Radiologic Response Assessment in Pediatric Soft Tissue Sarcoma: Computed-Assisted Volume Evaluation

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Objectives To compare 3 methods of dimensional assessment, with particular attention to a new software assisted method of volume calculation, in soft tissue sarcoma, and to investigate the interobserver agreement and the intermethod agreement in chemotherapy response classification and resultant clinical repercussions.

Study design We studied 34 pediatric patients with nonmetastatic soft tissue sarcoma who had undergone only diagnostic biopsy. Tumor size was measured both at diagnosis and after induction chemotherapy by 3 observers and using 3 measurement methods: maximum axis (1 diameter), estimated volume (3 diameters), and computed volume (software-assisted volume calculation). We used overall concordance correlation coefficient and Bland-Altman statistical methods to assess interobserver agreement and overall concordance correlation coefficient and the κ Cohen coefficient to assess intermethod agreement.

Results According to overall concordance correlation coefficient, the interobserver agreement was very high for each method, with a slight superiority of the software assisted method; this agreement was not confirmed in Bland-Altman plots for maximum axis and estimated volume methods. According to kappa coefficients, the intermethod agreement in chemotherapy response evaluation was poor.

Conclusions Computed volume was the most accurate method in soft tissue sarcoma tumor size assessment. One- and 3-dimensional methods are not concordant in chemotherapy response classification. In particular, the maximum axis method underestimates chemotherapy response and can lead to switching the chemotherapy regimen erroneously. *(J Pediatr 2017;182:327-34).*

Soft tissue sarcomas (STS) represent about 7.4% of all pediatric cancers in the US population.[1,2] Rhabdomyosarcoma (RMS) is the most frequent STS in children 0-14 years of age and accounts for 50% of tumors in this age group; nonrhabdomyosarcoma STS includes an heterogeneous group of tumors and the most common are synovial sarcoma, malignant peripheral nerve sheath tumor, and fibrosarcoma.[3-8]

Tumor size at diagnosis represents one of the most significant variables for risk stratification; tumor size assessment during follow-up is, therefore, of importance to evaluate chemotherapy response and to address a surgical or radiotherapeutic approach.[9] It remains controversial if an initial tumor size reduction after induction therapy may predict patient's outcome.[10-15] There remains also debate about which is the most informative tumor size measurement method in computed tomography (CT) and magnetic resonance imaging (MRI) scans and whether this should be expressed in 1, 2, or 3 dimensions. In adults, the most used methods are based on 1-dimensional (1D) measurements (ie, the criteria for Response Evaluation in Solid Tumors [RECIST 1.1]) or 2-dimensional measurements (cross-section of the area, according to World Health Organization guidelines).[12,13,16,17] The European Pediatric Soft-Tissue Sarcoma Study Group (EpSSG) and the North American Children's Oncology Group proposed a volumetric method based on the measurement of the 3 maximum diameters of the tumor[18,19]; however, World Health Organization guidelines[20] and RECIST 1.1 criteria are still used widely. The maximum diameter of the tumor may be illustrative of tumor size in case of spherical masses, but most of STS grow in asymmetric way.[10] Nevertheless, there have been few studies comparing EpSSG and RECIST 1.1 criteria[10,21] and neither technique has shown superiority. We hypothesize that a volumetric software-assisted evaluation could be the most accurate method in determining tumor extension. Therefore, the purpose of this study is to determine the best and more widespread applicable tumor

1D	One-dimensional
2D	Two-dimensional
3D	Three-dimensional
CT	Computed tomography
CV	Computed volume
EpSSG	European Pediatric Soft-Tissue Sarcoma Study Group
EV	Estimated volume
MA	Maximum axis
MRI	Magnetic resonance imaging
OCCC	Overall concordance correlation coefficient
RECIST	Response Evaluation Criteria in Solid Tumors
STS	Soft tissue sarcoma(s)

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The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.11.040

measurement method among 1D (RECIST 1.1 criteria), 3-dimensional (3D) (EpSSG criteria) and volumetric-computed assisted method (software Osirix; Rosset, Geneva, Switzerland); in particular, it aims to investigate interobserver agreement in tumor size assessment at diagnosis and after induction therapy, and intermethod agreement in chemotherapy response quantification.

Methods

This retrospective, single-center study included 34 patients (**Table I**) among 105 cases with STS registered in our pediatric oncology archive from September 2005 until December 2013, according to the following criteria: <18 years of age, evidence of a single mass at diagnosis, measurable disease at the primary tumor site after initial surgery (patients who underwent only incisional biopsy, corresponding with IIIa stage in the Intergroup Rhabdomyosarcoma Study postsurgical staging system, Intergroup Rhabdomyosarcoma Study IV),[22] and the availability of CT or MRI studies in Digital Imaging and Communications in Medicine format acquired at diagnosis and after induction chemotherapy. Images were stored in a Picture Archiving and Communication System and visualized on a Macintosh workstation (Apple, Cupertino, California) that allows image processing.

We included both rhabdomyosarcoma and NRMS; the histologic diagnosis was made by an experienced pathologist before starting any treatment. Patients were treated according to the EpSSG Rhabdomyosarcoma 2005 protocol. Ethics committee approval and informed consent were obtained.

Tumor Measurements

Twenty-seven patients were evaluated using MRI and 7 using CT (68 examinations in total—54 MR and 14 CT). For each patient, MRI and CT images were analyzed before and after 3 courses of chemotherapy. All MRI scans were done with a 1.5 T unit (Avanto; Siemens, Erlangen, Germany) with phased-array body coils and patients in the supine position. Each series of images included (1) isotropic T2-weighted turbo spin echo with axial, sagittal, and coronal reconstructions (echo time 91 ms; repetition time 4870 ms; slice thickness 3 mm); (2) isotropic fat-suppressed T2-weighted turbo spin echo with axial, sagittal, and coronal reconstructions (repetition time 6060 ms; echo time 93 ms; slice thickness 3 mm); (3) precontrast isotropic fat-suppressed T1-weighted volumetric interpolated breath-hold examination with axial, sagittal, and coronal reconstructions (echo time 2.39 ms; repetition time; 7.06 ms; FA 10°; slice thickness 3 mm); (4) contrast-enhanced isotropic fat-suppressed T1-weighted volumetric interpolated breath-hold examination obtained after 60 seconds of intravenous administration of contrast medium (gadoteric acid [Dotarem] 0.2 mL/kg), followed by a 20-mL saline flush, with axial, sagittal, and coronal reconstructions.

All CT scans were performed with a 64-slice CT (Somatome Sensation 64; Siemens). Each examination included precontrast, arterial, and venous contrast-enhanced scans (slice thickness 3 or 5 mm) with intravenous injection of iodine contrast medium (iohexol 300 mg I/mL; iohexol 1.8 mL/kg) followed by a 30-mL saline flush with a mean phases time depending on patients age (arterial mean time, 30 seconds; venous mean time, 80 seconds). Not all CT examinations were performed with multiplanar reformation. The similar MRI sequence was used for sequential measurements choosing contrast-enhanced T1-weighted sequences. Contrast-enhanced CT scans were also used.

Imaging studies were evaluated independently and retrospectively by 3 radiologists experienced in the evaluation of pediatric STS. They measured tumor size for each patient both in radiologic examinations performed at diagnosis and after induction therapy (at week 9), using 3 different measurement methods. First, "maximum axis" (MA) (1D), which is the longest tumor diameter was measured in any plane (axial, coronal, or sagittal) according to RECIST 1.1 protocol guidelines. For CT scans without isotropic reconstructions in coronal or sagittal planes, we measured the maximum diameter in the axial plan only according to the revised RECIST guidelines, even if there was the possibility that the longest diameter was more in the craniocaudal direction. In the posttreatment evaluation, the maximum diameter was measured in the same plane used at diagnosis; indeed it is undesirable to measure the lesion in one plane at one assessment point and in a different plane at a subsequent assessment, but not necessarily in the same slice level or in the same direction. Second, estimated volume (EV) (3D) determined the tumor volume, 3 diameters were measured according to the EpSSG Rhabdomyosarcoma 2005 protocol: the 2 maximal perpendicular diameters (*a* and *b*) of the tumor size were measured in the axial plane on the section with the largest tumor surface area. The craniocaudal tumor dimension (*c*) was measured using sagittal or coronal sequences; when this dimension was not available in the original dataset in CT imaging, we derived the third diameter from the sum of the number of axial section containing visible tumor

Table I. Main patient and disease characteristics

Sex	
Males	19
Female	15
Total	34
Age	
Range	6 months-18 years
Median	10 years
Histologic subtypes	
RMS	20
NRMS	14
PNET/Ewing sarcoma	6
Rhabdoid tumor	3
Aggressive fibromatosis	2
Infantile fibrosarcoma	1
Liposarcoma	1
Synovial sarcoma	1
Tumor site	
Head/neck parameningeal	10
Head/neck nonparameningeal	2
Limbs	5
Genitourinary tract	6
Other sites	11

NRMS, nonrhabdmyosarcoma; *PNET*, primitive neuroectodermal tumor; *RMS*, rhabdomyosarcoma.