High-Grade Soft-Tissue Sarcomas: Tumor Response Assessment—Pilot Study to Assess the Correlation between Radiologic and Pathologic Response by Using RECIST and Choi Criteria[1]

Silvia Stacchiotti, MD
Paola Collini, MD
Antonella Messina, MD
Carlo Morosi, MD
Marta Barisella, MD
Rossella Bertulli, MD
Claudio Piovesan, MD
Palma Dileo, MD
Valter Torri, MD
Alessandro Gronchi, MD
Paolo Giovanni Casali, MD

Purpose: To compare radiologic response as defined according to both Response Evaluation Criteria in Solid Tumors (RECIST) and the new Choi criteria recently proposed for gastrointestinal stromal tumors with pathologic response in high-grade soft-tissue sarcomas (STSs) treated with preoperative chemotherapy and radiation therapy.

Materials and Methods: The institutional ethical committee approved the trial in which patients were enrolled. Signed informed consent was obtained. Thirty-seven patients (21 men, 16 women; mean age, 44.2 years) enrolled in a collaborative randomized trial on preoperative chemotherapy and radiation therapy in localized high-risk STS at a single institution were selected for this retrospective analysis. Tumor response to preoperative treatment was assessed by using both RECIST and Choi criteria at computed tomography (CT) and was adapted to be used at magnetic resonance (MR) imaging. Pathologic response was assessed as either good or very good. Sensitivity, specificity, and predictive value of RECIST and Choi criteria were calculated with pathologic response as the reference standard and were reported with 95% confidence intervals.

Results: For 28 patients without synovial sarcomas, sensitivity of RECIST versus adapted Choi criteria was 32.0% versus 88.0% for good response and 41.2% versus 82.4% for very good response, respectively; specificity for pathologic response was 100% versus 100% for not a good response and 90.9% versus 27.3% for not a very good response, respectively. In synovial sarcoma, the nontreatment-related neoplastic cystic component of the tumor was a major obstacle for both RECIST and Choi criteria.

Conclusion: In STS treated with chemotherapy and radiation therapy, tumor size may be insufficient to render actual tumor response. Tumor attenuation at CT or tumor contrast material enhancement at MR imaging may complement tumor size, thus making Choi criteria more predictive of pathologic response.

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[1] From the Departments of Cancer Medicine (S.S., R.B., C.P., P.D., P.G.C.), Pathology (P.C., M.B.), Radiology (A.M., C.M.), and Surgery (A.G.), Fondazione IRCCS Istituto Nazionale Tumori, Via Venezian 1, 20133 Milan, Italy; and Department of Statistics, Istituto Mario Negri, Milan, Italy (V.T.). From the 2007 RSNA Annual Meeting. Received August 8, 2008; revision requested September 23; revision received October 14; accepted November 24; final version accepted December 10. **Address correspondence to** S.S. (e-mail: *silvia.stacchiotti@istitutotumori.mi.it*).

Radiology

There is much debate today about tumor response criteria in solid tumors. From Karnofsky's attempts to codify response in lung cancer to the most recent Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, tumor size has been virtually the only criterion used (1–5). There has always been debate about these criteria, because it often has been difficult to correlate response and survival in advanced solid tumors. The introduction of the newest molecular-targeted therapies has fostered further discussion (6–15). For example, patterns of tumor response of gastrointestinal stromal tumors (GISTs) being treated with imatinib are peculiar (16–22). In a proportion of patients, there is no decrease in tumor size, despite the appearance of hypoattenuation within the lesions at computed tomography (CT). So, new criteria have been recently proposed for GISTs and incorporate tumor attenuation in addition to tumor size (11). These criteria have been demonstrated to correlate with patient outcomes better than RECIST criteria. Molecular-targeted therapies are not the only example of the limitations of RECIST criteria. With regard to the sarcomas, it has been long appreciated that osteosarcomas may have a dramatic pathologic response without any decrease in size (23–25). Recently, pathologic responses without any decrease in size were reported in myxoid liposarcomas being treated with a new agent, trabectedin (26).

This prompted us to compare radiologic response as defined according to both RECIST and the new Choi criteria recently proposed for GISTs with pathologic response in high-grade soft-tissue sarcomas (STSs) treated with preoperative chemotherapy and radiation therapy (hereafter, chemoradiation therapy).

Advances in Knowledge

- Choi criteria, which are based on changes in tumor size and attenuation after contrast material administration at CT, can be applied to MR imaging data, assuming that changes in contrast enhancement on subtracted contrast-enhanced T1-weighted MR images parallel changes in attenuation on CT images, both being markers of tumor vascularization.
- In all patients without synovial sarcomas, the sensitivity of Response Evaluation Criteria in Solid Tumors (RECIST) versus that of adapted Choi criteria was 32.0% (eight of 25) versus 88.0% (22 of 25) when the reference standard was a pathologic good response and 41.2% (seven of 17) versus 82.4% (14 of 17) when the reference standard was a pathologic very good response.
- The specificity for pathologic response of RECIST versus that of adapted Choi criteria was 100% (three of three) versus 100% (three of three) for not a good response and 90.9% (10 of 11) versus 27.3% (three of 11) for not a very good response.

Materials and Methods

The institutional ethical committee approved the trial in which all patients of this study were entered. Signed informed consent was obtained for all patients.

Patients

From April 2002 to May 2006, 325 patients in Italy and Spain were enrolled in a prospective randomized study on preoperative chemoradiation therapy in localized STS. All patients who presented at the National Cancer Institute, Milan, Italy, with localized, primary, naive, and high-risk (high-grade, deep, size > 5 cm) STSs of the extremities or the superficial trunk were offered enrollment in that trial. Among 95 patients enrolled in the study by the National Cancer Institute, we retrospectively identified 37 patients (21 men, 16 women; mean age, 44.2 years) who could be fully evaluated for both radiologic and pathologic tumor response. We included in the analysis only patients with measurable disease evaluated prior to and after treatment at the National Cancer Institute by using the same technique (magnetic resonance [MR] imaging or CT scanning) and the same device. We excluded from the analysis 28 patients who had no measurable disease at the time of study entry, as well as another 30 patients because their pre- and posttreatment radiologic assessments were not comparable (different techniques or modalities used).

In all these patients, radiologic response was recorded according to both RECIST and Choi criteria. We then compared RECIST with Choi criteria and used pathologic response as a reference standard.

In all cases, the histologic type and French National Federation of Cancer Centres grade were assessed by using biopsy results obtained before treatment. Before surgery, patients received three cycles of epirubicin (Farmorubicina; Pfizer Italia, Nerviano, Italy) (120 mg per square meter of body surface)

Implication for Patient Care

- This study provides preliminary evidence that tumor attenuation at contrast-enhanced CT or tumor contrast enhancement at MR imaging may complement the use of tumor size, thus making Choi criteria more predictive of pathologic response than only the dimensional criteria as defined according to RECIST guidelines.

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Abbreviations:
GIST = gastrointestinal stromal tumor
RECIST = Response Evaluation Criteria in Solid Tumors
STS = soft-tissue sarcoma
TSE = turbo spin echo

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plus ifosfamide (Holoxan; Baxter Oncology, Halle Künsebeck, Germany) (9000 mg per square meter of body surface) for each course. Concomitant radiation therapy was added at the discretion of the multidisciplinary team. The mean administered dose was 50 Gy. Surgery was performed within 4–6 weeks after the end of the preoperative treatment.

MR Imaging and CT Techniques

In all cases, MR imaging or CT scanning was performed before the preoperative treatment and after chemoradiation therapy, 1 day before surgery.

The examinations were performed, and the images were evaluated by two radiologists (A.M. for MR imaging and C.M. for CT, with 15 years of experience each and with a specialization in imaging sarcomas).

MR imaging was performed with one of two 1.5-T systems (Magnetom Vision or Avanto; Siemens, Erlangen, Germany) by using similar pulse sequences (Table 1). In all cases, standard unenhanced T2-weighted TSE and T1-weighted TSE (section thickness, 5 mm) sequences were followed by a contrast-enhanced T1-weighted TSE sequence and, in a small subgroup (five patients) of patients, also by a dynamic contrast-enhanced three-dimensional T1-weighted gradient-echo sequence. The intravenous bolus injection of 0.2 mmol per kilogram of body weight gadopentetate dimeglumine (Magnevist; Bayer-Schering, Berlin, Germany) was started before initiation of data acquisition (delay of 30 seconds for contrast-enhanced T1-weighted TSE sequence and 0 second for dynamic contrast-enhanced three-dimensional T1-weighted gradient-echo sequence). The injection rate was 2 mL/sec.

Contrast-enhanced T1-weighted TSE images and, when available, contrast-enhanced three-dimensional T1-weighted gradient-echo images were evaluated before and after digital subtraction by a radiologist (A.M.). All data sets were qualitatively and semiquantitatively evaluated. The percentage of contrast enhancement was assessed as follows: On subtracted contrast-enhanced T1-weighted images, the radiologist (A.M.) measured the contrast enhancement of the tumor by manually drawing a region of interest around the margin of the whole lesion on sections taken every 5 mm, thus encompassing the entire tumor mass. All cystic and necrotic areas were included. Muscle was used as the reference tissue because it was always available in the field. The contrast enhancement measurements of all sections were added, and the average contrast enhancement for each lesion was calculated. Because they were available in only five cases, dynamic contrast-enhanced three-dimensional T1-weighted gradient-echo images were not considered in this analysis (although results were in line with what was seen otherwise).

Table 1

MR Imaging Pulse Sequence Parameters for Patients with STS

Sequence*	Matrix	Section Thickness (mm)	Intersection Gap (mm)	Repetition Time (msec)	Echo Time (msec)	Flip Angle (degrees)
T2-weighted TSE	256 × 256	5	2	4730	153	. . .
T1-weighted TSE	254 × 384	5	2	616	11	. . .
Contrast material–enhanced T1-weighted TSE	254 × 384	5	2	616	11	. . .
T1-weighted gradient echo	128 × 100	5	2	6.08	4.30	30

* TSE = turbo spin echo.

Table 2

Tumor Response according to RECIST and Choi Criteria

Response	RECIST Criteria	Choi Criteria
Complete response	Disappearance of all lesions	Disappearance of all lesions
	No new lesions	No new lesions
Partial response	≥30% decrease in the sum of greatest diameters	≥10% decrease in the greatest maximal diameter or a ≥15% decrease in tumor attenuation at CT or contrast enhancement at MR imaging
	No new lesions	No new lesions
Stable disease	Does not meet criteria for complete response, partial response, or progressive disease	Does not met criteria for complete response, partial response, or progressive disease
Progressive disease	≥20% increase in the sum of greatest diameters	≥10% increase in the greatest maximal diameter and does not meet criteria for partial response by using tumor attenuation at CT or contrast enhancement at MR imaging or ≥15% increase in tumor attenuation at CT or contrast enhancement at MR imaging and does not meet the criteria for partial response by using tumor size
	New lesion	New lesion
		New intratumoral nodule or increase in the size of existing intratumoral nodule

Scanning was performed with a 16-section CT scanner (Somatom Sensation 16; Siemens Healthcare, Forchheim, Germany), and images were reconstructed with a 5-mm section thickness and a 5-mm reconstruction increment. A biphasic scanning technique was performed with scanning delays of 20 and 60 seconds for arterial and portal phases, respectively, after intravenous injection of 130 mL of contrast medium (Iopamidol 370; Bracco, Milan, Italy) at a rate of 4 mL/sec. A workstation (Syngo Multi-Modality Workplace or Leonardo; Siemens Healthcare) was used for post-processing. A radiologist (C.M.) measured CT attenuation values of the tumor lesion (in Hounsfield units) on CT images obtained during the portal venous phase. Two-dimensional regions of interest of the entire lesion were drawn, and all axial sections encompassing the lesion were included. To accurately define the lesion, a radiologist (C.M.) edited manually the contours of the regions of interest on each axial section. The volume of interest, covering the whole lesion, was defined as the sum of all the two-dimensional regions of interest. Both cystic and necrotic areas were included. Software calculated semiquantitatively the mean tumor attenuation (in Hounsfield units) defined as the average of all the pixels enclosed in the volume of interest.

The radiologists (A.M. and C.M.) retrospectively reviewed all MR and CT images without any knowledge of histologic responses. The percentage of change in mean tumor attenuation or contrast enhancement before and after treatment was computed for each lesion.

Tumor response was evaluated according to RECIST and Choi criteria as defined for GISTs and adapted for MR imaging (Table 2) (5,16). Therefore, according to adapted Choi criteria, the definition of a radiologic response was the presence of at least a 10% decrease in tumor size or at least a 15% decrease in tumor attenuation on contrast-enhanced CT images or in contrast enhancement on MR images.

Table 3

Comparison between Radiologic and Pathologic Response in Patients with STS

Criteria	Radiologic Assessment	Pathologic Good Response	Pathologic Very Good Response
RECIST			
Progressive disease	3/28 (10.7) [2.3, 28.2]	3/3 (100) [29.2, 100]	2/3 (66.7) [9.4, 99.2]
Stable disease	17/28 (60.7) [40.6, 78.5]	14/17 (82.4) [56.6, 96.2]	6/17 (35.3) [14.2, 61.7]
Partial response	8/28 (28.6) [13.2, 48.7]	8/8 (100) [63.1, 100]	7/8 (87.5) [47.3, 99.7]
Choi			
Progressive disease	0/28 (0) [0, 12.3]	0	0
Stable disease	6/28 (21.4) [8.3, 41]	3/6 (50.0) [11.8, 88.2]	0/6 (0) [0, 45.9]
Partial response	22/28 (78.6) [59, 91.7]	22/22 (100) [84.6, 100]	14/22 (63.6) [40.7, 82.8]

Note.—Data are numbers of patients, with percentages in parentheses and 95% confidence intervals in brackets.

Table 4

Comparison between Radiologic Partial Response and Pathologic Response in Patients with STS

Response	Pathologic Assessment	RECIST Partial Response	Choi Partial Response
Good response	25/28 (89.3) [71.8, 97.7]	8/25 (32.0) [14.9, 53.5]	22/25 (88.0) [68.8, 97.5]
Not a good response	3/28 (10.7) [2.3, 28.2]	0	0
Very good response	17/28 (60.7) [40.6, 68.5]	7/17 (41.2) [18.4, 67.1]	14/17 (82.4) [56.6, 96.2]
Not a very good response	11/28 (39.3) [21.5, 59.4]	1/11 (9.1) [0.2, 41.3]	8/11 (72.7) [39, 94]

Note.—Data are numbers of patients, with percentages in parentheses and 95% confidence intervals in brackets.

Pathologic Assessment of Surgical Specimen

All surgical specimens were sampled consistently (27). The neoplasm was mapped on its largest section, taking about a sample per 1 cm. In addition, all the macroscopically different areas (ie, solid, necrotic) were described and separately sampled. The result reflected the average mapping of the whole tumor mass. When the lesion was predominantly cystic, the diameters of the cystic and solid areas were measured and reported in the gross description, and samples were taken from the cystic wall. The following characteristics of the treated tumor mass were assessed by two pathologists (P.C. and M.B., with, respectively, 15 and 6 years of experience and both devoted to sarcomas): *(a)* percentage of residual viable tumor and *(b)* percentages of necrosis, hemorrhage, sclerosis, sclerohyalinosis, fibrohistiocytic reaction with hemosiderin, myxoid component, and cystic component.

Pathologic Assessment of Response

We codified the pathologic response on the basis of the percentage of residual viable tumor, if at least 10% of the mass demonstrated treatment-related changes, like sclerohyalinosis or fibrohistiocytic reaction with hemosiderin, because these features are usually not present at baseline in a high-grade STS. We considered two different cutoffs, which were selected prior to the evaluation of the radiologic data: good response consisted of less than 50% residual viable tumor, and very good response consisted of less than 10% residual viable tumor.

If both the above-mentioned criteria were not met (ie, <10% of the mass had changes known to be treatment-related and/or there was >50% residual viable tumor for a good response or >10% residual viable tumor for a very good response), the case was classified as a

Figure 1

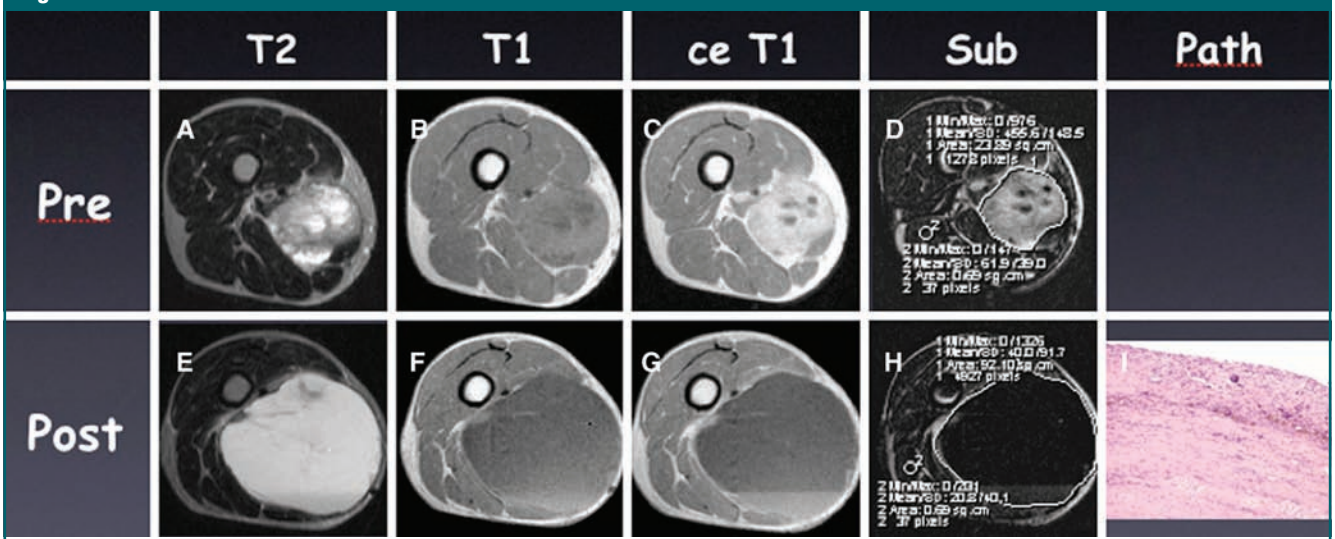

Figure 1: *A,* Axial T2-weighted TSE, *B,* T1-weighted TSE, *C,* contrast-enhanced *(ce)* T1-weighted TSE, and *D,* subtracted *(Sub)* contrast-enhanced T1-weighted TSE MR images in 39-year-old man with pleomorphic sarcoma of posterior compartment of the thigh with heterogeneous appearance before treatment *(Pre). C,* Diffuse enhancement is noted surrounding well-circumscribed areas of low signal intensity, which are consistent with necrotic spaces. After treatment *(Post), E,* axial T2-weighted TSE, *F,* T1-weighted TSE, *G,* contrast-enhanced T1-weighted TSE, and *H,* subtracted contrast-enhanced T1-weighted TSE MR images show a marked increase in size (more than 85% increase in maximum diameter, which is progressive disease according to RECIST criteria), with homogeneous hyperintensity on T2-weighted image and evident decrease in tumor contrast enhancement (decrease of 89%, which is partial response according to adapted Choi criteria). These images show a fluid-fluid level due to blood products within the lesion. *I,* Posttreatment histopathologic finding *(Path)* (hematoxylin-eosin stain; magnification, ×200) shows signs of response to chemotherapy. The residual mass is composed of a pseudocystic cavity full of necrotic debris and hemorrhagic fluid, surrounded by a wall formed by less than 5% residual viable tumor cells in the presence of more than 10% sclerohyalinosis and fibrohistiocytic reaction. This is a very good pathologic response.

nonresponder (not a good response, not a very good response).

Definition of Sensitivity and Specificity of RECIST and Choi Criteria

We evaluated the diagnostic performance of RECIST and adapted Choi radiologic criteria. Sensitivity, specificity, and predictive value of RECIST and Choi criteria were calculated with two different pathologic response levels as the reference standard and were reported with their 95% confidence intervals. We defined the sensitivity for a response to be the proportion of patients with a given radiologic response among patients with an actual pathologic response. We defined specificity for a lack of response as the proportion of patients with no radiologic response among patients without evidence of any pathologic response. We considered the predictive value of a response (positive predictive value: probability of a pathologic response in a patient with radiologic evidence of response) and of a lack of response (negative predictive value: probability of no pathologic response in a patient without radiologic evidence of response) according to both RECIST and adapted Choi criteria. In view of the preliminary nature of the data, no formal statistical comparison between specificity and sensitivity of the two radiologic criteria was performed.

Tumor response was dichotomized as responders versus nonresponders.

Results

Enrolled Patients

Patient characteristics of the study population are listed in Table E1 *(http://radiology.rsnajnls.org/cgi/content/full/2512081403/DC1)*. Thirty-four patients were evaluated with MR imaging, and three were evaluated with CT scanning.

The following analysis refers to all patients with STSs (28 patients), except those with a diagnosis of synovial sarcoma who were separately analyzed.

MR Imaging and CT Findings

According to RECIST criteria (Table E1, *http://radiology.rsnajnls.org/cgi/content/full/2512081403/DC1*), 28% (eight of 28) of patients had a partial response, 61% (17 of 28) had stable disease, and 11% (three of 28) had progressive disease. According to adapted Choi criteria, 79% (22 of 28) of patients had a partial response, 21% (six of 28) had stable disease, and none had progressive disease.

Pathologic Findings

Of 28 cases, a good response was present in 25 (89%) cases, and a very good response was present in 15 (54%) cases. In all these cases, there was more than 10% sclerohya-

linosis and/or fibrohistiocytic reaction with hemosiderin.

Correlation between Pathologic and Radiologic Findings

The comparison between radiologic determination of response and pathologic response is summarized in Tables 3 and 4. Examples are shown in Figures 1 and 2.

The accuracy of both RECIST and adapted Choi criteria is summarized in Table 5. Of 25 patients with a pathologic good response, only eight had a partial response according to RECIST criteria, while 22 were partially responsive according to adapted Choi criteria. Of 17 patients with a pathologic very good response, a response was seen in seven patients according to RECIST criteria and in 14 patients according to adapted Choi criteria. The sensitivity of RECIST criteria was less than 50% for both good response (32.0% [eight of 25]) and very good response (41.2% [seven of 17]), while the sensitivity of adapted Choi criteria was more than 80% for both groups (88.0% [22 of 25] for good response and 82.4% [14 of 17] for very good response). The three cases without a pathologic good response were all found to be nonresponders according to both RECIST and adapted Choi criteria. The specificity was 100% for both criteria when a good response was selected as the reference standard. If a very good response was considered the reference standard, the specificity was 90.9% (10 of 11) for RECIST and 27.3% (three of 11) for adapted Choi criteria.

The predictive value of a nonresponder (Table 5) according to RECIST criteria was 15.0% (three of 20) with a pathologic good response as a reference standard and 60.0% (12 of 20) with a pathologic very good response as a reference standard. Of 20 patients without a response according to RECIST criteria, there were only three patients in whom pathologic evidence of a good response was not found. On the contrary, when a pathologic very good response was selected as a criterion, a pathologic response was not found in 12 of 20 cases according to RECIST criteria. The positive predictive value of a response according to either RECIST or adapted Choi criteria was 100% if we considered a pathologic good response (eight of eight for RECIST criteria and 22 of 22 for Choi criteria) as the criterion, while positive predictive value was 87.5% (seven of eight) and 63.6% (14 of 22), respectively, for RECIST and adapted Choi criteria if we considered a pathologic very good response as the criterion.

Synovial Sarcoma

Of nine synovial sarcomas, five patients had partial response and four had stable disease according to RECIST criteria. According to adapted Choi criteria, there were seven partial responses and two with stable disease. Evidence of a response at pathologic examination was

Figure 2

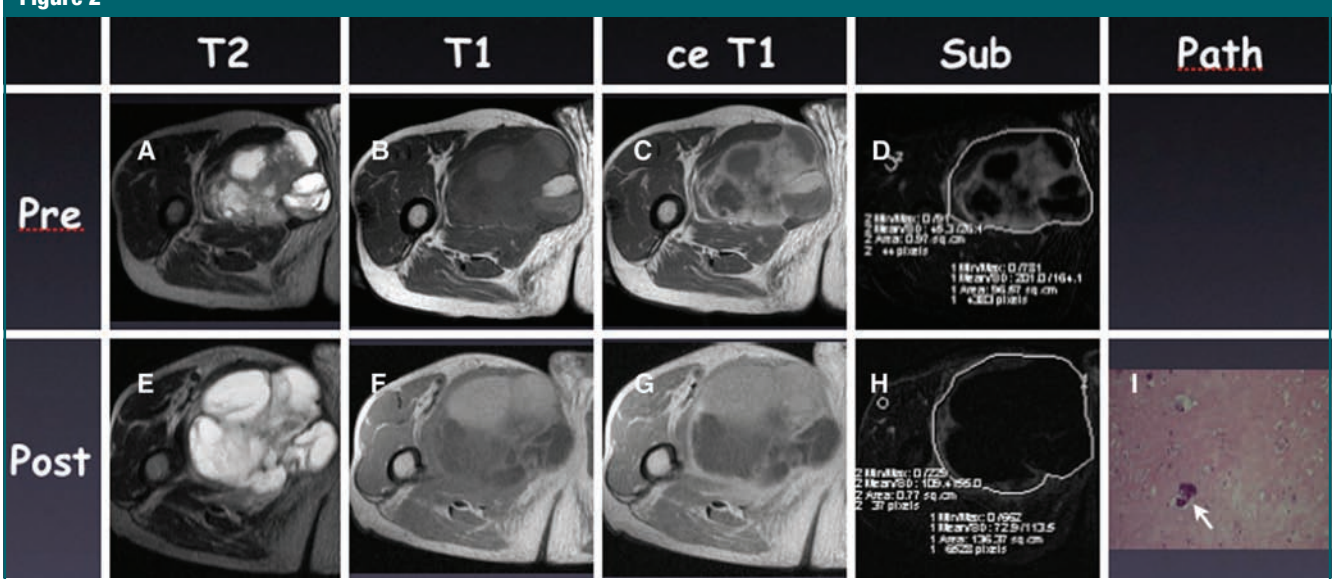

Figure 2: *A,* Axial T2-weighted TSE, *B,* T1-weighted TSE, *C,* contrast-enhanced *(ce)* T1-weighted TSE, and *D,* subtracted *(Sub)* contrast-enhanced T1-weighted TSE MR images in 69-year-old man with pleomorphic sarcoma of the thigh before treatment *(Pre).* The mass is heterogeneous in appearance. *C,* Diffuse enhancement is noted surrounding well-circumscribed areas of low signal intensity, consistent with necrotic spaces. After treatment *(Post), E,* T2-weighted TSE, *F,* T1-weighted TSE, *G,* contrast-enhanced T1-weighted TSE, and *H,* subtracted contrast-enhanced T1-weighted TSE MR images show an increase in maximum diameter (<20%, which is stable disease according to RECIST criteria), with heterogeneous hyperintensity on T2-weighted image and consistent decrease in tumor contrast enhancement (decrease of 51%, which is partial response according to adapted Choi criteria). These images show hyperintensity on T1-weighted images due to presence of blood products within the lesion. *I,* Histopathologic finding *(Path)* (hematoxylin-eosin stain; magnification, ×200) after chemoradiation therapy shows evidence of pathologic response to treatment, with only a few isolated residual viable tumor cells (arrow) within diffuse sclerohyaline tissue (15% residual viable tumor cells and more than 10% sclerohyalinosis, which is a good response).

Table 5

Diagnostic Performance of Imaging Criteria in Identifying Treatment Response in Patients with STS

A: Sensitivity for Response

	Sensitivity (%)			
Response	Partial Response according to RECIST Criteria	95% Confidence Interval	Partial Response according to Choi Criteria	95% Confidence Interval
Pathologic good response ($n = 25$)	32 (8/25)	14.9, 53.5	88 (22/25)	68.8, 97.5
Pathologic very good response ($n = 17$)	41.2 (7/17)	18.4, 67.1	82.4 (14/17)	56.6, 96.2

B: Specificity for No Response

	Specificity (%)			
Response	No Response according to RECIST Criteria	95% Confidence Interval	No Response according to Choi Criteria	95% Confidence Interval
Pathologic not a good response ($n = 3$)	100 (3/3)	29.2, 100	100 (3/3)	29.2, 100
Pathologic not a very good response ($n = 11$)	90.9 (10/11)	58.7, 99.8	27.3 (3/11)	6, 61

C: Predictive Value of Radiologic Response

	Positive Predictive Value (%)			
Response	Pathologic Good Response	95% Confidence Interval	Pathologic Very Good Response	95% Confidence Interval
Partial response according to RECIST criteria ($n = 8$)	100 (8/8)	63.1, 100	87.5 (7/8)	47.3, 99.7
Partial response according to Choi criteria ($n = 22$)	100 (22/22)	84.6, 100	63.6 (14/22)	40.7, 82.8

D: Predictive Value of Radiologic No Response

	Negative Predictive Value (%)			
Response	Pathologic Not a Good Response	95% Confidence Interval	Pathologic Not a Very Good Response	95% Confidence Interval
No response according to RECIST criteria ($n = 20$)	15 (3/20)	3.2, 37.9	60 (12/20)	36.1, 80.9
No response according to Choi criteria ($n = 6$)	50 (3/6)	11.8, 88.2	100 (6/6)	54.1, 100

Note.—Numbers in parentheses were used to calculate percentages.

found in two cases, and both were very good responses. In these two patients, there was a partial response according to adapted Choi and RECIST criteria. In all cases of partial response according to RECIST and adapted Choi criteria without a pathologic response, there was no tissue response (ie, no contrast enhancement decrease) in the solid component of the tumor (Fig 3).

Discussion

The response of solid tumors to medical therapies has long been evaluated on the basis of tumor size. In spite of the effort made by the radiologists to improve response assessment with new techniques (28,29), the standard tumor response criteria in clinical trials are still based only on tumor size. Several criteria have been used (eg, World Health Organization, Eastern Cooperative Oncology Group, Southwest Oncology Group, RECIST) (1–5). By and large, the criteria are equivalent, inasmuch as a 50% reduction in an area (World Health Organization, Eastern Cooperative Oncology Group, Southwest Oncology Group) is tantamount to a 30% reduction in a single diameter (RECIST). More recently, the appropriateness of such criteria has been challenged with regard to the tumor response of GISTs to imatinib (16–22). This has been observed also in other tumors (30–32). In GISTs, new response assessment criteria proposed by Haesun Choi, incorporating not only tumor size but also changes in tumor attenuation after contrast enhancement on CT scans, were shown to predict prognosis better than RECIST criteria.

It has always been difficult to demonstrate partial response to therapy at imaging in many advanced solid tumors (10–15). Molecular-targeted therapies give rise to a different antitumor effect and highlight the limitations of size criteria in the assessment of tumor response to these agents. These problems in tumor response assessment may apply also to cytotoxic chemotherapy. This prompted us to apply Choi criteria in this study. Indeed, these preliminary data show that this may be worthwhile.

In our study of localized, high-risk STSs treated with preoperative chemoradiation therapy, radiologic changes in tumor size as defined according to RECIST criteria were less sensitive than those of adapted Choi criteria in predicting pathologic tumor response; sensitivity was 32.0% versus 88.0% for good response, respectively, and 41.2% versus 82.4% for very good response, respectively. With respect to specificity, adapted Choi criteria tended to overrate the response only if we used the criterion of less than 10% residual viable tumor cells (ie, a very good response) as the reference standard for

pathologic response, while there was a full correspondence if the reference standard for pathologic response was considered the presence of less than 50% residual viable cells (ie, a good response).

Most patients in our study were evaluated with MR imaging, which is often used to study STS of the extremities. We therefore had to adapt Choi criteria to MR imaging. To this end, we selected changes in contrast enhancement on subtracted contrast-enhanced T1-weighted images to parallel hypoattenuation on postcontrast CT scans, both being markers of tumor vascularization.

In GISTs, Choi criteria were validated by analyzing progression-free survival as a criterion (11). Unfortunately, this was not feasible in our study. We could not take any outcome measure as a criterion, because it has not yet been demonstrated if adjuvant chemotherapy has any prognostic effect in STS (28,33–37). We therefore chose to analyze pathologic response as the reference standard. To this end, we noted the percentage of residual viable tumor and chose two arbitrary cutoffs (10% for very good response and 50% for good response), provided we could find alterations that were definitively related to posttreatment changes. Necrosis and hemorrhage were not considered because they can be present at baseline in high-grade STSs.

Our data suggest that RECIST criteria for treatment response have a lower sensitivity for pathologic response than adapted Choi criteria. This reflects the fact that in some patients, responses to treatment were not accompanied by decrease in tumor size. In some responding patients, tumor size did in fact increase. This closely parallels what is seen in GISTs being treated with molecular-targeted therapies. If we use pathologically determined very good response (<10% residual viable tumor) as the reference standard, adapted Choi criteria show low specificity (ie, a lack of pathologic major response was predicted less by using adapted Choi criteria). In only 63.6% (14 of 22) of patients with evidence of a response according to adapted Choi criteria, there was a major response to therapy (very good response) according to pathologic findings.

The identification of a treatment response at CT or MR imaging in patients with synovial sarcoma poses additional challenges. Synovial sarcoma masses may commonly demonstrate a nontreatment-related cystic truly neoplastic component. On images, it may be impossible to distinguish these cystic areas from tumor response. The cystic areas in synovial sarcoma are histologically different from necrosis because these cystic areas are lined by intact

Figure 3

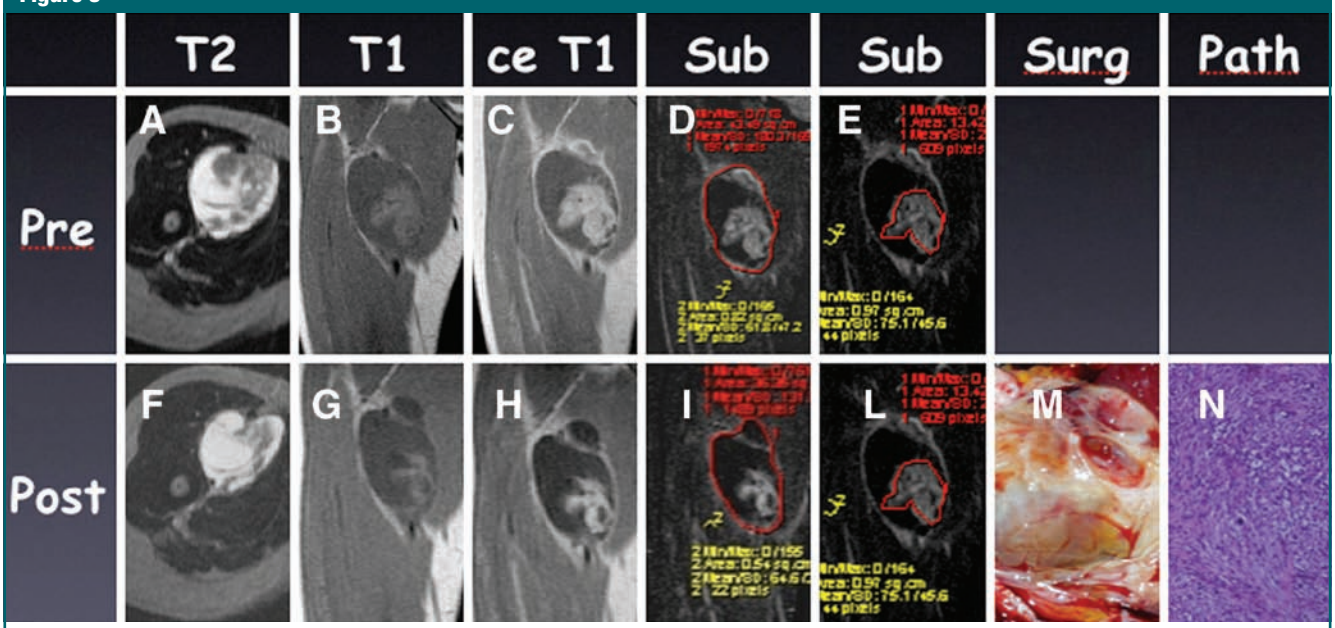

Figure 3: MR images, surgical specimen *(Surg),* and histopathologic finding *(Path)* in 22-year-old woman with synovial sarcoma of the thigh with cystic components. *A,* Axial T2-weighted TSE, *B,* coronal T1-weighted TSE, and *C,* coronal contrast-enhanced *(ce)* T1-weighted TSE MR images at baseline *(Pre). D, E,* Subtracted *(Sub)* contrast-enhanced T1-weighted TSE MR images. *F,* Axial T2-weighted TSE, *G,* coronal T1-weighted TSE, and *H,* coronal contrast-enhanced T1-weighted TSE MR images of lesion after treatment *(Post). I, L,* Subtracted *(Sub)* contrast-enhanced T1-weighted TSE MR images. *M,* Posttreatment surgical specimen with cystic component erroneously interpretable as necrotic area. *N,* Histopathologic finding (hematoxylin-eosin stain; magnification, ×200). After treatment, there is no change in size (stable disease according to RECIST criteria), but there is a 20% decrease in contrast enhancement when calculated on the whole lesion (*D* and *I*) because of an increase of cystic component (partial response according to Choi criteria). Contrast enhancement is increased (>30%) if only the solid part is considered (*E* and *L*). *M,* The solid part of the tumor located beside the true cystic area full of serous fluid is composed of 90% residual viable tumor cells without posttreatment alterations.

neoplastic cells. In our study, a cystic component at baseline was observed in four of nine patients with synovial sarcoma. After therapy, these components remained stable or even increased in size. As they are hypovascular, the radiologist may interpret an increase in cystic area size as a response to therapy. However, the pathologist can identify the active tumor cells in the walls of the cysts and readily recognize the lack of response to therapy. For these reasons, Choi criteria as currently defined do not seem to be appropriate for the assessment of the response of a synovial sarcoma, which must be further evaluated.

Our study had a number of limitations. It was a retrospective study (although within a prospective trial), performed on a small series of cases, which does not allow a good precision of results, as shown by wide confidence intervals of estimates. Second, we could not correlate response with overall survival or progression-free survival. Third, we arbitrarily chose pathologic response as a criterion to assess the value of adapted Choi versus RECIST criteria. Even the threshold for pathologic response was arbitrarily chosen because of the lack of standard criteria for response evaluation in STSs. However, this should be viewed as a hypothesis-generating study. Prospective correlative analyses with the outcome as a criterion are needed. In regard to STS, when constructing new criteria, the complex architecture of some histologic types, such as synovial sarcoma, should be considered.

In conclusion, our study suggests that even in solid tumors being treated with cytotoxic chemotherapy, the criterion of tumor size alone may be insufficient. Tumor attenuation at CT or tumor contrast enhancement at MR imaging may complement tumor size as a criterion.

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