Taipei Veterans General Hospital
Practices Guidelines
Oncology

Soft Tissue Sarcoma

Extremity and Superficial Trunk

Version 2021

Proofing at Bone and Sarcoma MDT Conference

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Summary of Guidelines Updates

- **This is the first version (2021) of Taipei VGH guidelines for soft tissue sarcoma of extremities and superficial trunk.**

Principles for Guideline's Application and Revision

- **This guideline is for medical fitted patients, adjustment might be considered for medical unfitted patients or for individual considerations under good clinical practices.**
- **Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy.**
- **Pediatric rhabdomyosarcoma (RMS) is a special form of soft tissue sarcoma and is not fully addressed in this guideline. Of all subtypes of RMS, only adult pleomorphic RMS could be managed as other soft tissue sarcoma.**
- **Any physician consulting this guideline is expected to use independent medical judgment of individual clinical circumstances to determine and apply optimal customized treatment for the cancer patient.**
- **This guideline is based on consensus of the authors regarding the current evidence for appropriate approaches to workup and treatment.**
- **This guideline will be systemically reviewed in an annual guideline revision meeting within the bone and sarcoma multidisciplinary conference.**

Multidisciplinary Team

- **Surgical Oncology specialized in soft tissue sarcoma of extremities and superficial trunk**
  - Orthopedic Surgery
  - Plastic Surgery
- **Medical Oncology**
- **Pediatric Oncology**
- **Radiation Oncology**
- **Pathology**
- **Diagnostic Radiology**
- **Nuclear Medicine**
- **Specialized Nursing Care**
- **Clinical Pharmacology**
- **Social Workers**
- **Nutritional Support**

Pretreatment Workup

- General medical history and physical examination

Serum Tests

- CBC, aPTT/PT, ±FDP
- Complete serum metabolite analyses, including liver/renal function test, Alk-P and LDH
- Hepatitis B and C markers, and CCr if chemotherapy is indicated

Imaging Studies

- Tomographical medical imaging studies: MRI with or without contrast enhanced CT
- Ultrasonography for primary site
- Plain x-rays study of the primary site
- PET scan, optional
- Chest X-rays
- Chest CT
- Bone scan; optional if PET-CT performed

Special Exams

- Option: heart function (multigated blood pool analysis or cardioechogram)

American Joint Committee On Cancer (AJCC) Staging System For Soft Tissue Sarcoma on the trunk and extremities(8th ed, 2017)

TX	Primary tumor cannot be assessed
T0	No evidence for primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension

Regional Lymph Nodes (N)

N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Definition of Grade (G)

FNCLCC Histologic Grade - see Histologic Grade (G)

GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7 or 8

Anatomic Stage/Prognostic Groups

Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
Stage II	T1	N0	M0	G2, G3
Stage IIIA	T2	N0	M0	G2, G3
Stage IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
Stage IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Federation Nationale des Centres de Lutte Contre le Cancer histological grading criteria (FNCLCC)

Histologic Grade (G)

The FNCLCC grade is determined by three parameters: differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as follows: differentiation (1-3), mitotic activity (1-3), and necrosis (0-2). The scores are added to determine the grade.

Tumor Differentiation

1 Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)

2 Sarcomas for which histologic typing is certain (e.g., myxoid/round cell liposarcoma)

3 Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400× magnification= 0.1734 mm^2) are assessed using a 40× objective.

1 0-9 mitoses per 10 HPF

2 10-19 mitoses per 10 HPF

3 ≥20 mitoses per 10 HPF

Tumor Necrosis

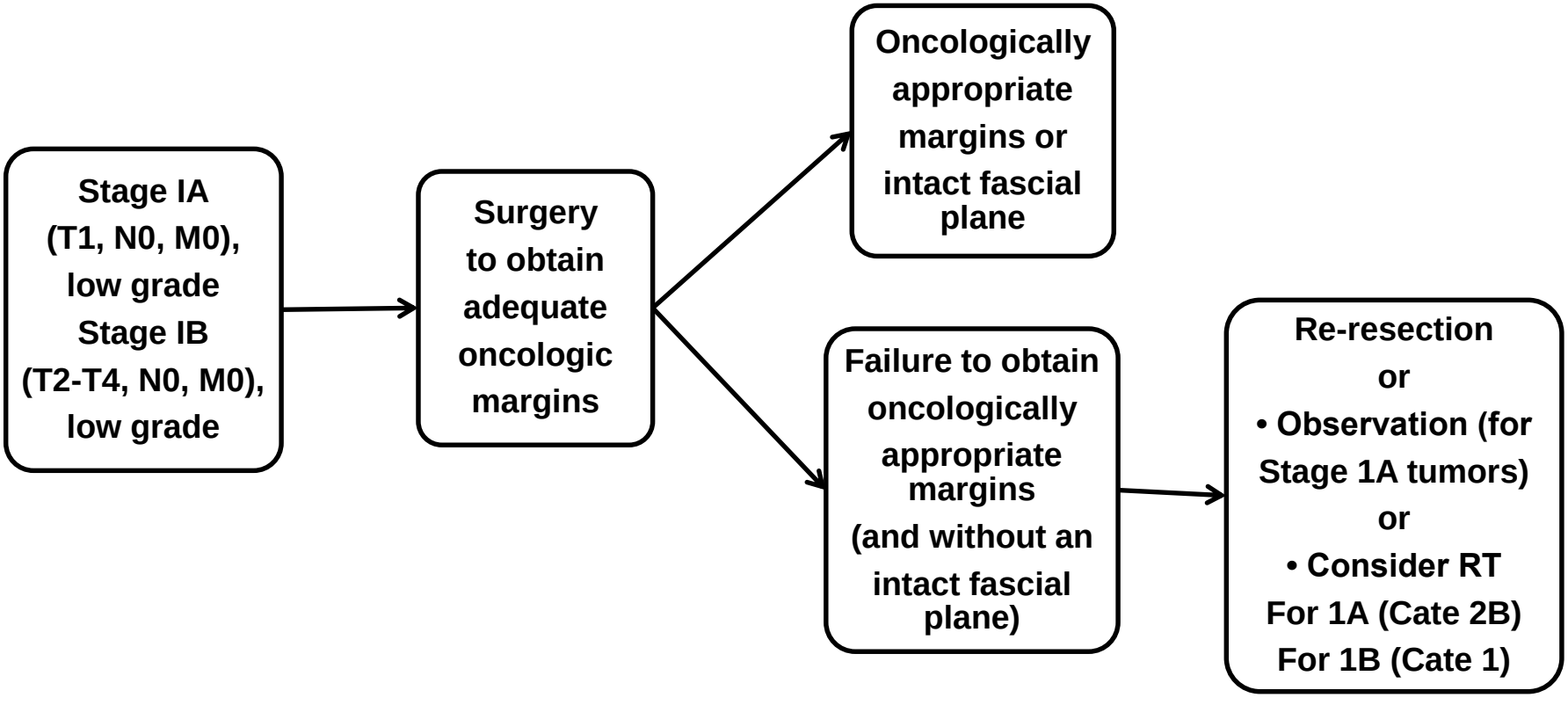
Evaluated on gross examination and validated with histologic sections.

0 No necrosis

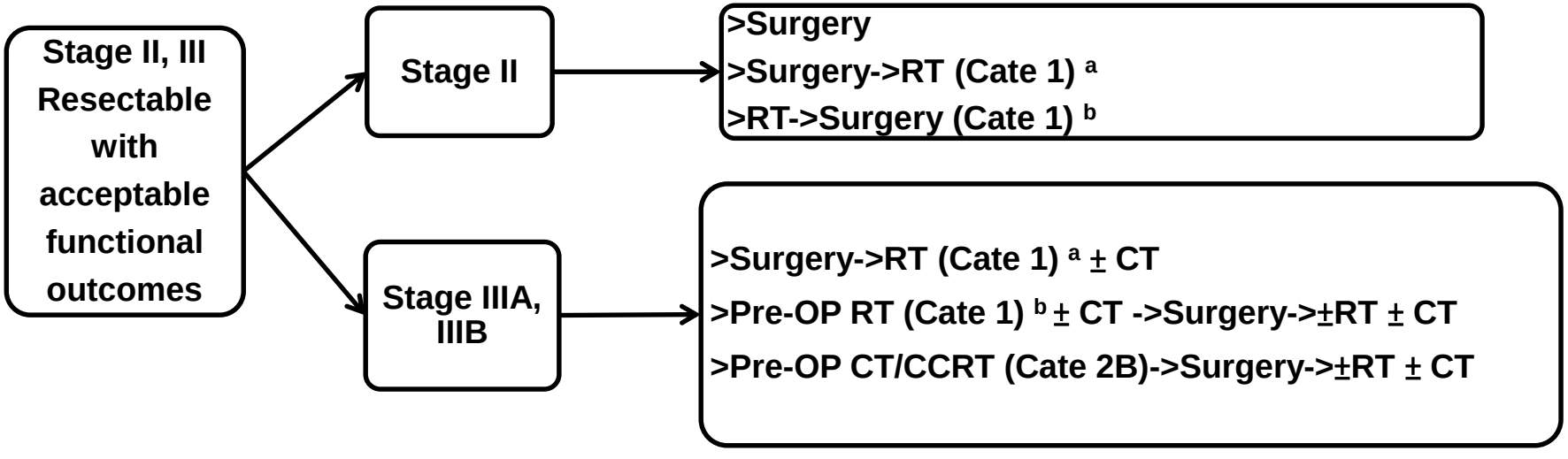
1 <50% tumor necrosis

2 ≥50% tumor necrosis

Stage I


Stage IA
(T1, N0, M0),
low grade
Stage IB
(T2-T4, N0, M0),
low grade
Surgery
to obtain
adequate
oncologic
margins
Oncologically
appropriate
margins or
intact fascial
plane
Failure to obtain
oncologically
appropriate
margins
(and without an
intact fascial
plane)
Re-resection
or
• Observation (for
Stage 1A tumors)
or
• Consider RT
For 1A (Cate 2B)
For 1B (Cate 1)

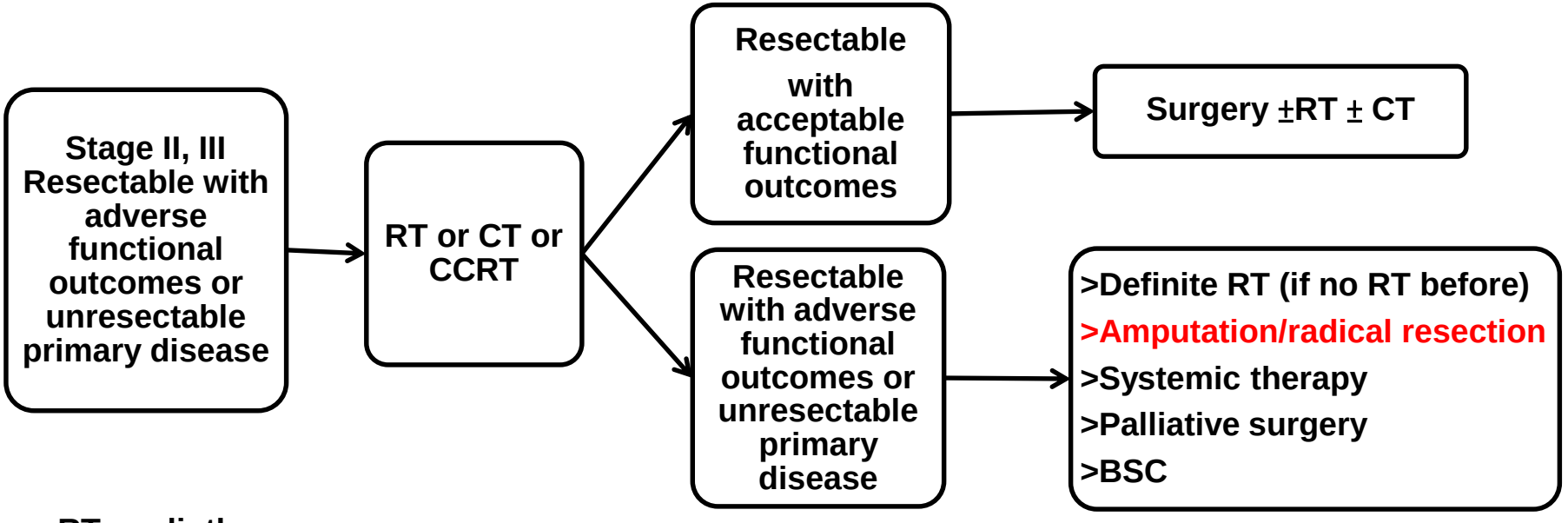
Stage II-III



RT: radiotherapy
CT: chemotherapy
OP: surgery
± : with or without

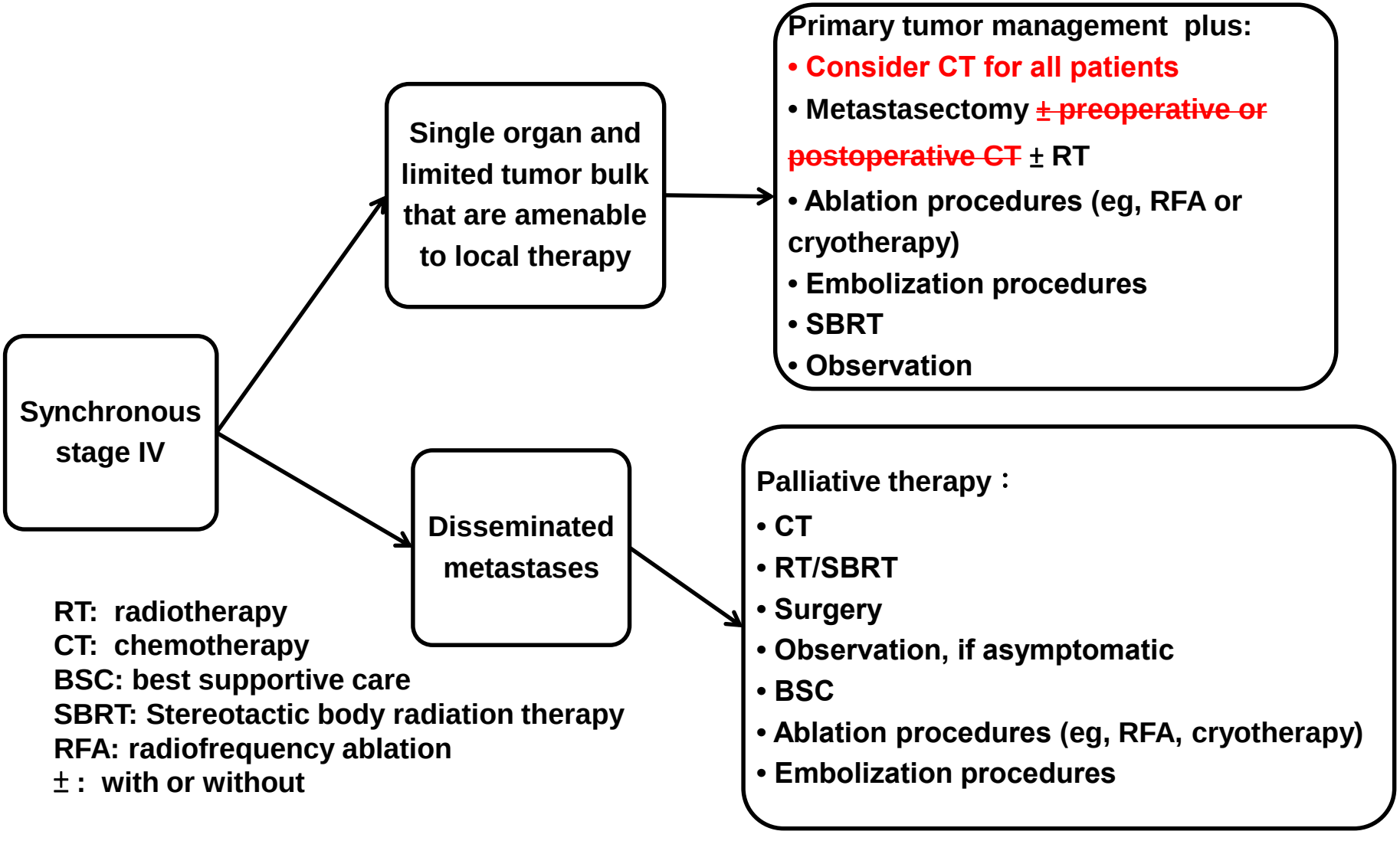
[a] Yang JC, ChangAE, BakerAR,et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998;16:197-203
[b] Davis AM, O'Sullivan B, Bell RS et al. Function and health status outcomes in a randomized trial comparing preoperatlve and postoperative radiotherapy in extremity soft tissue sarcoma. J Clin Oncol 2002;20:4472-4477

Stage II-III



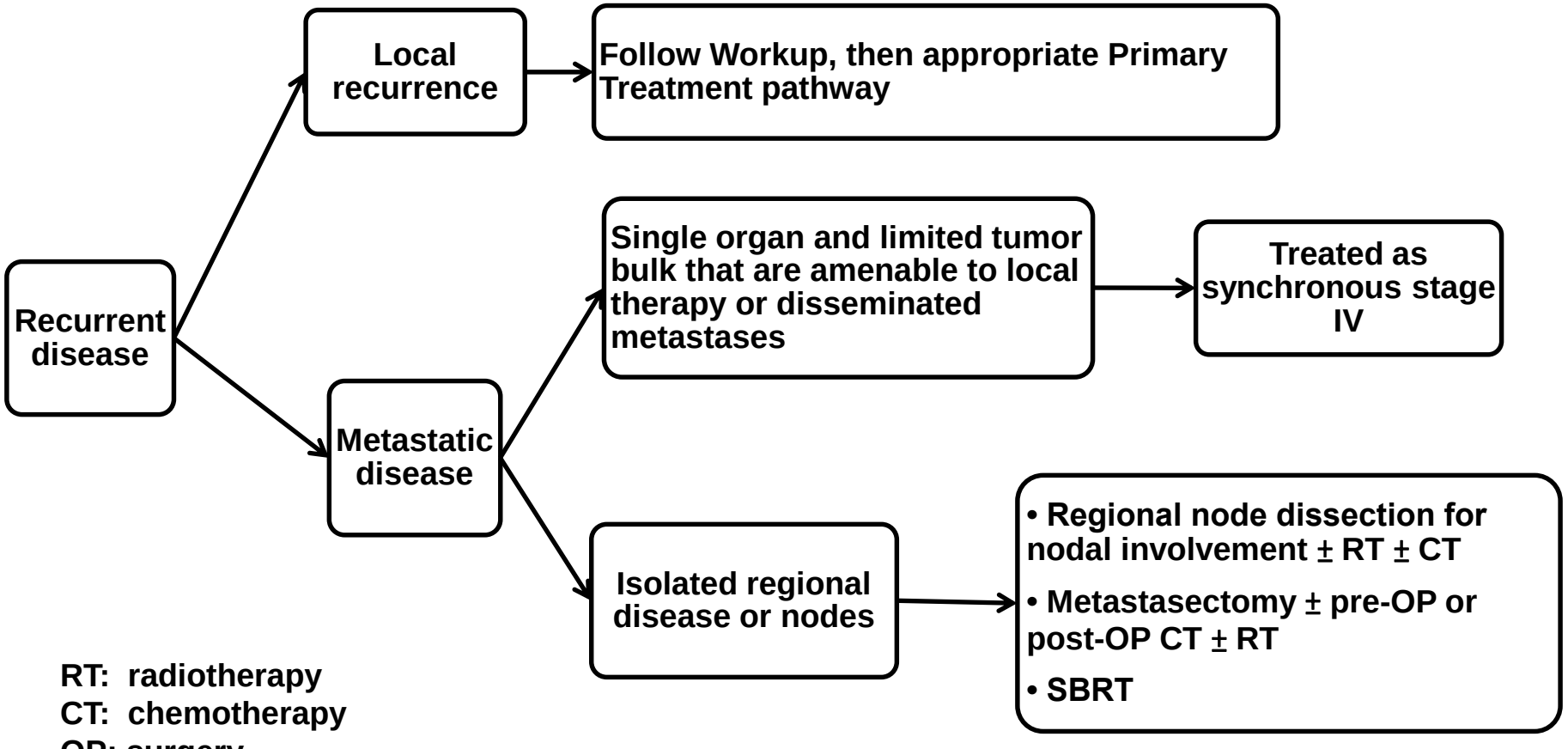
RT: radiotherapy
CT: chemotherapy
CCRT: combined CT and RT
BSC: best supportive care
± : with or without

Synchronous Stage IV



RT: radiotherapy
CT: chemotherapy
BSC: best supportive care
SBRT: Stereotactic body radiation therapy
RFA: radiofrequency ablation
±: with or without

Recurrent disease



RT: radiotherapy
CT: chemotherapy
OP: surgery
BSC: best supportive care
SBRT: Stereotactic body radiation therapy
± : with or without

Post treatment surveillance

- **Evaluation for rehabilitation (OT, PT) Continue until maximal function is achieved**
- **H&P and imaging of chest and other known sites of metastatic disease (plain radiograph or chest CT) every 3–6 mo for 2–3 y, then every 6 mo for next 2 y, then annually**
- **Consider obtaining postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence (MRI, CT, consider ultrasound)**

Principle of surgery (1)

Biopsy

• A pretreatment biopsy to diagnose and grade a sarcoma is highly preferred. Biopsy should be carried out by an experienced surgeon (or radiologist) and may be accomplished by open incisional or needle technique. Core needle biopsy is preferred;
however, an open incisional biopsy may be considered by an experienced surgeon. Image-guided needle biopsy may be indicated for deep tumor.

Surgery

• The surgical procedure necessary to resect the tumor with oncologically appropriate margins should be used. Close margins may be necessary to preserve critical neurovascular structures, bones, joints, etc.

• Ideally, the biopsy site should be excised en bloc with the definitive surgical specimen. Dissection should be through grossly normal tissue planes uncontaminated by tumor. If the tumor is close to or displaces major vessels or nerves, these need not be resected if the adventitia or perineurium is removed and the underlying neurovascular structures are not involved with gross tumor.

• Radical excision/entire anatomic compartment resection is not routinely necessary.

•Surgical clips should be placed to mark the periphery of the surgical field and other relevant structures to help guide potential future radiation therapy. If closed suction drainage is used, the drains should exit the skin close to the edge of the surgical incision (in case re-resection or radiation is indicated).

Principle of surgery (2)

Resection Margins

• Surgical margins should be documented by both the surgeon and the pathologist in evaluating a resected specimen.

• If surgical resection margins are positive on final pathology (other than bone, nerve, or major blood vessels), surgical re-resection to obtain negative margins should strongly be considered if it will not have a significant impact upon functionality.

• Consideration for adjuvant radiation therapy should be given for a close soft tissue margin or a microscopically positive margin on bone, major blood vessels, or a major nerve. (ALT/WDLS RT is not indicated in most cases)

• In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended.

R0 resection - No residual microscopic disease

R1 resection - Microscopic residual disease

R2 resection - Gross residual disease

• Special consideration should be given to infiltrative histologies such as myxofibrosarcoma, DFSP, and angiosarcoma.

Principle of surgery (3)

Limb Sparing Surgery

• For extremity sarcomas, the goal of surgery should be functional limb preservation, if possible, within the realm of an appropriate oncologic resection.

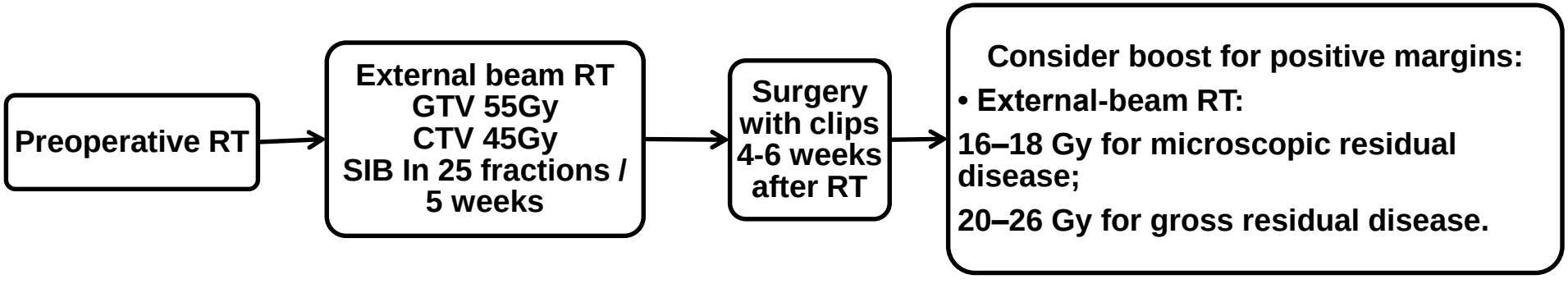
Amputation

• Prior to considering amputation, patients should be evaluated by a surgeon with expertise in the treatment of soft tissue sarcomas.

• Consideration for amputation to treat an extremity sarcoma should be made for patient preference or if gross total resection of the tumor is expected to render the limb nonfunctional.

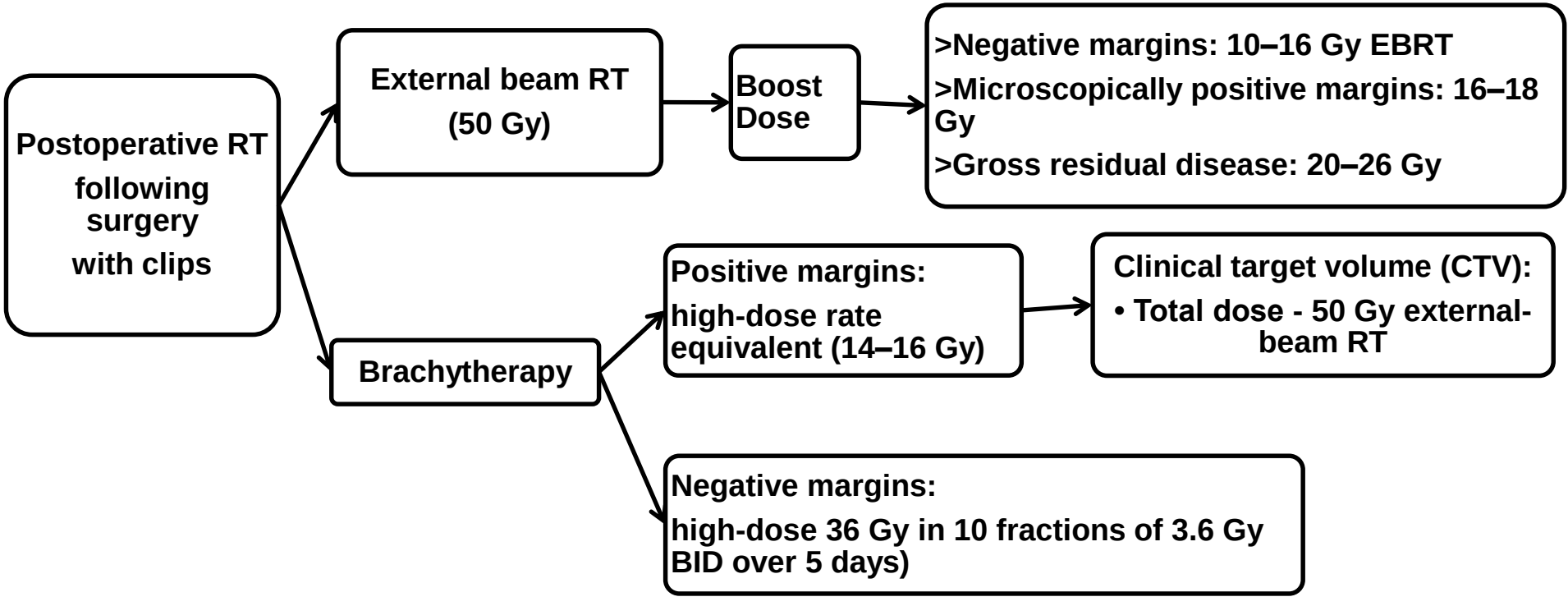
• Evaluate preoperatively for rehabilitation (PT, OT) for patients with extremity sarcoma. Continue rehabilitation until maximal function is achieved.

Principle of RT: Preoperative RT



SIB: Simultaneous Integrated Boost

Principle of RT: Postoperative RT



Other Modalities

- **Used as palliative modalities**
  - RFA (Radiofrequency Tumor Ablation)
  - TAE (Transarterial Embolization)
  - Cryotherapy

Principles of pathologic review

Common Malignant Histopathologic Type

Adipocytic Tumors
- Dedifferentiated liposarcoma*
- Myxoid/round cell liposarcoma
- Pleomorphic liposarcoma

Fibroblastic/Myofibroblastic Tumors
- Fibrosarcoma**
- Myxofibrosarcoma, low grade
- Low-grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma

So-called Fibrohistiocytic Tumors
- Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (MFH) (including pleomorphic, giant cell, myxoid/high-grade myxofibrosarcoma and inflammatory forms)

Smooth Muscle Tumors
- Leiomyosarcoma

Skeletal Muscle Tumors
- Rhabdomyosarcoma (embryonal, alveolar, and pleomorphic forms)

Vascular Tumors
- Epithelioid hemangioendothelioma
- Angiosarcoma, deep***

Tumors of Peripheral Nerves
- Malignant peripheral nerve sheath tumor

Chondro-osseous Tumors
- Extraskeletal chondrosarcoma (mesenchymal and other variants)
- Extraskeletal osteosarcoma

Tumors of Uncertain Differentiation
- Synovial sarcoma
- Epithelioid sarcoma
- Alveolar soft-part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Primitive neuroectodermal tumor (PNET)/extraskeletal Ewing tumor
- Desmoplastic small round cell tumor
- Extrarenal rhabdoid tumor
- Undifferentiated sarcoma; sarcoma, not otherwise specified (NOS)

Notes: *It is recognized that dedifferentiated liposarcoma primarily arises in the context of deep atypical lipomatous tumor/well-differentiated liposarcoma, a sarcoma of intermediate malignancy due to lack of metastatic capacity.
**The category of fibrosarcoma can be considered to be inclusive of fibrosarcomatous differentiation in dermatofibrosarcoma protuberans.
***Cutaneous angiosarcoma may be difficult to stage using the AJCC system.

The following histologic types are not included: inflammatory myofibroblastic tumor, fibromatosis (desmoid tumor), mesothelioma, sarcomas arising in tissues apart from soft tissue (eg, parenchymal organs).

Principles of pathologic review (1)

- **Biopsy should establish malignancy, provide a specific diagnosis where possible, and provide a grade where appropriate or feasible, recognizing that limited biopsy material may underestimate grade.**
- **In patients without a definitive diagnosis following initial biopsy due to limited sampling size, repeat image-guided core needle biopsy should be considered to make a diagnosis.**
- **Pathologic assessment of biopsies and resection specimens should be carried out by an experienced sarcoma pathologist.**
- **Morphologic diagnosis based on microscopic examination of histologic sections remains the gold standard for sarcoma diagnosis. However, since several ancillary techniques are useful in support of morphologic diagnosis (including immunohistochemistry, classical cytogenetics, and molecular genetic testing), sarcoma diagnosis should be carried out by pathologists who have access to these ancillary methods.**

Principles of pathologic review (2)

The pathologic assessment should include evaluation of the following features, all of which should be specifically addressed in the pathology report:

- Organ, site, and operative procedure
- Primary diagnosis (using standardized nomenclature, such as the World Health Organization Classification of Soft Tissue Tumors)
- Depth of tumor
  - Superficial (tumor does not involve the superficial fascia)
  - Deep
- Size of tumor
- Histologic grade (at the least, specify low or high grade if applicable); ideally, grade using the French Federation of Cancer
- Centers Sarcoma Group (FNCLCC) or NCI system
- Necrosis
  - Present or absent
  - Microscopic or macroscopic
  - Approximate extent (percentage)
- Status of margins of excision
  - Uninvolved
  - Involved (state which margins)
  - Close (state which margins and measured distance)
- Status of lymph nodes
  - Site
  - Number examined
  - Number positive
- Results of ancillary studies
  - Type of testing (electron microscopy, immunohistochemistry, molecular genetic analysis)
  - Where performed
- Additional tumor features of potential clinical value
  - Mitotic rate
  - Presence or absence of vascular invasion
  - Character of tumor margin (well circumscribed or infiltrative)
  - Inflammatory infiltrate (type and extent)
- TNM Stage

Principles of pathologic review (1)
Ancillary diagnostic tool
Fluorescence in situ hybridization (FISH) approaches *or* polymerase chain reaction (PCR)-based methods
Already in Practice

TUMOR	ABERRATION	GENE(S) INVOLVED
Malignant Round Cell Tumors		
Alveolar RMS	t(2;13)(q35;q14) t(1;13)(p36;q14) t(X;2)(q13;q35)	*PAX3-FOXO1* *PAX7-FOXO1* *PAX3-AFX*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWSR1-WT1*
Embryonal RMS	Complex alterations	Multiple, *MYOD1* mutation
Ewing sarcoma/peripheral neuroectodermal tumor	t(11;22)(q24;q12) t(21;22)(q22;q12) t(2;22)(q33;q12) t(7;22)(p22;q12) t(17;22)(q12;q12) inv(22)(q12q;12) t(16;21)(p11;q22)	*EWSR1-FLI1* *EWSR1-ERG* *EWSR1-FEV* *EWSR1-ETV1* *EWSR1-E1AF* *EWSR1-ZSG* *FUS-ERG*
Undifferentiated round cell sarcoma	t(4;19)(q35;q13) or t(10;19)(q26;q13) inv(X)(p11.4p11.22)	*CIC-DUX4*[3] *BCOR-CCNB3*[4]

Principles of pathologic review (2)

TUMOR	ABERRATION	GENE(S) INVOLVED
Lipomatous Tumors		
Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS)	Supernumerary ring chromosomes; giant marker chromosomes	Amplification of region 12q14-15, including *MDM2, CDK4, HMGA2, SAS, GLI*
Dedifferentiated liposarcoma	Same as for ALT/WDLS	Same as for ALT/WDLS
Myxoid/round cell liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	*FUS-DDIT3* *EWSR1-DDIT3*
Pleomorphic liposarcoma	Complex alterations	Unknown
Other Sarcomas		
Alveolar soft part sarcoma	der(17)t(X;17)(p11;q25)	*ASPL-TFE3*
Angiomatoid fibrous histiocytoma	t(12;22)(q13;q12) t(2;22)(q33;q12) t(12;16)(q13;p11)	*EWSR1-ATF1* *EWSR1-CREB1* *FUS-ATF1*
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q33;q12)	*EWSR1-ATF1* *EWSR1-CREB1*
Congenital/infantile fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*[5]
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13) and derivative ring chromosomes	*COL1A1-PDGFB*
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q21	*CTNNB1* or *APC* mutations
High-grade endometrial stromal sarcoma	t(10;17)(q22;p13) t(x;22)(p11;q13)	*YWHAE-NUTM2* *ZC3H7B-BCOR*[6]
Epithelioid hemangioendothelioma	t(1;13)(p36;q25) t(X;11)(q22;p11.23)	*WWTR1-CAMTA1* *YAP1 - TFE3*

Principles of pathologic review (3)

TUMOR	ABERRATION	GENE(S) INVOLVED
Other Sarcomas - continued		
Epithelioid sarcoma	Inactivation, deletion, or mutation of *INI1 (SMARCB-1)*	*INI1 (SMARCB-1)*
Extrarenal rhabdoid tumor	Inactivation of *INI1 (SMARCB-1)*	*INI1 (SMARCB-1)*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12) t(9;17)(q22;q11) t(9;15)(q22;q21) t(3;9)(q11;q22)	*EWSR1-NR4A3* *TAF2N-NR4A3* *TCF12-NR4A3* *TFG-NR4A3*
Sporadic and familial GIST Carney-Stratakis syndrome (gastric GIST and paraganglioma)	Activating kinase mutations Krebs cycle mutation	*KIT* or *PDGFRA* *Germline SDH* subunit mutations
Inflammatory myofibroblastic tumor (IMT)	t(1;2)(q22;p23) t(2;19)(p23;p13) t(2;17)(p23;q23) t(2;2)(p23;q13) t(2;11)(p23;p15) inv(2)(p23;q35)	*TPM3-ALK*[5] *TPM4-ALK*[5] *CLTC-ALK*[5] *RANBP2-ALK*[5] *CARS-ALK*[5] *ATIC-ALK*[5]
Leiomyosarcoma	Complex alterations	Unknown
Low-grade fibromyxoid sarcoma	t(7;16)(q33;p11) t(11;16)(p11;p11)	*FUS-CREB3L2* *FUS-CREB3L1*
Malignant peripheral nerve sheath tumor		*NF1*, *CDKN2A* and *EED* or *SUZ12*
Mesenchymal chondrosarcoma	t(8;8)(q13;q21)	*HEY1 - NCOA2*
Solitary fibrous tumor	inv(12)(q13q13)	*NAB2 - STAT6*
Synovial sarcoma	t(X;18)(p11;q11) t(X;18)(p11;q11) t(X;18)(p11;q11)	*SS18-SSX1* *SS18-SSX2* *SS18-SSX4*
Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS)	t(1;2)(p13;q35)	*CSF1*

Principles of pathologic review (4)

- **Archer Sarcoma Target fusion panel (VGHTPE)**
- **55 genes：**

GENE			
ALK	FOSB	NTRK1	STAT6
BCOR	FOXO1	NTRK2	TAF15
BRAF	FUS	NTRK3	TCF12
CAMTA1	GLI1	NUTM1	TFE3
CIC	HMGA2	PAX3	TFG
CSF1	JAZF1	PDGFB	USP6
EGFR	MDM2	PHF1	VCP
EPC1	MEAF6	PLAG1	VGLL2
ERG	MET	PRKCA	YAP1
ESR1	MGEA5	PRKCB	YWHAE
EWSR1	MKL2	PRKCD	
FGFR1	MYOD1	RAF1	
FGFR2	NCOA1	RET	
FGFR3	NCOA2	ROS1	
FOS	NR4A3	SS18	

Principles of radiological evaluation

- **X ray: preliminary study for tumor, e.g. calcification, bone invasion.**
- **Ultrasound: for sono-guided biopsy, tumor nature and necrosis survey**
- **MR Imaging: for pre-surgical planning and tumor staging, e.g. tumor location, content, margin, tumor necrosis, neurovascular bundle, joint, lymph node, and metastasis.**
- **CT scan: for lung metastasis survey, CT - guided biopsy.**
- **Bone scan or PET CT: for bone metastasis screening**

Systemic therapy

Neoadjuvant/adjuvant therapy

- AIM (doxorubicin, ifosfamide, mesna)
- Ifosfamide, epirubicin, mesna

First-line treatment

- **Combination regimens**
  - AD (doxorubicin, dacarbazine)
  - AIM (doxorubicin, ifosfamide, mesna)
  - MAID (mesna, doxorubicin, ifosfamide, dacarbazine)
  - Ifosfamide, epirubicin, mesna
- **Single agents**
  - Doxorubicin
  - Epirubicin
  - Liposomal doxorubicin

◆ Alveolar soft part sarcoma (ASPS), well-differentiated liposarcoma/atypical lipomatous tumor, and clear cell sarcomas are generally not sensitive to cytotoxic chemotherapy.
◆ These regimens appropriate for pleomorphic rhabdomyosarcoma.
* Only available with project application

Systemic therapy- 2nd line or optional regimens

Alternative regimens

- **Gemcitabine-based regimens**
  - Gemcitabine, docetaxel ± Cisplatin ± everolimus
  - Gemcitabine and vinorelbine
  - Gemcitabine and dacarbazine

- **Single agents**
  - **Ifosfamide**
  - **Gemcitabine**
  - **Dacarbazine**
  - **Temozolomide**
  - **Vinorelbine**
  - **Pazopanib (STS but not liposarcoma, leiomyosarcoma, Ewing's sarcoma, primitive neuroectodermal tumor, GIST)**
  - **Regorafenib**
  - **Eribulin (liposarcoma)**
  - **Trabectin* (liposarcoma and leiomyosarcoma)**
  - **Larotrectinib, Entrectinib (NTRK gene-fusion)**
  - **Pembrolizumab (Myxofibrosarcoma, UPS, cutaneous angiosarcoma, undifferentiated sarcoma)**

◆ **Alveolar soft part sarcoma (ASPS), well-differentiated liposarcoma/atypical lipomatous tumor, and clear cell sarcomas are generally not sensitive to cytotoxic chemotherapy.**
◆ **These regimens appropriate for pleomorphic rhabdomyosarcoma.**
*** Only available with project application**

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