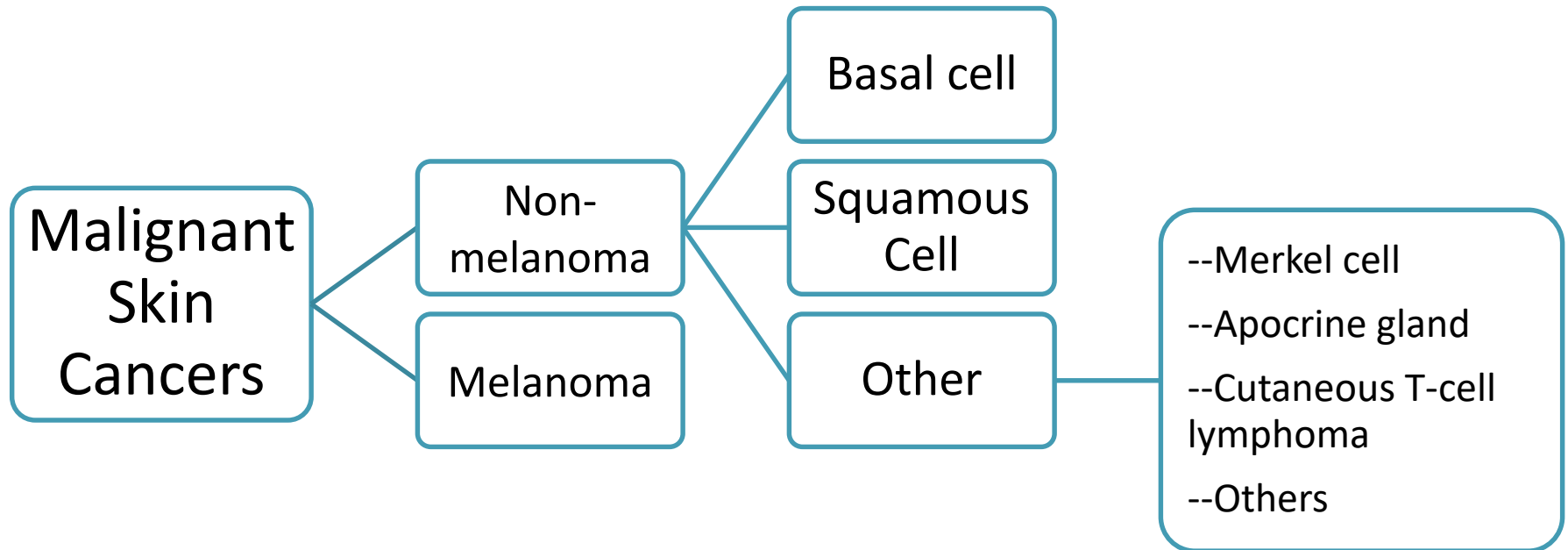
- Lower half
- 8Gy in 1 fraction (9-10 MeV photons)
- Upper half
- 6-8Gy in 1 fraction (9-10 MeV photons)

SBRT of bone metastases



Zeng KL, et al. Stereotactic Body Radiotherapy (SBRT) for Oligometastatic Spine Metastases: An Overview. *Front Oncol* 2019;9:337.

Types of skin cancer



When is radiation therapy used?

- Radiation therapy is not suitable for all types of skin cancers. Some of the factors affecting whether radiation therapy can be used include:
 - Type of cancer
 - Site of the cancer
 - Previous use of radiation therapy
 - Suitability of other treatments
 - Patient preference

Skin cancer treatment

- **Surgery** is a basic method of treatment of patients with skin cancer. It is aimed at a total resection of the tumor/neoplastic infiltration, with a wide margin of the healthy skin adjacent to the infiltrate circumferentially and subcutaneous tissue underlying at the bottom.
- **Radiotherapy** may be an alternative to surgery only in some selected sites (e.g.: head) and in early stages of advancement (I and II) of the Squamous Cell Carcinoma (SCC) or Basal Cell Carcinoma (BCC)

Types of radiotherapy

- Superficial or orthovoltage radiotherapy
- Electron radiotherapy
- Brachytherapy:
- Photon radiotherapy

Indications for definitive radiotherapy

- SCC and BCC localized on the face (palpebrae, nose, lips, and external acoustic meatus).
- SCC and BCC—localized elsewhere, tumor advancement—stages T1-2, and in cases of lack of the informed consent to surgical procedure.

Indications for adjuvant radiotherapy

- Non-radical surgical procedure for SCC and BCC (microscopically positive or doubtful margin of the healthy tissue, meaning < 10 mm),
- Extra-capsular infiltration due to metastases of SCC to the lymph nodes,
- Peri-neural infiltrates of the SCC and BCC,
- Clinical stage IIB and III of malignant melanoma.

Dose prescriptions

- 45 Gy, administered in 9 - 15 fractionated doses over 21 days, to 60 Gy administered in 30 fractionated doses, over 6 weeks, for electron or mixed type of irradiation;
- 18 - 22 Gy, in a single dose, to 40 - 45 Gy, administered in 10 - 12 fractionated doses, over 2-2, 5 weeks;
- 42 Gy, administered in 14 fractionated doses, over 3 weeks, to 80 Gy, administered in 45 fractionated doses, over 8 weeks.

THANK
YOU!

