European Radiology (2019) 29:545–555
https://doi.org/10.1007/s00330-018-5635-4

ONCOLOGY

High-grade soft-tissue sarcoma: optimizing injection improves MRI evaluation of tumor response

Amandine Crombé[1,2,3] · François Le Loarer[3,4] · François Cornelis[5] · Eberhardt Stoeckle[6] · Xavier Buy[1] · Sophie Cousin[7] · Antoine Italiano[3,7] · Michèle Kind[1]

Received: 19 April 2018 / Revised: 31 May 2018 / Accepted: 27 June 2018 / Published online: 23 July 2018

Abstract

Objectives To determine the acquisition delay after gadolinium-chelate injection that optimizes the prediction of the histological response during anthracycline-based neoadjuvant chemotherapy (NAC) for locally advanced high-grade soft-tissue sarcomas (STS).

Methods Thirty patients (mean age 62 years) were included in this IRB-approved study. All patients received 5-6 cycles of NAC followed by surgery. A good response was defined as ≤ 10% viable cells on histological analysis of the surgical specimen. DCE-MRI was performed before treatment (MRI_0) and after two cycles (MRI_1). Images were obtained every 8 s. Change in contrast enhancement (CE) between MRI_0 and MRI_1 was calculated for each acquisition delay 't' on the whole tumor volume. Area under the receiver-operating characteristics curves (AUROC) for change in CE was calculated at each acquisition delay, as well as the accuracy of the Choi criteria.

Results There were 22 (73.3%) poor responders. Acquisition delay had a significant effect on change in CE and on the response status according to Choi (p = 0.0014 and 0.0270, respectively). The highest AUROC was obtained at t = 58 s (0.792) with an optimal threshold of a -30.5% decrease in CE. At t = 58 s, accuracy to predict a poor response was 82.8% above this threshold, while it was 72.4% and 70% with no objective response according to the Choi criteria and RECIST1.1, respectively.

Conclusion Optimization of acquisition delay after injection to estimate change in CE improves the prediction of histological response. For STS undergoing NAC, a 60-s delay can be recommended with MRI.

Key points

- *Accuracy of response criteria based on contrast enhancement, like the Choi criteria, is dependent on the acquisition delay after gadolinium-chelate injection.*
- *DCE-MRI helps determine the optimal acquisition delay after gadolinium-chelate injection for improving evaluation of tumor response.*
- *In soft tissue sarcoma, an acquisition delay at 60 s optimizes the evaluation of the response and accuracy of the Choi criteria.*

Keywords Response evaluation criteria in solid tumors · Sarcoma · Magnetic resonance imaging · Chemotherapy

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00330-018-5635-4) contains supplementary material, which is available to authorized users.

✉ Amandine Crombé
amandine.crombe@ens-lyon.fr

[1] Department of Diagnostic and Interventional Radiology, Institut Bergonie, Comprehensive Cancer Center, 229 cours de l'Argonne, F-33000 Bordeaux, France

[2] Modelisation in Oncology (MOnc) Team, INRIA Bordeaux-Sud-Ouest, CNRS UMR 5251 & Université de Bordeaux, F-33405 Talence, France

[3] University of Bordeaux, F-33000 Bordeaux, France

[4] Department of Pathology, Institut Bergonie, F-33000 Bordeaux, France

[5] Department of Radiology, Tenon Hospital, Sorbonne University, APHP, F-75020 Paris, France

[6] Department of Surgery, Institut Bergonie, F-33000 Bordeaux, France

[7] Department of Medical Oncology, Institut Bergonie, F-33000 Bordeaux, France

Abbreviations

ADC	Apparent diffusion coefficient
AUROC	Area under the ROC curve
CE	Contrast enhancement
$CI_{95\%}$	95% confidence interval
DWI	Diffusion-weighted imaging
EORTC	European Organization for Research and Treatment of Cancer
FNCLCC	Fédération Nationale des Centres de Lutte contre le Cancer
Good-HR	Good histological responder
GRE	Gradient-recalled echo
LD	Longest diameter
MRI	Magnetic resonance imaging
NAC	Neoadjuvant chemotherapy
NPV	Negative predictive value
OR	Odds ratio
Poor-HR	Poor histological responder
PPV	Predictive positive value
RECIST	Response evaluation criteria in solid tumors
Se	Sensitivity
SI	Signal intensity
SNR	Signal-to-noise ratio
Sp	Specificity
STS	Soft-tissue sarcoma
TSE	Turbo spin echo

Introduction

Soft tissue sarcomas (STSs) are a heterogeneous group of malignant mesenchymal tumors for which neoadjuvant chemotherapy (NAC) is becoming the new standard of care. Anthracycline-based NAC helps increase overall survival and disease-free survival of high-grade STS [1–4]. To date, histology remains the gold standard to evaluate therapeutic response on surgical specimens through the scoring of fibrosis, necrosis and viable tumor cells [5]. Indeed, histological response is an independent predictor of overall and disease-free survival [6].

Yet, there is a need for an early non-invasive assessment of response, before the end of NAC. In case of inefficient chemotherapy, alternative treatments could be proposed, for instance radiotherapy, CT-guided ^{125}I brachytherapy, isolated limb perfusion, immunotherapy or targeted therapy after molecular screening [7, 8]. Anthracycline toxicity could be avoided. In clinical trials involving STS, response evaluation mostly relies on the RECIST 1.1 criteria, which are based on the change in the longest diameter (LD) [9]. However, RECIST-based assessment can underestimate the response because good responders to treatment may demonstrate a paradoxical size increase because of tumor necrosis and because the borders to detect partial response and progressive disease may be too large at early evaluation. In addition, RECIST does not integrate the change in contrast enhancement (CE), which decreases during fibrotic and necrotic processes secondary to treatment efficacy. To address the limits of RECIST, prior studies have investigated the added value of $^{18}FDG/PET-CT$ [10], advanced MRI techniques such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) and the Choi criteria adapted to MRI [11–17]. Interestingly, taking into account the change in CE through Choi-like criteria better predicted the response to NAC and prognosis than RECIST [17, 18].

We hypothesized that there may be an optimum acquisition delay after contrast agent injection to maximize the difference in tumor enhancement between good and poor responders. We used T1-weighted DCE-MRI, which consists of rapid serial acquisition of the same volume after a standardized injection of a gadolinium-chelate bolus. By post-treating DCE-MRI, we were able to extract several regularly repeated subtracted T1-weighted imagings (-wi), before and after two cycles of NAC, to calculate change in CE at different acquisition delays. The aims of this study are to (1) determine if the acquisition delay has a significant effect on the change in CE and on the accuracy of adapted Choi criteria that include change in CE and (2) to determine the optimal acquisition delay to predict response to treatment.

Methods

Study design and patients

The institutional review board approved the retrospective single-center study, and informed consent was waived. From July 2012 to July 2017, 155 patients with a histologically proven STS and prescription for a NAC according to the regional sarcoma reference center board were identified through the database of our hospital pharmacy. Visceral sarcomas were excluded (n = 57), as well as non-anthracycline-based NAC (n = 10), ≤ 4 cycles of NAC (n = 15), no DCE-MRI acquisition at baseline (n = 41), no DCE-MRI after two cycles of NAC (n = 1) and final rejection of the curative surgery (n = 1). Finally, 30 patients were included. They all presented with newly diagnosed high-grade STS of the extremities and trunk wall, without metastasis on whole-body CT, evidence of a tumor that was measurable with MRI, available MRI with a DCE-MRI sequence performed < 28 days before the first cycle of NAC and after two cycles of NAC on the same MR system, a total of five to six cycles of NAC before curative surgery and pathological analysis of the surgical specimen.

Acquisition technique

MRIs were acquired by two senior radiologists (AC and MK) with expertise in musculoskeletal tumors. Acquisitions were made on the same 1.5-T MR imaging system (Magnetom Aera, Siemens Healthineers) with adapted coils depending on tumor location. The conventional MRI protocol included at least: T2-wi, T1-wi and T1-wi with fat suppression after gadolinium-chelate injection.

DCE-MRI acquisition The DCE-MRI sequence consisted of a 3D fast spoiled gradient echo sequence with the following acquisition parameters: TR/TE = 4.3/1.7 ms, flip angle = 25°, FoV and matrix adjusted for in-plane resolution of 1.1 × 1. 1 mm^2 and thickness = 4 mm. The volume acquisition (or phase) was repeated every 8-9 s. At least two baseline phases were acquired prior to contrast agent injection; 0.1 mM/kg of gadoteric acid (Dotarem®, Guerbet, n = 8 patients) or 0.2 ml/kg of gadobenate dimeglunine (MultiHance®, Bracco Imaging n = 22 patients) were injected intravenously at a rate of 2 ml/s followed by a 20 ml flush of 0.9% NaCl solution helped by an MR-compatible automatic injector (Sonic Shot 7, Nemoto Kyorindo Co., Ltd.) (https://imaging.bracco.com/sites/braccoimaging.com/files/technica_sheet_pdf/us-en-2018-01-26-spc-MultiHance.pdf, http://www.guerbet-us.com/fileadmin/user_upload/usa_home/products/2017_0825_Dotarem_PI_FINAL_FROM_FDA.pdf).

MRI post-processing (Fig. 1) Post-processing and MRI analysis were done by one of the two senior radiologists (AC), blinded to patients' data. The decision was made to work on the subtracted phase rather than on the raw phase since STS can demonstrate hemorrhagic alterations during NAC leading to high signal on T1-wi. The baseline MRI was called MRI_0 and the one after two cycles of NAC was called MRI_1. The phase 't = 0' was defined as the first phase where contrast agent was seen in the arteries of the acquired volume. The subtracted phases were built by subtracting each post-injection phase by the least artifacted baseline phase. They were called '(Sub n-0_i),' where 'n' is the phase at the acquisition delay 't = n' for the DCE-MRI_i. A quality control was made to verify whether phase 'n' on DCE-MRI_0 corresponded to phase 'n' on DCE-MRI_1 by a comparative visual assessment of the enhancement of surrounding tissue (arteries, veins, muscles).

Image analysis

MRIs were all post-processed with Olea Sphere (version 3.0, Olea Medical®). First, motion artifacts were corrected with a rigid-body co-registration method. The radiologist carefully and manually delineated the whole tumor volume, slice by slice, on the last phase of the DCE-MRI acquisition. Then, the segmented volume of interest was propagated on all the subtracted phases.

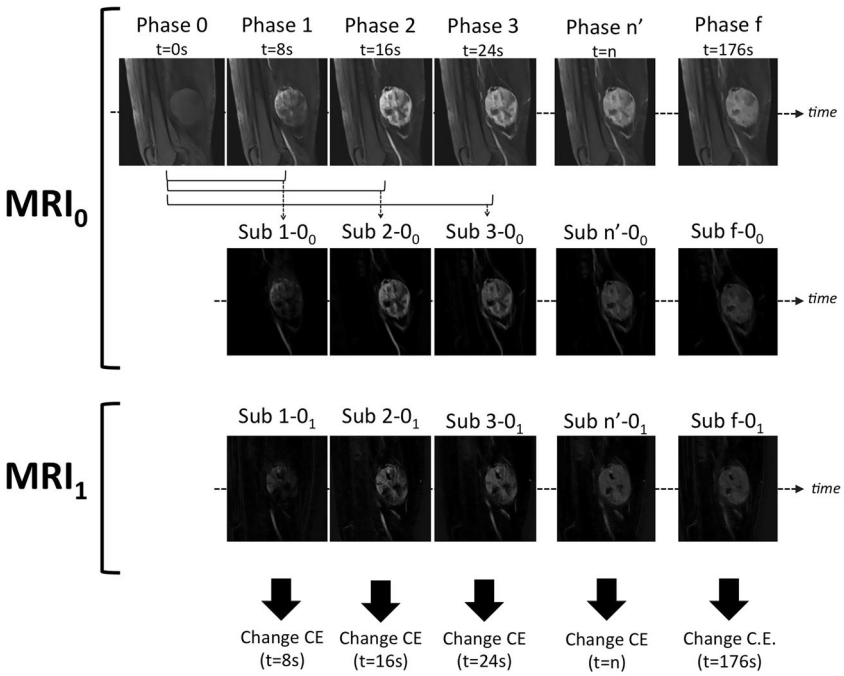

Fig. 1 Post-processing pipeline. MRI_0 corresponds to the baseline MRI and MRI_1 to the MRI performed between the second and third cycles. The first step for both MRI_0 and MRI_1 was building the subtracted phase for each acquisition delay following contrast agent injection. After verifying that the acquisition delay was similar on MRI_0 and MRI_1 by a visual quality control, the radiologist delineated the whole tumor volume, slice by slice, on the last phase on DCE-MRI sequence and propagated this volume of interest on all the subtracted phases. This post-processing enabled calculating the change in contrast enhancement at each acquisition delay of the DCE-MRI [Change in CE (t = n)], given by the formula at the bottom of the figure

Thus, the mean signal intensity (SI) of the whole tumor volume on each subtracted phase was extracted [called: 'Mean SI (Sub n-0_i)$_{Tumor\ Volume}$')], enabling the calculation of the relative change in CE at each acquisition delay, given by the formula: 'Change CE (t = n) = 100 × (Mean SI (Sub n-0_1)$_{Tumor\ Volume}$ - Mean SI (Sub n-0_0)$_{Tumor\ Volume}$)/Mean SI (Sub n-0_0)$_{Tumor\ Volume}$.'

In addition, the LD at baseline and at early evaluation was measured to estimate the relative change in LD and response status according to RECIST 1.1.

With the knowledge of change in LD and change in CE at each acquisition delay, the response status according to the Choi criteria was evaluated as a function of the acquisition delay 't' (Table 1).

Pathological analysis

All cases were reviewed by a soft tissue pathologist (FLL) at our sarcoma reference center. The histotype and histological grade were assessed on needle-core biopsy samples. Tumors were graded according to the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system, which takes into account the mitotic activity, differentiation and amount of necrosis [19]. High grade was defined as FNCLCC grade 3. Histological response assessment was performed according to European Organization for Research and Treatment of Cancer (EORTC) guidelines [5]. Viable tumor cells are defined as stainable cells as opposed to necrotic tumor cells. Patients were classified as good histological responders (Good-HR) if viable cells were ≤ 10% and poor histological responders (Poor-HR) if > 10% of the tumor surface [6].

Statistical analyses

Identification of the optimal acquisition delay to predict response was made by investigating the influence of acquisition delays on change in CE (continuous aspect) and on response status according to the Choi criteria (ordinal or categorical aspect).

Normality was assessed for each continuous value by using the Shapiro-Wilk test.

First, the Friedman test (with post-hoc Dunn test), which is the non-parametric equivalent of repeated-measures ANOVA, was used to assess if there was a significant effect of the acquisition delay on the change in CE and response status according to the Choi criteria.

For discrete variables, we estimated the accuracy of the RECIST and Choi criteria at each acquisition delay, defined as the percentage of correctly predicted patients: accuracy (%) = 100 × (Nb of true Poor-HR and true Good-HR)/(total Nb of patients). The highest accuracy of the Choi criteria was used to find the optimal acquisition delay. In this part of the study, the Choi and RECIST criteria were dichotomized as 'objective response' (complete response or partial response) versus 'non-objective response' (stable disease or progressive disease). Indeed, the aim of NAC in the setting of the study is curative and not disease control.

For continuous variables (change in LD and change in CE at different acquisition delays), receiver-operating characteristic (ROC) curves were built to quantify their diagnostic performance. After identifying the acquisition delay with the highest area under the ROC curve (AUROC), we used the Youden index J (J = sensibility + specificity -1, the point farthest from chance to minimize the rate of misclassification) to determine the optimal threshold to predict a poor response

Table 1 Definition of RECIST 1.1 and Choi response criteria

	RECIST 1.1	Choi
Complete response (CR)	♦ Disappearance of all lesions ♦ No new lesion	♦ Disappearance of all lesions ♦ No new lesion
Partial response (PR)	♦ ≥ 30% Decrease in the sum of greatest diameters ♦ No new lesion	♦ ≥ 10% Decrease in the greatest maximal diameter **OR** a ≥ 15% decrease in contrast enhancement ♦ No new lesion
Stable disease (SD)	♦ Does not meet criteria for CR, PR or PD	♦ Does not meet criteria for CR, PR or PD
Progressive disease (PD)	♦ ≥ 20% Increase in the sum of greatest diameters ♦ New lesion	♦ ≥ 10% Increase in the greatest maximal diameter **AND** does not meet criteria for partial response by using contrast enhancement; ♦ **OR** ≥ 15% increase in contrast enhancement using contrast enhancement **AND** does not meet criteria for a partial response by using tumor size; ♦ New lesion

Contrast enhancement in this study is calculated on whole tumor volume delineated on subtracted T1-weighted imaging with fat suppression and after gadolinium-chelate injection

[20]. This continuous variable was then dichotomized as a dummy variable (0: under the cutoff, 1: above).

Comparisons of continuous variables (change in LD, change in CE) between good and poor histological responders were made with the unpaired Mann-Whitney test.

Finally, we estimated the sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR) for RECIST 1.1, Choi criteria and dichotomized change in CE at the most relevant acquisition delay.

All tests were two-tailed. Statistical analyses were done using the SPSS statistical package (version 21.0, IBM) and GraphPad Prism (version 7, GraphPad Software). Variables are expressed as average, standard deviation, median and range, as appropriate. $P < 0.05$ was deemed significant.

Results

Patients (Table 2)

Thirty patients were included [18 male, median age 62, range (31–76)]. Eight were Good-HR and 22 Poor-HR on pathological analysis of the surgical specimen. The most common histotypes were undifferentiated sarcomas (15/30, 50%). Average duration of the DCE-MRI acquisition following gadolinium-chelate injection was 144 s (range 33-268). One of the patients was removed from the analyses for acquisition delay ≥ 42 s because of movement artifacts on DCE-MRI_0 after this phase. Therefore, all patients were analyzable for change in CE and response status according to the Choi criteria until an acquisition delay of 42 s and 29 patients until an acquisition delay of 100 s. None of the patients showed a complete response at early evaluation whatever the response criterion.

Influence of acquisition delay on change in CE and response status according to Choi

There was a statistically significant effect of acquisition delay on change in CE and response status according to Choi (Friedman statistics = 30.33 and 20.25, $p = 0.0014$ and 0.0270, respectively, 29 analyzed patients).

After dichotomizing the response status of the Choi criteria as 'objective response' versus 'non-objective response,' its accuracy varied depending on the acquisition delay (Fig. 2.A, Supplementary Table 1). The highest accuracy was obtained at t = 58 s (72.4%, 21 of 29 correctly predicted patients), and then it progressively decreased. Of note, RECIST 1.1 correctly classified 70% of patients in this 'objective response' setting.

The highest AUROC for change in CE was also reached at an acquisition delay of t = 58 s [AUROC (t = 58 s) = 0.792, $CI_{95\%}$ = (0.596-0.987), 29 analyzed patients]. After this delay, AUROC(t) progressively decreased (Fig 2.B, Supplementary Table 2). At t = 92 s, it was 0.645 [$CI_{95\%}$ = (0.396-0.893), 29 analyzed patients]. Of note, the AUROC of change in LD was 0.540 [$CI_{95\%}$ = (0.270-0.810), 30 analyzed patients].

When comparing 'change in LD' between Good-HR and Poor-HR, no significant difference was found (-4.6 ± 19.9% versus -4.7 ± 17.5%, respectively, Mann-Whitney test, $p = 0.8358$), whereas comparison for change in CE at t = 58 s

Table 2 Clinical and histological data of the population study

Characteristics	Patients ($n = 30$)
Age in years (median, range)	62 (31 – 76)
Gender	
Female	12 (40%)
Male	18 (60%)
Histotypes	
M/RC-LPS	1 (3.3%)
Other types of LPS	3 (10%)
Undifferentiated sarcoma	15 (50%)
Leiomyosarcoma	2 (6.7%)
Pleomorphic RMS	5 (16.7%)
Synovial sarcoma	3 (10%)
MPNST	1 (3.3%)
Longest diameter at baseline in mm (mean ± SD, range)	117.5 ± 69.6 (40 – 269)
Depth	
Superficial	0 (0%)
Deep + superficial	10 (33.3%)
Deep	20 (66.7%)
Location	
Shoulder girdle	4 (13.3%)
Pelvic girdle	1 (3.3%)
Upper limb	2 (6.7%)
Lower limb	17 (56.7%)
Trunk wall	6 (20%)
Histological response	
> 50% stainable cells	9 (30%)
11-50% stainable cells	13 (43.3%)
≤ 10% stainable cells	8 (26.7%)
Duration MRI_0 to surgery in days (median, range)	146 (111 - 196)
Duration 1st cycle to MRI_1 in days (median, range)	40 (30-57)
Duration last cycle to surgery in days (median, range)	32 (22 - 81)

M/RC-LPS Myxoid/round cell liposarcoma, *LPS* liposarcoma, *MPNST* malignant peripheral nerve sheath tumor. Undifferentiated sarcoma corresponded to myxofibrosarcoma and undifferentiated pleomorphic sarcoma. Other types of LPS corresponded to dedifferentiated LPS and pleomorphic LPS, *RMS* rhabdomyosarcoma

SD standard deviation

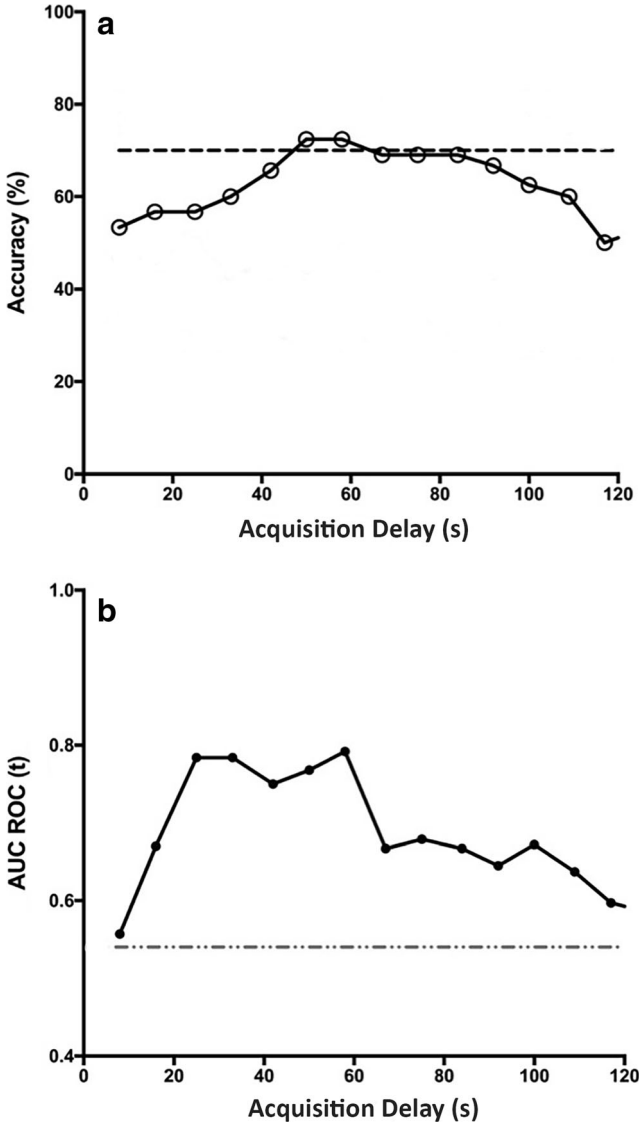

Fig. 2 Influence of acquisition delay following gadolinium-chelate injection on the accuracy of the Choi criteria (**a**) and on the AUROC of change in contrast enhancement (**b**). For calculation of accuracy (i.e., percentage of correctly classified patients), a favorable radiological response was considered as a partial response of a complete response (objective response setting). Dotted lines correspond to the accuracy of the RECIST criteria in (**a**) and to the AUROC of change in LD in (**b**)

provided a significant difference between these two groups (18.9 ± 61.6% versus -32.8 ± 58.0%, respectively, Mann-Whitney test, $p = 0.0358$) (Fig. 3).

Determination of the optimal threshold of 'change in CE' for an acquisition delay of 58 s and corresponding diagnostic performances of response criteria

The best Youden index was obtained for a cutoff of -30.5% (J = 0.607), which was a decrease of -30.5% of CE on subtracted phases.

Twenty of 29 patients did not have a decrease in CE below -30.5% and 18 of these 20 patients (90%) were indeed Poor-HR. Conversely, nine patients were below the cutoff, and six of these nine patients (66.7%) were indeed Good-HR (Table 3).

Choi (t = 58 s) provided 10/29 (34.4%) partial responses, 9/29 (31%) stable disease and 10/29 (34.5%) progressive disease. Five of the eight Good-HR (62.5%) were classified as partial response, one of eight (12.5%) as stable disease and two of eight (25%) as progressive disease.

RECIST 1.1. provided 3/30 (10%) partial responses, 25/30 (83.3%) stable disease and 2/30 (6.7%) progressive disease (Table 3). Among the three patients with partial response, only one was a Good-HR. Most patients with a pathological response were classified as having stable disease according to RECIST1.1 (six of the eight Good-HR), and one of the two patients with progressive disease was, in fact, a Good-HR.

The positive predictive value to predict Poor-HR was 0.74 for RECIST1.1, 0.84 with Choi and 0.90 with a cutoff of a -30.5% decrease in CE (Table 4). Change in CE > -30.5% at t = 58 s was significantly associated with a poor histological response [OR = 18, $CI_{95\%}$ = (2.13-103.6)], whereas a 'non-objective response' according to RECIST and Choi were not [OR = 1.43 with $CI_{95\%}$ = (0.08-13.63) and OR = 5.33 with $CI_{95\%}$ = (0.79-24.36), respectively].

Figure 4 shows an example of added value of incorporation of change in tumor enhancement to predict response to treatment.

Discussion

In this study, joint analyses of the change in CE and accuracy of the Choi criteria as functions of acquisition were used to identify the acquisition delay following gadolinium-chelate injection, which optimizes the early prediction of response to treatment. Our results suggest an acquisition delay of about 60 s, for which we found that change in CE was significantly associated with response, whereas RECIST 1.1 was not, and that a threshold of a -30.5% decrease in CE could be useful to predict early response.

Our results are in agreement with previous publications that investigated change in STS enhancement during chemotherapy through the Choi criteria and demonstrated better prediction of response and prognosis than with the RECIST 1.1 criteria [17, 18, 21]. It should be noted that the Choi criteria adapted to MRI in the studies by Stacchiotti et al were assessed on the whole tumor volume and turbo spin echo T1-WI (T1-TSE) after gadolinium-chelate injection, reflecting a global enhancement during 2 min 30 s-3 min 30 s. We built our subtracted T1-wi sequences from a fat-suppressed T1-weighted gradient-recalled echo sequence (T1-GRE) instead of conventional T1-TSE because T1-GRE enables rapid serial

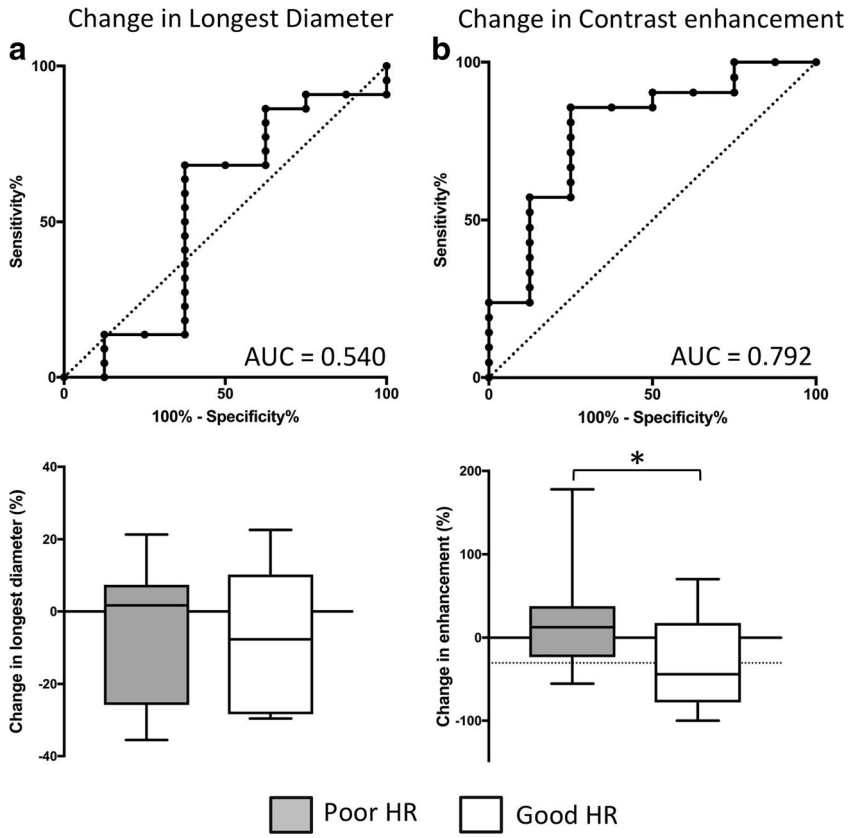

Fig. 3 Diagnostic performance of change in the longest diameter (**a**) and change in CE at 58 s (**b**). For each of these two continuous variables, an AUROC and boxplot were drawn to compare Good-HR (in white) and Poor-HR (in gray)

acquisitions. However, the counterparts of T1-GRE imaging are slightly larger in-plane resolution and a slightly lower signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR) and enhancement ratio at 1.5 T [22, 23]. Thus, our sequence may have decreased performance to capture tissue enhancement, leading to underestimation of the change in CE and the accuracy of the Choi criteria.

The pathological processes during cytotoxic anthracycline-based chemotherapy can explain the variation of change in CE. On time-intensity curves derived from DCE-MRI, the

Table 3 Comparison of radiological assessment and histological response for RECIST 1.1, for the Choi criteria at the optimized acquisition delay (t = 58 s post-injection) and for change in contrast enhancement alone at the optimized acquisition delay (t = 58 s) considering the best cutoff (-30.5% decrease) after ROC curve analysis

Response criteria	Radiological assessment	Good histological response
RECIST 1.1		
CR	0/30 (0%)	0/0 (-)
PR	3/30 (10%)	1/3 (33.3%)
SD	25/30 (83.3%)	6/25 (24%)
PD	2/30 (6.7%)	1/2 (50%)
Choi (t = 58 s)		
CR	0/29 (0%)	0/0 (-)
PR	10/29 (34.5%)	5/10 (50%)
SD	9/29 (31%)	1/9 (11.1%)
PD	10/29 (34.5%)	2/10 (20%)
Change in contrast enhancement at t = 58 s		
Decrease > 30.5%	9/29 (31%)	6/9 (66.7%)
Decrease < 30.5%	20/29 (69%)	2/20 (10%)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Data are given as number of patients and corresponding percentage in coda

Table 4 Diagnostic performances of response criteria to predict a poor histological response. Choi response criteria and change in contrast enhancement are evaluated for an acquisition delay of t = 58 s

	Se	Sp	PPV	NPV	Accuracy	OR
No objective response according to RECIST	0.91 (0.09-0.93)	0.13 (0.01-0.47)	0.74 (0.55-0.87)	0.33 (0.02-0.88)	70%	1.43 (0.08-13.63) $p > 0.9999$
No objective response according to Choi	0.76 (0.55-0.89)	0.63 (0.31-0.86)	0.84 (0.62-0.95)	0.5 (0.24-0.76)	72.4%	5.33 (0.79-24.36) $p = 0.0834$
Change in contrast enhancement ≥ -30.5%	0.86 (0.65-0.95)	0.75 (0.41-0.96)	0.90 (0.70-0.98)	0.67 (0.35-0.88)	82.8%	18 (2.13-103.6) $p = 0.0039$**

Se sensitivity, *Sp* specificity, *PPV* predictive positive value, *NPV* negative predictive value, *OR* odds ratio

Accuracy is defined as the percentage of correctly predicted patients among all patients

Se, Sp, PPV, NPV are given with 95% confidence interval.

ORs are given with 95% confidence interval and *p* value. **$p < 0.005$

viable tumor compartment usually demonstrates an early arterial enhancement after injection followed by a plateau and/or wash-out—a continuous decrease of signal intensity due to relapse of contrast agent from the tumor to circulation [12–15]. Conversely, necrosis does not display any enhancement. Granulation tissue exhibits a continuous and moderate

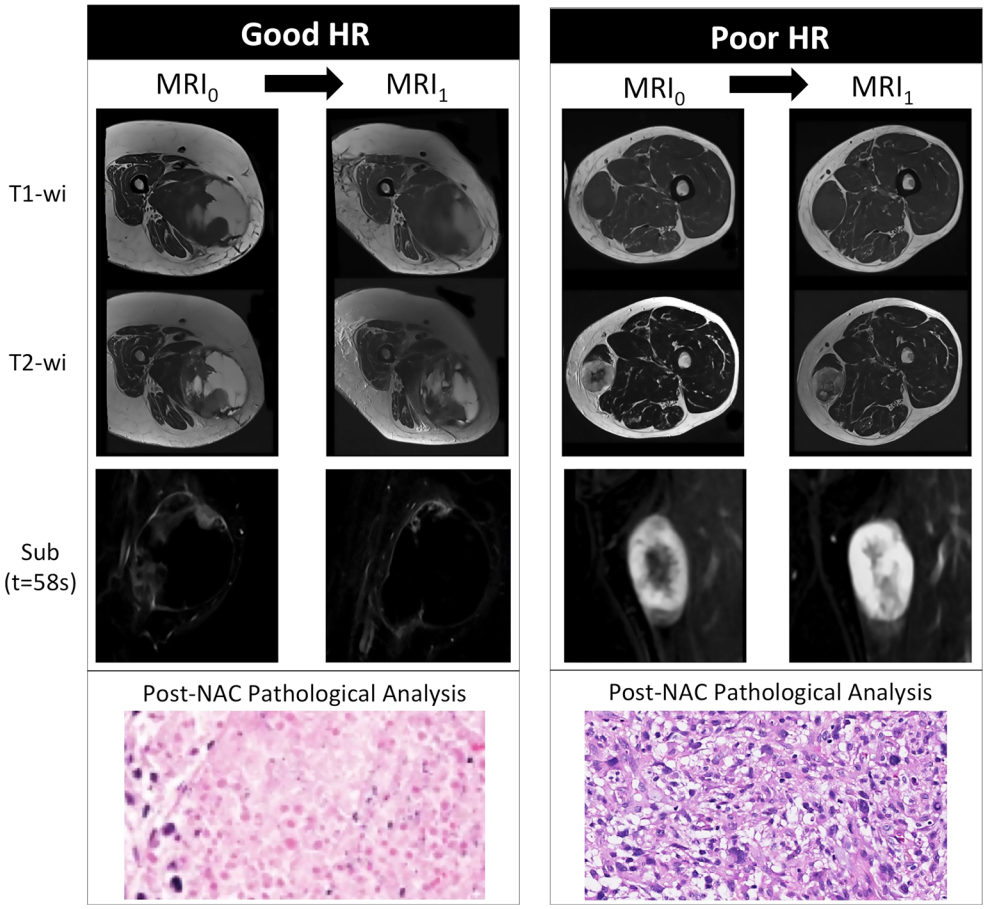

Fig. 4 Examples. Good-HR: Female patient presented with a deep non-metastatic grade III undifferentiated pleomorphic sarcoma of the thigh. After two cycles of NAC, change in LD was + 23% (due to necrotic inflation), while change in CE was - 52.6% at 58 s. The case was classified as progressive disease according to RECIST 1.1, as stable disease according to the Choi and as good response using a cutoff of a decrease of - 30.5% in CE. Pathological analysis of the surgical specimen revealed a Good-HR with 10% stainable cells, 85% necrosis and 5% fibrosis. Poor-HR: Male patient presented with a deep non-metastatic grade III undifferentiated pleomorphic sarcoma of the thigh. After two cycles of NAC, change in LD was 0% and change in CE was + 20.5%. Thus, the patient was diagnosed with stable disease according to RECIST1.1, with progressive disease according to Choi and with a poor response using a cutoff of a decrease of -30.5% in CE. Pathological analysis of the surgical specimen revealed a poor response (poor-HR) with 85% stainable cells

enhancement. Tissue becoming necrotic or fibrotic can show intermediate enhancement patterns. We have two hypotheses to explain why a 60-s delay appears to be a good compromise. First, this acquisition delay is not excessively early and avoids the risk of overestimating the ratio in case of a slight decay of the phases between two evaluations. Second, it is not a late acquisition and avoids confusion between continuous enhancement of granulation tissue and late wash-out of residual tumor. It should be noted that we calculated the acquisition delay from the moment when the contrast agent was viewable in the acquisition volume. Therefore, the true optimal acquisition delay corresponds to 60 s plus the delay necessary for the contrast agent to reach the acquisition volume, which depends on the tumor location. This is why one could simplify the acquisition delay to a classical portal phase.

Our approach strictly focused on tumor enhancement but further studies should integrate quantitative markers from other MRI sequences to build composite response criteria tailored to STS. Indeed, other potential imaging biomarkers have been recently highlighted in the field of soft-tissue tumors. For instance, adding a shape feature such as roundness to size and age could improve the discrimination between benign and malignant soft-tissue masses [24]. Joint analyses of ^{18}FDG/PET-CT and DWI could help to distinguish low- from high-grade STS through the value of the correlation coefficients of standardized uptake values and apparent diffusion coefficient (ADC) [25]. Regarding the prediction of tumor response, the tumor percentage with low ADC values has been shown to correlate with the response and change in tumor volume [11, 15]. Qualitative, semiquantitative and quantitative evaluations of DCE-MRI may also provide clues to predict histological response [12–16]. Nonetheless, the predictive value of relative change in these potential biomarkers from baseline to early evaluation, textural and shape analysis of conventional and functional MRI sequences and multivariate analysis with classical and machine-learning classifiers remain to be investigated.

Our study has limitations. First, this is a retrospective single-center study. However, all the MRIs were performed with the same sequence on the exact same MR system with the same coils for each patient at each MRI evaluation on uniformly treated patients. Hence, there is no possible technical bias, except the use of two different contrast agents, gadoteric acid or gadobenate dimeglunine with potentially slight differences in tissue enhancement because gadobenate dimeglunine demonstrated transient interactions with serum proteins [26]. In addition, it should be noted that, since the end of this study in July 2017, the European Medicines Agency has restricted the use of gadobenate dimeglunine (MultiHance®) to liver scans because of the risk of gadolinium deposition (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_contrast_agents_31/European_Commission_final_decision/WC500240575.pdf).

Second, volumetric segmentation was manually performed by a single radiologist. However, we limited the subjectivity of this step by clear definitions of the rules to perform segmentation. It was done on the last phase of the DCE-MRI sequence on which the tumor shows the maximum enhancement with the help of T2-wi sequences.

Third, all patients did not have the same numbers of acquired phases during DCE-MRI. One patient was removed from the analysis after t = 42 s because of a motion artifact on one of the baseline DCE-MRIs. After quality control, 29 of 30 patients had acquisitions until 100 s, and the numbers of patients at each later acquisition delay progressively decreased.

Fourth, we decided not to remove the three synovial sarcomas from our study although they were separately analyzed by Stachiotti et al [16]. Their justification was the bias induced by the cystic component of this histotype. In our case, none of these three tumors had extensive cystic changes. In our opinion, it would be a strength of the response criteria to continue to be informative despite the occurrence of complex architectural alterations such as hemorrhage, cystic change, infarction and necrosis.

Fifth, our population of 30 patients might seem small, but this size was not exceeded by any of the other neoadjuvant studies that evaluated MRI biomarkers to predict STS response [11–17].

Finally, the outcome of the study can be questioned. The percentage of viable cells on surgical specimens does not take into account the amount of necrosis at baseline, which could not be correctly estimated on small biopsy samples. Nonetheless, we applied EORTC recommendations for pathological examination following NAC [5]. We used a cutoff of 10% viable cells, which has been identified as an independent predictor of overall and metastasis-free survivals [6]. Beyond the association with the histological response, future studies should investigate the prognostic value of early change in CE during NAC.

In conclusion, the key point of this study is that choosing an appropriate acquisition delay following gadolinium-chelate injection can optimize early prediction of the STS response during NAC. We identified a delay of about 60 s. The next step is to incorporate these results in prospective multicenter decision-making studies that include other MRI modalities such as DWI and DCE-MRI.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Xavier Buy (interventional radiologist, head of the Department of Radiology of Institut Bergonié, comprehensive cancer center of Bordeaux, France, x.buy@bordeaux.unicancer.fr).

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical method was necessary for this paper. Statistical analysis was performed by A. Crombe, a PhD student in applied mathematics at the Institut de Mathématiques de Bordeaux (MOnc Team, INRIA Bordeaux Sud-Ouest CNRS UMR 5251).

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

References

1. Issels RD, Lindner LH, Verweij J et al (2010) Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. Lancet Oncol 11:561–570. https://doi.org/10.1016/S1470-2045(10)70071-1
2. Saponara M, Stacchiotti S, Casali PG, Gronchi A (2017) (Neo)adjuvant treatment in localised soft tissue sarcoma: The unsolved affair. Eur J Cancer 70:1–11. https://doi.org/10.1016/j.ejca.2016.09.030
3. Pasquali S, Gronchi A (2017) Neoadjuvant chemotherapy in soft tissue sarcomas: latest evidence and clinical implications. Ther Adv Med Oncol 9:415–429
4. Gronchi A, Ferrari S, Quagliuolo V et al (2017) Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol 18:812–822. https://doi.org/10.1016/S1470-2045(17)30334-0
5. Wardelmann E, Haas RL, Bovée JV et al (2016) Evaluation of response after neoadjuvant treatment in soft tissue sarcomas; the European Organization for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC–STBSG) recommendations for pathological examination and reporting. Eur J Cancer 53:84–95. https://doi.org/10.1016/j.ejca.2015.09.021
6. Cousin S, Crombé A, Italiano A et al (2017) Clinical, radiological and genetic features associated with the histopathologic response to neoadjuvant chemotherapy (NAC) and outcomes in locally advanced soft tissue sarcoma (STS) patients. J Clin Oncol 35(15_suppl):11014
7. Mo Z, Zhang T, Zhang F et al (2018) Feasibility and clinical value of CT-guided 125I brachytherapy for metastatic soft tissue sarcoma after first-line chemotherapy failure. Eur Radiol 28:1194–1203. https://doi.org/10.1007/s00330-017-5036-0
8. Pollack SM, Ingham M, Spraker MB, Schwartz GK (2018) Emerging targeted and immune-based therapies in sarcoma. J Clin Oncol 36:125–135. https://doi.org/10.1200/JCO.2017.75.1610
9. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247. https://doi.org/10.1016/j.ejca.2008.10.026
10. Benz MR, Czernin J, Eilber FC et al (2009) FDG-PET/CT imaging predicts histopathologic treatment responses after the initial cycle of neoadjuvant chemotherapy in high-grade soft-tissue sarcomas. Clin Cancer Res 15:2856–2863. https://doi.org/10.1158/1078-0432.CCR-08-2537
11. Dudeck O, Zeile M, Hamm B et al (2008) Diffusion-weighted magnetic resonance imaging allows monitoring of anticancer treatment effects in patients with soft-tissue sarcomas. J Magn Reson Imaging 27:1109–1113. https://doi.org/10.1002/jmri.21358
12. van Rijswijk CS, Geirnaerdt MJ, Hogendoorn PC et al (2003) Dynamic contrast-enhanced MR imaging in monitoring response to isolated limb perfusion in high-grade soft tissue sarcoma: initial results. Eur Radiol 13:1849–1858. https://doi.org/10.1007/s00330-002-1785-4
13. Meyer JM, Perlewitz KS, Ryan CW et al (2013) Phase I trial of preoperative chemoradiation plus sorafenib for high-risk extremity soft tissue sarcomas with dynamic contrast-enhanced MRI correlates. Clin Cancer Res 19:6902–6911. https://doi.org/10.1158/1078-0432.CCR-13-1594
14. Huang W, Beckett BR, Ryan CW et al (2016) Evaluation of soft tissue sarcoma response to preoperative chemoradiotherapy using dynamic contrast-enhanced magnetic resonance imaging. Tomography 2:308–316
15. Soldatos T, Ahlawat S, Montgomery E, Chalian M, Jacobs MA, Fayad LM (2015) Multiparametric assessment of treatment response in high-grade soft-tissue sarcomas with anatomic and functional MR imaging sequences. Radiology 278:831–840
16. Xia W, Yan Z, Gao X (2017) Volume fractions of DCE-MRI parameter as early predictor of histologic response in soft tissue sarcoma: A feasibility study. Eur J Radiol 95:228–235. https://doi.org/10.1016/j.ejrad.2017.08.021
17. Stacchiotti S, Collini P, Messina A et al (2009) 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. Radiology 251:447–456
18. Stacchiotti S, Verderio P, Messina A et al (2012) Tumor response assessment by modified Choi criteria in localized high-risk soft tissue sarcoma treated with chemotherapy. Cancer 118:5857–5866. https://doi.org/10.1002/cncr.27624
19. Trojani M, Contesso G, Coindre JM et al (1984) Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer 33:37–42
20. Perkins NJ, Schisterman EF (2006) The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am J Epidemiol 163:670–675. https://doi.org/10.1093/aje/kwj063
21. Taieb S, Saada-Bouzid E, Tresch E et al (1990) (2015) Comparison of response evaluation criteria in solid tumours and Choi criteria for response evaluation in patients with advanced soft tissue sarcoma treated with trabectedin: a retrospective analysis. Eur J Cancer 51:202–209. https://doi.org/10.1016/j.ejca.2014.11.008
22. Hargreaves BA (2012) Rapid gradient-echo imaging. J Magn Reson Imaging 36:1300–1313. https://doi.org/10.1002/jmri.23742
23. Zur Y, Wood ML, Neuringer LJ (1991) Spoiling of transverse magnetization in steady-state sequences. Magn Reson Med 21:251–263
24. Gruber L, Loizides A, Ostermann L, Glodny B, Plaikner M, Gruber H (2016) Does size reliably predict malignancy in soft tissue tumours? Eur Radiol 26:4640–4648

25. Sagiyama K, Watanabe Y, Honda H et al (2017) Multiparametric voxel-based analyses of standardized uptake values and apparent diffusion coefficients of soft-tissue tumours with a positron emission tomography/magnetic resonance system: Preliminary results. Eur Radiol 27:5024–5033. https://doi.org/10.1007/s00330-017-4912-y

26. Liang J, Sammet S, Yang X, Jia G, Takayama Y, Knopp MV (2010) Intraindividual in vivo comparison of gadolinium contrast agents for pharmacokinetic analysis using dynamic contrast enhanced magnetic resonance imaging. Invest Radiol 45:233–244