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Review

Radiotherapy for pediatric non-rhabdomyosarcoma soft tissue sarcomas: a comprehensive review

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ABSTRACT

Background. For children with non-rhabdomyosarcoma soft tissue sarcomas, a risk-adapted treatment approach is generally used in order to minimize treatment-related morbidity and mortality in low-risk patients and maximize the benefit in high-risk patients. Our aim in this review is to discuss the prognostic factors, risk-adapted treatment options and the details of radiotherapy.

Methods. The publications reached by searching the keywords 'pediatric soft tissue sarcoma', 'non-rhabdomyosarcoma soft tissue sarcoma (NRSTS)', and 'radiotherapy' in Pubmed database were evaluated in detail.

Results. Today, based on prospective COG-ARST0332 and EpSSG studies, a risk-adapted multimodal treatment approach has become the standard in pediatric NRSTS. According to them, adjuvant chemotherapy/radiotherapy can be safely omitted in low-risk patients, while adjuvant chemotherapy/radiotherapy or both are recommended in intermediate and high-risk groups. Recent prospective studies for pediatric patients have reported excellent treatment outcomes with smaller radiotherapy fields and lower doses than adult series. The primary goal of surgery is maximal tumor resection with negative margins. In cases that are initially unresectable, neoadjuvant chemotherapy and radiotherapy should be considered.

Conclusions. A risk-adapted multimodal treatment approach is the standard in pediatric NRSTS . Surgery alone is sufficient in low-risk patients, and adjuvant therapies may safely be omitted. On the contrary, in intermediate- and high-risk patients, adjuvant treatments should be applied to reduce recurrence rates. In unresectable patients, the chance of surgery increases with the neoadjuvant treatment approach and thus treatment results may improve. In the future, outcome might be improved with further clarification of molecular features and targeted therapies in such patients.

Key words: Non-rhabdomyosarcoma soft tissue sarcoma, pediatric sarcoma, radiotherapy, sarcoma, treatment.

Pediatric soft tissue sarcomas originate from mesenchyme and accounts for 7% of all childhood cancers.[1] They are divided into two groups as rhabdomyosarcomas (RMS) and non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) with an incidence of 40 and 60%, respectively.[2,3] NRSTS shows a bimodal age distribution in childhood, with the incidence being high in infants and adolescents.[4]

There are several genetic syndromes and molecular alterations that have been associated with the development of NRSTS. The risk of developing malignant peripheral nerve sheath tumor (MPNST) in children with neurofibromatosis 1 (NF-1) is three times higher than in the general population.[5] The risk of NRSTS is also higher in Li-Fraumeni Syndrome, which is characterized by p53 gene mutation.[6] In addition, ionizing radiation and chemotherapy (CHT) may also play a role in their etiology. However, in most patients the etiology is unclear.

NRSTS are quite complex and heterogeneous group of tumors including nearly 50

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histological subtypes. Pediatric NRSTS includes special histological subtypes such as infantile fibrosarcoma and the distribution of histological subtypes which are quite differed from adult cases. Synovial sarcomas, MPNST and fibrosarcomas are the most common histological subtypes in pediatric cases.[4] These tumors are usually observed in the trunk or extremities. The most common initial symptom is a painless mass. As they are usually tumors with local infiltrative growth pattern, symptoms associated with infiltration of adjacent neurovascular structures or organs may accompany. Regional lymph node (LN) metastases are generally rare but can be observed in some subtypes such as synovial, clear cell or epithelioid sarcomas.[7] Distant metastases are present in 15% of newly diagnosed cases, and the most common site is the lungs.[8]

A detailed anamnesis, including family history, is essential to detect underlying genetic disorders. A careful physical examination is required to determine the local characteristics of the tumor. Computed tomography (CT) or magnetic resonance imaging (MRI) is also recommended to evaluate the size and extension of the tumor, its relationship with adjacent structures, and treatment planning. Chest X-ray or thorax CT should be taken for evaluation of lung metastases. Fluorine-18-fluorodeoxyglucose positron emission tomography (PET-CT), widely used today, may also help in the staging of the disease.

In the presence of a soft tissue mass suspected of malignancy, a histological diagnosis must be obtained by core needle biopsy or open surgical biopsy. Classification of NRSTS causes challenges for pathologists and there is wide interobserver variability. Therefore, pathological examination should be performed by a pathologist with expertise in sarcomas, according to the World Health Organization (WHO) Classification.[9] Immuno histochemical study and molecular profiling are useful for accurate classification. The two most commonly used systems for the histological grading are those developed by the Pediatric Oncology Group (POG) and the Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC).[10] In the prospectively validated POG system, cases are graded as low, intermediate and high based on histological subtype, necrosis rate, and cellular pleomorphism.[11] According to this system, mortality rates are 15% in grade 1 and 2 tumors and 73% in grade 3 tumors.[12] In the FNCLCC system, grading is based on tumor differentiation, presence of necrosis and the number of mitoses.[13]

Although there is no standard consensus for pediatric NRSTS staging, the most commonly used staging system is the American Joint Committee on Cancer (AJCC). In this system, tumor size (T1 ≤5 cm, T2 >5 cm), tumor depth (a=superficial, b=deep), nodal involvement (N), distant metastasis (M) and histological grade (G) are taken into account.[14] Another staging system used after surgery is the 'Intergroup RMS Study Group (IRSG)' classification. It is determined based on the completeness of surgical resection: initial complete resection (R0) is classified as group 1, complete resection with microscopic residual disease (R1) and/or regional LN involvement (N1)refers to group 2, macroscopic residual disease (R2) or biopsy alone (not resected) is classified as group 3 and metastatic disease is classified as group 4. However, as a limitation, important factors such as tumor grade and width of surgical margins are not considered in this system.[15]

The most significant poor prognostic factors in pediatric NRSTS are tumor grade (high), tumor size of >5 cm, positive or close surgical margins, and presence of metastatic disease.[16,17] In a meta-analysis including unresectable patients, age, delayed complete surgical resection, histological subtype, response to neoadjuvant CHT, tumor site and presence of radiotherapy (RT) were also defined as prognostic factors. Trunk, intra-abdominal or intrathoracic localization, MPNST histology, age >10 years were poor prognostic factors for survival. NF-1-associated MPNSTs had the worst CHT response and survival rate in all NRSTS.[18]

Researchers at St. Jude Children's Research Hospital identified three risk groups with significantly different overall survival (OS) rates according to the prognostic features. Group 1 includes completely resected and non-metastatic patients, Group 2 includes unresectable and non-metastatic patients, and Group 3 includes metastatic patients, with 5-year OS rates of 89%, 56%, and 15%, respectively.[8,16,17] In the Children's Oncology Group (COG) risk classification used today, the cases are divided into low-, intermediate-, and high-risk groups according to resection width, POG tumor grade, tumor size, and presence of distant metastases. Five-year OS rates are 90%, 50%, and 15% for the low-, intermediate-, and high-risk groups, respectively.[16,17,19]

Treatment

A multidisciplinary approach is mandatory in the treatment of this special disease. In the past, due to the rarity of prospective studies on NRSTS in the pediatric age group, cases were often treated similar to adult patients. Following the definition of prognostic factors in the two large single-center series in pediatric NRSTS, prospective studies including a multimodal risk-adapted treatment approach were designed by the COG and the European pediatric Soft Tissue Sarcoma Study Group (EpSSG).[16,17,20] These comprehensive studies have led to the definition of a standard of care for pediatric NRSTS and both will be discussed in detail below.[19,21] Again, the INternational Soft Tissue SaRcoma ConsorTium (INSTRuCT), formed by COG, EpSSG and Cooperative Weichteilsarkom Studiengruppe, aimed to provide treatment standardization and improve treatment outcomes in pediatric NRSTS, and has recently published its recommendations.[22] In general, patients are classified according to key prognostic factors such as presence of distant or LN metastases, histologic grade, primary tumor size (≤5 cm vs. >5 cm) and extent of surgical resection, and a risk-adapted treatment approach is applied (Table I).

Surgery

While determining the local treatment method, tumor grade, tumor size, tumor localization, surgical margins and patient age should be considered. The main treatment component of the multimodal treatment strategy is complete surgical resection with negative margins prior to or after CHT and/or RT. One of the most important goals should be to avoid any microscopic or macroscopic disease left behind. Although negative surgical margins after resection are essential, surgical procedures with high morbidity or mutilation should be avoided since similar local control rates can be achieved with modern RT techniques. A cornerstone randomized trial including both adult and pediatric patients with soft tissue sarcoma showed that limb-sparing surgery and adjuvant RT had similar survival rates when compared to amputation.[23]

Table I. INSTRuCT risk-adapted treatment recommendations for NRSTS.[22]

IRS Group	Grade	Tumor Size	Surgical Status	Treatment
I-II	Low	-	R0-R1	Surgery alone
I	High	≤5 cm	R0	Surgery alone
II	High	>5 cm*	R1	Adjuvant RT
I-II	High	>5 cm**	R0-R1	Adjuvant CHT (4-6 cycles of I&D) ± RT
III	High	>5 cm	Unresectable or delayed resection planned	Neoadjuvant CHT (6 cycles of I&D) and RT
Metastatic	-	-	-	Neoadjuvant CHT (6 cycles of I&D) and RT

CHT: chemotherapy, D: doxorubicin, I: ifosfamide, INSTRuCT: INternational Soft Tissue SaRcoma ConsorTium, IRS: Intergroup Rhabdomyosarcoma Study, NRSTS: non-rhabdomyosarcoma soft tissue sarcomas, R0: negative resection margins, R1: microscopic tumor infiltration, RT: radiotherapy.
*Eventually size ≤5 cm.
**Eventually synovial sarcoma IRS group II with ≤5 cm tumor and/or axial location.

Since lymphatic metastasis is rare, routine LN dissection is not recommended. However, clinically suspicious LNs should be sampled, especially in tumors of specific histological types at risk of regional LN metastasis. Although this is an evolving area, the utility of sentinel LN biopsy has been reported in pediatric NRSTS at high risk for nodal involvement and can be considered in some cases.[24] The optimal management of pathologically confirmed metastatic LNs is unknown due to the rarity of these cases, but overall, LN dissection with adjuvant RT is generally the preferred approach.

Systemic Treatment

NRSTSs are generally accepted chemoresistant tumors except synovial sarcoma. Although they are defined as chemoresistant, CHT plays a vital role in selected patients. It has been shown that the regimen with the highest response rates among the different chemotherapeutic agents was a combination of ifosfamide and doxorubicin.[20] CHT is generally used with an aim to increase the resectability rates of unresectable tumors and is always used with RT since the highest resectability rates are achieved with combined approaches rather than CHT alone.[17] Also, CHT can provide systemic disease control in metastatic patients. Again, it can be applied as adjuvant therapy to provide systemic control in tumors with high metastatic potential in the postoperative period. In a retrospective analysis of 36 patients it was shown that patients with high-grade or tumors larger than 5 cm had better 5-year metastasis-free survival and OS rates with adjuvant CHT than those who had not.[25] However, a large trial in pediatric patients failed to demonstrate any survival benefit with adjuvant CHT compared to observation alone.[26]

With a better definition of molecular features and the integration of genetic data in NRSTS, molecular targeted therapies such as specific tyrosine kinase inhibitors, such as imatinib, sunitinib, pazopanib etc., can be used as new agents in pediatric NRSTS. The prospective ARST1321 study showed that pathological near complete response rates increased with the addition of pazopanib to neoadjuvant chemoradiotherapy (CRT).[27] However, comprehensive prospective studies are needed to clarify whether survival rates are improved with targeted therapies.

Radiotherapy

RT plays an essential role in the treatment of NRSTS. It can often be applied to patients with a high risk of local recurrence, either preoperatively or postoperatively. Indications for adjuvant RT in current clinical practice are determined by surgical margin status, tumor grade, tumor size, invasion of adjacent structures, histological subtype, age, and underlying genetic syndromes (e.g., Li Fraumeni Syndrome). Surgery alone is a sufficient therapy for patients with localized, low-grade tumors with negative surgical margins. If the surgical margin is close or positive, re-excision should be the first choice and RT in these patients is generally reserved for recurrence. With this approach, excellent survival rates can be achieved with re-excision and adjuvant RT, even if there is recurrence.[16] Exceptionally, if limb-sparing surgery cannot be performed in case of recurrence or the morbidity of the surgery to be performed is unacceptable, adjuvant RT may be considered without delay. In the presence of high-grade tumors >5 cm or marginally-resected high grade tumors, adjuvant RT is recommended to increase local control.[28]

The treatment approach used in pediatric NRSTS in recent years is based on the risk grouping, in which more intensive treatments are applied to increase survival in high-risk cases and de-escalated treatment approach in low-risk patients in order to avoid treatment related morbidity. In summary, treatment plans vary from surgery alone to more aggressive neoadjuvant or adjuvant CHT and RT regimens. This approach was tested in the recently published prospective 'ARST0332' trial designed by COG.[19] In this study patients were categorized into low-, intermediate-, and high-risk groups according to the POG tumor grade, tumor size, distant metastasis status, initial extent of surgery and surgical margins, and four different treatment arms (A-D) were defined (Table II). Five hundred twenty-nine patients under 30 years of age with more than 30 histological subtypes were included in this study. The absence of microscopic tumor cells in the surgical margins was accepted as R0 resection, while the adequate surgical margin was determined as ≥5 mm. According to this protocol, surgery alone was performed in low-risk patients, except those with high-grade tumors and R1 resection. Adjuvant RT with a total dose of 55.8 Gy was applied to patients with high-grade tumors and positive microscopic margins. Adjuvant CHT containing ifosfamide and doxorubicin plus adjuvant RT (55.8 Gy) starting after the second cycle of CHT was applied to resected patients in the intermediate and high-risk groups. Initially unresectable patients underwent surgery after neoadjuvant CRT. After surgery, adjuvant CHT and RT boost were applied according to the surgical margin status. The total dose of neoadjuvant RT was 45 Gy. After surgery, 10.8 Gy boost was applied to patients who underwent R1 resection, and 19.8 Gy boost to patients who underwent R2 resection or were unresectable. No adjuvant therapy was applied for low-grade tumors that were initially metastatic if all lesions were grossly resected. However, metastasis-directed RT at a dose of 50 Gy in 25 fractions was applied to all residual metastatic lesions at the end of the therapy. Whole lung or whole abdomen or pelvis RT was not recommended. At the end of a median follow-up period of 6.5 years, risk groups were shown to have a significant predictive effect on survival rates. The 5-year OS and event-free survival (EFS) rates were 96.2% and 88.9%, 79.2% and 65%, and 35.5% and 21.2% for low-, intermediate-, and high-risk patients, respectively. According to the ARST0332 study results, the oncological outcomes were excellent with surgery alone in low-risk patients, and late toxicities of adjuvant treatments could be avoided safely in these patients. In addition, it was underlined that a lower adjuvant RT dose (55.8 Gy at adjuvant setting and 45 Gy at neoadjuvant setting) rather than conventional doses provided satisfyingly high local control rates.

Table II. COG's ARST0332 Study: A risk-adapted treatment approach in NRSTS.[19]

Risk Group	Prognostic Factors				Treatment (Treatment Arm)
	Grade	Tumor Size	Metastasis*	Resection Status of Primary Tumor	
Low	Low	≤5 cm/>5 cm	(-)	Grossly resected (R0/R1)	Observation (A)
	High	≤5 cm	(-)	Microscopic margins (-)	Observation (A)
	High	≤5 cm	(-)	Microscopic margins (+)	Adjuvant RT (B)
Intermediate	High	>5 cm	(-)	Grossly resected (R0/R1)	Adjuvant CHT and RT (C)
	High	>5 cm	(-)	Unresected/R2**	Neoadjuvant CRT, surgery, adjuvant CHT ± RT (D)
High	Low	≤5 cm/>5 cm	(+)	Grossly resected (R0/R1)	Observation (A) or Adjuvant CHT and RT (C)***
	High	≤5 cm/>5 cm	(+)	Grossly resected (R0/R1)	Adjuvant CHT and RT (C)
	High	≤5 cm/>5 cm	(+)	Unresected/R2**	Neoadjuvant CRT, surgery, adjuvant CHT ± RT (D)

CHT: chemotherapy, COG: Children's Oncology Group, CRT: chemoradiotherapy, NRSTS: non-rhabdomyosarcoma soft tissue sarcomas, RT: radiotherapy.
*Lymph node and/or distant metastasis.
**Unresectable or high-grade tumor >5 cm where delayed resection planned.
***If all disease resected (A) or not (C).

Venkatramani et al.[29] also separately reported the characteristics and treatment outcomes of patients diagnosed with synovial sarcoma, the most common NRSTS, in the ARST0332 study. When 138 available patients were examined, risk-adapted treatment was found to be effective and safe. All parameters used in risk classification had a significant predictive effect on the outcomes. Adjuvant CHT and RT could be avoided in almost one third of patients. The 5-year OS rate was reported as 100% in patients who underwent surgery alone for low-risk disease. Sixty-nine (50%) of the synovial sarcoma patients were initially considered unresectable and treated with neoadjuvant CRT. The dose of RT in these patients was 45 Gy which is lower than the doses used in the postoperative adjuvant RT approach and gross total resection was performed in 87% of them. Since less than 20% had a microscopic residual disease, a boost of 10.8 Gy was applied postoperatively in the study. Although synovial sarcoma is considered as a chemosensitive tumor, it is interesting that high (>90%) necrosis rate was detected in only 28% of patients after neoadjuvant CRT. In the following ARST1321 Phase 2 study, it was shown that the addition of pazopanib to neoadjuvant CRT increased rates of pathological near complete response in children and adults with advanced NRSTS.[27] The long-term results of these trials will reveal the effect of pathological response rates on survival outcome.

Similar to the COG, the NRSTS 2005 study of EpSSG also examined the risk-adapted treatment in pediatric patients with NRSTS (Table III).[21] The EpSSG study included two

Table III. EpSSG's NRSTS 2005 Study: A risk-adapted treatment approach in NRSTS.[21]

Surgery Alone		
Synovial Sarcoma	IRSG I, ≤5 cm	
	IRSG I, ≤5 cm, any grade	Upfront surgery, no adjuvant treatment.
Adult type NRSTS	IRSG I, >5 cm, grade 1	
	IRSG II, any size, grade 1	
Adjuvant RT*		
	IRSG I, >5 cm, grade 2	
Adult type NRSTS	IRSG II, ≤5 cm, grade 2–3	Adjuvant RT (54.0 Gy)
	IRSG II, >5 cm, grade 2	
Adjuvant CHT (with or without RT)		
	IRSG I, >5 cm	4 cycles I&D
Synovial Sarcoma	IRSG II, ≤5 cm	3 cycles I&D + RT (50.4 Gy)
	IRSG II, >5 cm	
	Axial site or resected N1	3 cycles I&D + RT (54 Gy) with 2 cycles I + 1 cycle I&D
Adult type NRSTS	IRSG I–II, >5 cm, grade 3 or resected N1	
Neoadjuvant CHT (with or without RT)		
Synovial Sarcoma	IRS Group III (unresected) or unresected N1	3 cycles I&D + Surgery + RT** (50.4-59.4 Gy) with 2 cycles I + 1 cycle I&D ± 1 cycle I&D
Adult type NRSTS		

CHT: chemotherapy, D: doxorubicin, EpSSG: European pediatric Soft Tissue Sarcoma Study Group, I: ifosfamide, IRSG: Intergroup Rhabdomyosarcoma Study Group, N: nodal stage, NRSTS: non-rhabdomyosarcoma soft tissue sarcomas, RT: radiotherapy
* Following upfront surgery.
**50.4 Gy after R0, 54.0 Gy after R1, and 59.4 Gy after R2 resection.

different treatment protocols under the headings of synovial sarcomas and adult type NRSTS to create subgroups as homogeneous as possible. Unlike the COG study, metastatic patients were not included in this study. Patients with synovial sarcoma were stratified according to surgical stage, tumor size, nodal involvement, and tumor localization. The risk classification in the EpSSG study also included the IRSG classification system based on surgical resection status, which was previously mentioned, and grading was based on the FNCLCC grading system. In this study patients were divided into four treatment groups: surgery alone, adjuvant RT, adjuvant CHT (± RT), or neoadjuvant CHT (± RT). The main CHT regimen was ifosfamide plus doxorubicin. With a median follow up of 80 months, 5-year OS and EFS rates were 98.1% and 91.4 % in the surgery alone group, 88.2% and 75.5% in the adjuvant RT group, 75.8% and 65.6% in the adjuvant CHT group and 70.4% and 56.4% in the neoadjuvant CHT group, respectively. As a conclusion, the authors stated that risk-adapted treatment was safe and feasible.

Timing of Radiotherapy

RT can be used as preoperative, intraoperative, postoperative or as definitive therapy but it is usually recommended in the postoperative setting for NRSTS.[23,30] Preoperative RT, on the other hand, is increasingly popular because of its various advantages. A randomized trial in adult patients failed to show any local control or survival benefit with preoperative RT, but there are no studies confirming this for the pediatric population.[31] Advantages of preoperative RT include performing less morbid surgeries in large (>5 cm) tumors and tumors that are difficult to operate at the beginning, reducing the risk of tumor seeding during surgery, increasing the biological effect of radiation in tumors with intact vascularization and better oxygenation, better determination of target volumes during RT planning, smaller irradiated volumes with exclusion of surgically manipulated tissues, incision scars, and drain sites with lower RT doses and improved long-term functional outcomes.[31,32] However, there are possible disadvantages like increased wound complications, rare but possible progression during RT, and the inability to perform definitive surgery in cases with progressive tumors.[31] There are conflicting reports on whether acute wound complications are more common with preoperative RT. It has been reported in the literature that preoperative RT causes wound complications in approximately 11-29% of adult series.[33,34] In the ARST0332 study, which included the pediatric population, 11% of the patients who underwent delayed surgery following neoadjuvant CRT had wound complications requiring surgical intervention.[19] The slightly lower incidence of wound complications compared to adult series may be due to lower doses and smaller fields of RT, but more detailed prospective studies regarding predictive factors for wound complications are needed.

In the ARST0332 study, postoperative RT was administered within six weeks after surgery with completion of post-surgical wound healing in the adjuvant RT arm and patients in the adjuvant CRT arm received RT four weeks after the 2nd course of ifosfamide plus doxorubicin CHT.[19] Patients in the preoperative CRT arm received two cycles of ifosfamide plus doxorubicin and two cycles of only ifosfamide concurrently with RT starting at the 4th week after the second cycle of CHT. If feasible, definitive resection was done at week 13, and a postoperative boost was applied to patients with residual tumors after the first cycle of adjuvant CHT.

In the EpSSG study protocol, as the value of CHT is unclear, it's recommended to start RT without delay. In patients with initial gross resection, RT is started after the third cycle of CHT which corresponds to the postoperative 9th week.[21] If second-look surgery will not be performed in patients with macroscopically residual disease (IRSG III), RT is started 8 weeks after surgery. In patients who underwent second-look surgery, RT starts in the 3rd week unless there are postoperative complications. If preoperative RT is to be performed before second-look surgery, RT begins at week 9 after the first surgery, and the second surgery is performed at week 5 after RT.

Radiotherapy Technique

In the first and subsequent National Cancer Institute of Canada (NCIC) studies examining the organ preservation approach, only conventional two-dimensional (2D)-RT technique was used, including a large RT field and a sequential boost volume determined by surgical clips to reduce adjacent critical organ doses.[23] Although the standard RT technique today is three-dimensional (3D)-conformal RT (3D-CRT), several studies in adult patients have reported higher local control rates and lower toxicity rates with intensity modulated radiotherapy (IMRT) compared to 3D-CRT.[35,36]

The EpSSG protocol recommends 3D-CRT for all patients and includes megavoltage (MV) equipment, electrons, and brachytherapy (BRT).[21] Low energy (4 to 6 MV) photons are recommended for limb tumors and 6 to 20 MV photons for trunk tumors. While electrons can be used for superficial or slightly infiltrative tumors, BRT is generally reserved for incompletely resected tumors located in the vagina, perineum, prostate, bladder, and orbit. In a separate analysis of 56 patients with high-grade extremity tumors who underwent preoperative RT in the COG ARST0332 study, it was reported that target coverage increased with IMRT compared to 3D-CRT, at the same time, skin and adjacent joint doses decreased.[37] Reducing the skin dose is an essential advantage of IMRT, as clinicians' primary concern for preoperative RT is postoperative wound complications. However, it is especially important in pediatric cases that the low-dose areas with IMRT are higher than with 3D-CRT, which may increase the risk of secondary malignancies.[38,39] When deciding on the RT technique, evaluation should be made on a patient by patient basis. Insufficient immobilization, rapidly growing tumor or a large field size may be other reasons for preferring 3D-CRT over IMRT.

Image-guided RT (IGRT) improves the accuracy of RT delivery. With this technique, the safety margins given to the target volumes can be reduced and thus less toxicity is observed.[40] Therefore, it is recommended to perform IGRT regardless of the RT technique. Kilovoltage (KV) imaging is preferred over MV imaging for reducing the ionizing radiation exposure.

There are also promising results for proton beam therapy in Ewing sarcoma and RMS.[41,42] Proton beam therapy reduces normal tissue and organ doses with its Bragg peak feature. However, in a systematic review of 15 pediatric cancers, including sarcomas, it was concluded that clinical data supporting or rejecting proton beam therapy is insufficient, and high-quality clinical studies should be conducted on this subject.[43]

High doses of RT are often required for local control in NRSTS, resulting in increased normal tissue toxicity when external beam RT (EBRT) is administered. In many centers, single-fraction BRT or intraoperative RT (IORT) combined with lower-dose EBRT is applied to increase local control.[44,45] Local control rates are highest with BRT combined with EBRT, especially in positive surgical margins. However, it has been shown in the literature that the contribution of BRT is limited to high-grade tumors only.[46]

Simulation and Target Volumes of Radiotherapy

The use of appropriate immobilization devices during simulation is essential. Various devices such as limb masks, air or vacuum bags can be used for this purpose. Placing radiopaque markers on surgical scars before simulation facilitates target volume contouring. While contouring the target volumes, physical examination findings and radiological examinations should be used. When contouring the target volume in postoperative cases, performing fusion with the most appropriate preoperative imaging technique is essential. MRI is superior to CT in terms of better soft tissue contrast. Contrast-enhanced T1 MRI images are frequently used in target volume delineation. The definitions of gross tumor volume (GTV) and clinical target volume (CTV) are summarized in (Table IV). The planning target volume (PTV) margin is usually 3-5 mm and differs from center to center depending on the treatment modality.

Although a craniocaudal safety margin of 4-5 cm is traditionally given when determining RT volumes in patients diagnosed with adult STS, narrower margins have been given in recent studies.[31] However, the optimal margin in pediatric cases is unknown. In a prospective study by Krasin et al., local RT fields were created by giving a 2 cm safety margin to the initial tumor volume. In the follow-up of 32 patients, local failure was observed in 4 patients. The mean dose at the site of local recurrence in all four patients was 97% of the prescribed radiation dose. The authors concluded that limited field RT is effective, but since failure occurs in the high-dose region, new treatment strategies are required to increase local control.[47]

In the COG ARST0332 study, CTV margins were created by giving 1.5 cm to the GTV, and PTV margins were created by giving 0.5 cm to the CTV.[19] In the EpSSG study, a 1 cm safety margin is given to GTV for CTV contouring[21]. A longitudinal safety margin of 2 cm is given for lesions located in the extremities. Biopsy or surgical scars and drain sites should also be included in the CTV. For PTV, a safety margin of 1 cm is given to the CTV, but a safety margin of 2 cm should be given for the chest wall localization. If high RT doses are to be administered, a new CT simulation should be performed after 50.4 Gy, and a PTVboost volume should be created by giving the residual tumor a 1-2 cm safety margin.

Table IV. Target volume definitions by ARST0332 study.[19]

Target Volumes	Definitions
GTV1	Defined as the visible and/or palpable disease defined by physical examination, CT, MRI or PET-CT, operative notes, and pathology reports.
	For patients with initial tumors that extend into body cavities (i.e., thorax, abdomen) the GTV1 may require modification. If the tumor has been resected or responded to CHT and the normal tissues have returned to their normal positions, the GTV1 excludes the volume which extends into the cavity. Examples include tumors which compress but not invade the lung, intestine or bladder that radiographically return to normal anatomic position following surgery or CHT.
	Include all infiltrative disease detected at initial presentation.
GTV2	For resected tumors, the GTV2 (volume reduction) is defined as the region of positive surgical margins, microscopic or gross residual disease determined by operative note, pathology report and imaging studies.
	For unresected tumors, the GTV2 is defined as the pre-treatment residual soft tissue disease following induction CHT.
	For partially resected tumors, the GTV2 is defined as the residual soft tissue disease following induction CHT and surgical debulking.
CTV1	Defined as GTV1 + 1.5 cm (but not extending outside of the patient).
	Also includes regional LN chains that are known to harbor pathologically involved nodes.
	For some sites, CTV1 is modified to account for specific anatomic barriers to tumor spread.
CTV2	Defined as the GTV2 + 1.0 cm (but not extending outside the patient).
	For some sites, CTV2 is modified to account for specific anatomic barriers to tumor spread.

CHT: chemotherapy, CT: computed tomography, CTV: clinically target volume, GTV: gross tumor volume, LN: lymph node, MRI: magnetic resonance imaging, PET: positron emission tomography.

In BRT, the target volume contains the surgical bed alone. Scar or drain sites are not included. Catheters should be placed 1-1.5 cm apart, parallel, or perpendicular to the incision scar. Although there is no clear consensus for the safety margin, a minimum of 2 cm craniocaudal and 1-2 cm radial are recommended by American Brachytherapy Society (ABS).[48] There is a relationship between catheter loading in the early postoperative period and postoperative wound complications. For this reason, loading is not recommended in the first five days postoperatively.[46] Removal of critical structures such as intestines, nerves, ureters, and main vessels from the RT field is important in terms of side effects. Target volumes and the RT plan of a patient with synovial sarcoma is shown in Figure 1 and Figure 2.

Radiotherapy Dose

RT approach in pediatric RMS, which is clearly a distinct entity, RT dose, fraction scheme and target volumes were clearly defined based on the results of randomized trials. However, there is no standard recommendation for details of RT in pediatric NRSTS. RT target volume definitions and administered doses differ in COG and EpSSG studies (Table V). Conventional RT is applied in daily fraction doses of 1.8 Gy, five days a week. In the presence of large treatment fields or cases <3 years of age, smaller fraction doses such as 1.2-1.5 Gy should be preferred. The total dose in high dose rate BRT is 34 Gy, twice a day at a fractional dose of 3.4 Gy. Due to toxicity, doses of <12 Gy should be administered in cases <6 years of age.[49]

For pediatric NRSTS, postoperative boost is still controversial. Although many centers apply postoperative boost to patients who cannot achieve R0 resection after neoadjuvant CRT, no study clearly shows the benefit of a postoperative boost in the pediatric population. There are also controversial results in adult series in the literature. A study of 216 adult patients with positive surgical margins showed that post-operative 16 Gy boost after neoadjuvant 50 Gy RT did not contribute to the prevention of local recurrence.[50]

It is very important to protect normal tissues during RT, especially in pediatric cases. The skin and subcutaneous tissues should be protected medially as a longitudinal strip, and at least 50% should receive a dose of <20 Gy to minimize the lymphedema risk. It is also recommended that <50% of normal weight-bearing bones receive 50 Gy to reduce fracture risk.[40] Epiphyseal growth plates should be preserved as much as possible because of the risk of asymmetrical growth and deformity in growing children.

Today, based on prospective COG ARST0332 and EpSSG studies, a risk-adapted multimodal

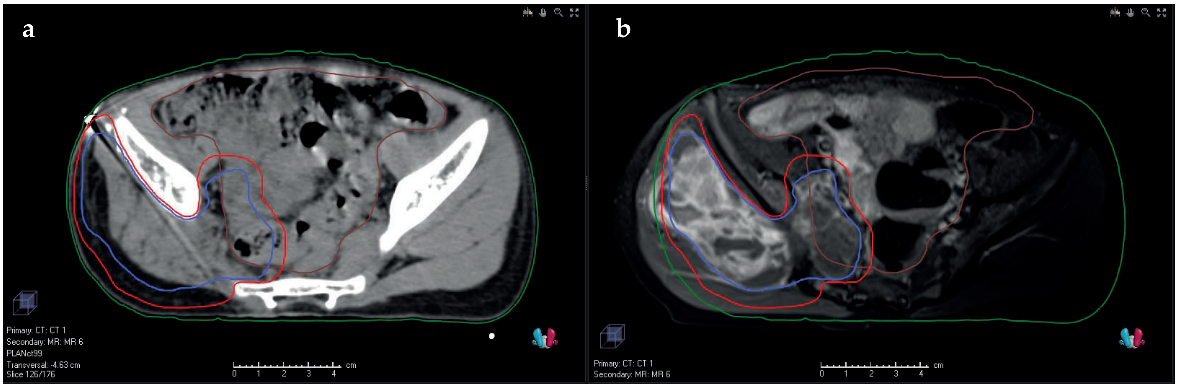

Fig. 1. Target volumes of radiotherapy in a patient with synovial sarcoma after surgery.

Fused images of simulation CT (a) and preoperative MRI (b). Blue contour is GTV-virtual (preoperative GTV). Red contour is CTV with 5 mm safety margin. Brown contour is bowel. Green contour is body.

CT: computed tomography; MRI: magnetic resonance imaging; GTV: gross tumor volume; CTV: clinically target volume

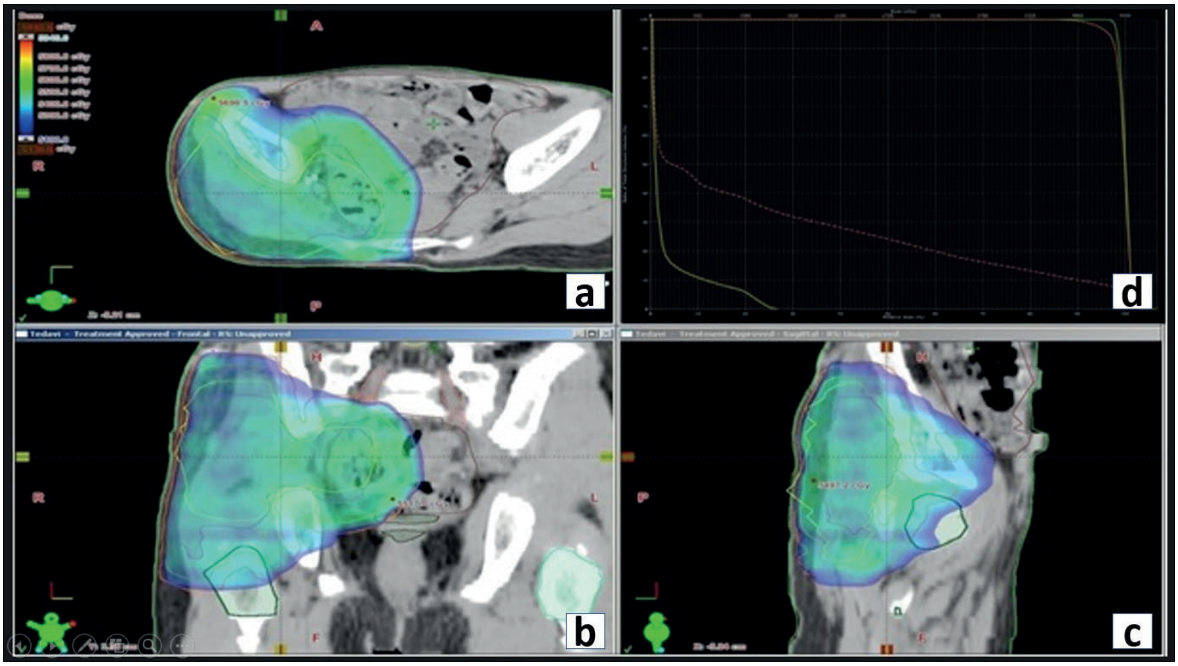

Fig. 2. Radiotherapy plan of a patient with synovial sarcoma.

Axial (a), coronal (b) and sagittal (c) simulation CT images of the RT plan and DVH (d). Blue dose-color wash is 95% isodose. At DVH, orange line is PTV, green line is CTV, dashed brown line is bowel, yellow line is spinal cord.

CT: computed tomography; RT: radiotherapy; DVH: dose-volume histogram; CTV: clinically target volume; PTV: planning target volume

Table V. Radiotherapy dose recommendations of the ARST0332 and EpSSG trials.[19,21]

COG ARST 0332	
High grade, ≤5 cm, R1 resection	Adjuvant RT (55.8 Gy)
High grade, >5 cm, R0/R1 resection	Adjuvant RT (55.8 Gy)
Initially unresectable	Neoadjuvant RT (45 Gy) ± postoperative boost (10.8 Gy for R1, 19.8 Gy for R2 resection or no surgery)
EpSSG – Synovial sarcoma	
R1 resection, ≤5 cm	Adjuvant RT (50.4 Gy)
R1 resection, >5 cm, axial site or resected N1	Adjuvant RT (54 Gy)
Unresected tumor or N1	Neoadjuvant RT (50.4 – 59.4 Gy)
EpSSG – Other NRSTS	
Grade 2, R0 resection, >5 cm	Adjuvant RT (50.4 Gy)
Grade 2-3, R1 resection, ≤5 cm	Adjuvant RT (54 Gy)
Grade 3, R0 or R1 resection, >5 cm or resected N1	Adjuvant RT (54 Gy)
Unresected tumor or N1	Neoadjuvant RT (50.4 – 59.4 Gy)

EpSSG: European pediatric Soft Tissue Sarcoma Study Group, NRSTS: non-rhabdomyosarcoma soft tissue sarcomas, R0: negative resection margins, R1: microscopic tumor infiltration, RT: radiotherapy, N1: nodal metastasis

treatment approach has become the standard in pediatric NRSTS. Surgery alone is sufficient in low-risk patients, and RT or CHT may safely be omitted. On the contrary, in intermediate- and high-risk patients, adjuvant treatment including RT, CHT, or both should be applied to reduce recurrence rates. In unresectable patients, the chance of surgery increases with the neoadjuvant treatment approach and thus treatment results may improve. However, distant metastases are an important problem even in low-risk patients. In the risk-based treatment approach, limited numbers of studies have shown that the application of smaller target volumes and lower doses compared to the conventional RT approach may be effective and promising in order to reduce treatment-related morbidities in pediatric cases. In the future, better results can be obtained with a clearer clarification of molecular features and targeted therapies in such patients.

Ethical approval

Ethics committee approval was not sought because the manuscript did not contain any patient data.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: MG, FY; data collection: AK, MG; analysis and interpretation of results: AK, MG; draft manuscript preparation: AK, MG, FY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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