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Transarterial chemoembolization in soft-tissue sarcoma metastases to the liver – The use of imaging biomarkers as predictors of patient survival

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Abstract

Background—The clinical management of patients with metastatic soft-tissue sarcoma of the liver is complicated by the paucity of reliable clinical data. This study evaluated the safety profile, survival outcome as well as the role of imaging biomarkers of tumor response in metastatic soft-tissue sarcoma (mSTS) of the liver treated with conventional transarterial chemoembolization (cTACE).

Materials/methods—This retrospective analysis included 30 patients with mSTS of the liver treated with cTACE. The safety profile, overall survival (OS) and progression-free survival (PFS) after the procedure were evaluated. Tumor response in each patient was assessed using RECIST, modified (m) RECIST and EASL guidelines. In addition, a 3D quantification of the enhancing tumor volume (quantitative [q] EASL) was performed. For each method, patients were classified as responders (R) and non-responders (NR), and evaluated using Kaplan-Meier and multivariate Cox proportional hazard ratio (HR) analysis.

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Conflict of Interest

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work:

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Results—No Grade III or IV toxicities were reported in a total of 77 procedures (mean, 2.6/patient). Median OS was 21.2 months (95% CI, 13.4–28.9) and PFS was 6.3 months (95% CI, 4.4–8.2). The enhancement-based techniques identified 11 (44%), 12 (48%) and 12 (48%) patients as R according to EASL, mRECIST and qEASL, respectively. No stratification was achieved with RECIST. Multivariate analysis identified tumor response according to mRECIST and qEASL as reliable predictors of improved patient survival ($P = 0.019$; HR 0.3 [0.1–0.8] and $P = 0.006$; HR 0.2 [0.1–0.6], respectively).

Conclusion—This study confirmed the role of cTACE as a safe salvage therapy option in patients with mSTS of the liver. The demonstrated advantages of enhancement-based tumor response assessment techniques over size-based criteria validate mRECIST and qEASL as preferable methods after intraarterial therapy.

Keywords

Liver cancer; Sarcoma; Transarterial chemoembolization; Volumetry; MRI; RECIST; mRECIST; EASL

1. Introduction

Soft-tissue sarcomas (STS) represent about 1% of all diagnosed adult malignancies in the United States [1,2]. With fewer than 12.000 new cases every year, the clinical management of STS is complicated by their relative rarity, histopathological heterogeneity and the paucity of clinical data with high levels of evidence [3]. Surgical resection as the mainstay for treatment of STS was reported to provide some survival benefits. However, not all patients are eligible for resection and more than 50% of these patients will eventually die from subsequent metastases to the liver and lungs [4,5]. Metastases to the liver occur in up to 60% of patients and represent a pattern of recurrence primarily in tumors of visceral and retroperitoneal origin [2,6]. Once metastasized, the prognosis becomes dismal with reported overall survival rates of no more than 15 months [2]. For most patients with liver metastases, systemic chemotherapy continues to be the first-line treatment; however, response rates are extremely low (10–25%) and survival benefits are minimal primarily because of the pronounced chemoresistance of most histological sarcoma types [7–9]. The marked ability of sarcoma cells to limit intracellular accumulation of most systemically applicable anti-neoplastic agents by active drug extrusion requires higher doses in order to achieve tumor response, which in return tips the balance between efficacy and toxicity towards the latter. This circumstance provides the opportunity for intraarterial therapies, such as transarterial chemoembolization (TACE), to fill the gap by delivering high doses of cytotoxic agents to the tumor while reducing systemic toxicity [10].

Because of the relative rarity of STS, only very few studies with small cohorts of patients are available to confirm the role of TACE as a reliable salvage option for this aggressive disease [10–12]. A particular lack of clinical data exists with regard to the post-procedural assessment of local tumor response on cross-sectional imaging. Most STS metastases to the liver present as large hypervascular lesions on arterial phase MRI. However, the assessment of these lesions is technically challenging as most patients present after several lines of systemic chemotherapy with tumors that typically demonstrate central necrosis as well as

rim and segmental enhancement with scattered foci of remaining viable tumor tissue [13]. In addition, most intraarterial therapies involve the element of embolization of the tumor-feeding arteries, thus causing tissue necrosis without immediate effects on the overall lesions size. These characteristics constitute a significant obstacle for conventional assessment techniques, such as the anatomic Response Evaluation Criteria in Solid Tumors (RECIST), to quantify tumor response and to properly identify non-responders which have been meanwhile identified as a challenge not only for local, but also for new systemic chemotherapies [14].

This study evaluated the safety profile, survival outcome as well as the role of imaging biomarkers of tumor response in soft-tissue sarcoma (STS) metastases to the liver treated with conventional transarterial chemoembolization (cTACE).

2. Materials and methods

2.1. Patients

This single-institution study was conducted in compliance with the Health Insurance Portability and Accountability Act and approved by the Institutional Review Board, which waived the need for informed consent in this retrospective analysis. Between December 2000 and December 2013, a total of 32 patients with liver-only or liver-dominant STS metastases underwent their first session of conventional TACE within our institution. Patients with secondary ongoing malignancies ($N = 2$) were excluded. The remaining 30 patients were included into the outcome analysis. An additional five patients lacked contrast-enhanced baseline imaging and were excluded from the tumor response analysis. A total of 25 patients (83%) had received contrast-enhanced CT (N = 5, on baseline only) or MR imaging ($N = 20$ on baseline, $N = 25$ on follow-up) within 6 weeks before and after the initial TACE session and were included into the imaging analysis. Table 1 summarizes the baseline characteristics of the selected patient cohort. Median patient age was 54.9 years (range, 18.9–70.6) and the majority of patients were female (63%). Median lesion size was 6.4 cm (mean, 6.9 cm; range, 1.2–16.9 cm). Periprocedural adverse events were recorded and reported for all treatment sessions in each patient according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03.

2.2. Intraarterial therapy, CT and MR imaging technique

All procedures were performed by one experienced interventional radiologist (XX with 16 years of experience in hepatic interventions). A consistent approach according to our standard institutional cTACE and Yttrium90-radioembolization protocols was used. A total of 5 patients received native and contrast-enhanced multi-detector CT on baseline using a multi-slice CT scanner (Sensation 64; Siemens Medical Solutions, Erlangen, Germany). The remaining scans were acquired using a standardized MRI protocol before and after the initial cTACE. MRI was performed on a 1.5 Tesla scanner (Siemens Magnetom Avanto, Erlangen, Germany). The details of the procedure protocols and image acquisition techniques can be found within the appendix.

2.3. Imaging data evaluation

Tumor assessment was performed by two independent readers (a radiologist with 9 years of experience in abdominal imaging and a radiology resident with 2 years of experience). Any ambiguity was resolved by consensus. A target lesion was defined as the largest, dominant lesion treated during the first session of cTACE. A single targeted lesion per patient was selected for analysis. The analysis of multiple target lesions was omitted as other studies did not confirm the benefit of this methodology [15].

The selected target lesions were assessed using RECIST, modified (m) RECIST as well as using the European Association for the Study of the Liver (EASL) guidelines [16]. All measurements made by the two readers were averaged for the survival analysis. Additionally to the conventional non-3D techniques, 3D quantitative image analysis was performed by a radiological reader (AA) with 1 year of experience with the software prototype used in the study (Medisys, Philips Research, Suresnes, France) [17]. The accuracy and reader-independent reproducibility of the semiautomatic tumor segmentation as well as the radiological–pathological correlation of the method have been previously reported [18–21]. The software employed semi-automated 3D tumor segmentation on the arterial phase contrast-enhanced CT or MRI acquired before and after the initial session of cTACE. The overall tumor volume was directly calculated based on this segmentation (Fig. 1, volumetric [v] RECIST). The quantitative [q] EASL calculation of the enhancing volume was based on image subtraction (between arterial-phase and native CT and T1-weighted MR imaging) [17,22]. In brief, the 3D segmentation mask was transferred onto the subtraction image and a region of interest (ROI) was placed into extra-tumoral liver parenchyma as a reference in order to calculate the relative enhancement values within the tumor (Fig. 1, qEASL). The patient-specific, average signal intensity within the ROI was then defined as a threshold in order to estimate enhancement within the 3D mask. Subsequently, enhancing regions were expressed as a percentage of the previously calculated overall tumor volume and visualized using a color map overlay on the arterial-phase CT and MRI scans (Fig. 1, qEASL). The workflow efficiency of the system has been previously reported and the time needed to assess a single patient in the current study did not exceed 120 s (range, 48–120 s) [17]. Additional methodological specifications can be found in the appendix.

Based on the degree of tumor response, patients were classified as responders (R) or non-responders (NR). As for the subgroups, patients with complete response (CR) and partial response (PR) were considered R, while patients with stable disease (SD) and progressive disease (PD) were considered NR (Table 2). The cutoff values for both volumetric techniques (vRECIST and qEASL) were adjusted according to the thresholds used for the corresponding uni-dimensional parameters (RECIST and mRECIST) [16], while taking into account the equation for the calculation of spheroid volumes:

$$Volume = \frac{4}{3}\pi r^3$$

Accordingly, a reduction of the overall/enhancing lesion diameter by 30% resulted in a concordant reduction of the volume by 65%, which was then interpreted as tumor response

(PR). By implication, an increase of the overall/enhancing lesion diameter by 20% would be translated into a volumetric increase by 73% and was interpreted as progressive disease (PD) [16].

2.4. Statistical analysis

Overall survival was defined from the date of the first IAT session until death, last available follow-up or the end-of-observation date (December 30th, 2013). Patients lost in follow-up, alive at the end-of-observation date (October 30th, 2013) or treated surgically were censored ($N = 5$). Progression-free survival (PFS) was defined as the time from the first TACE to either any progression of the disease on cross-sectional imaging or death from any cause. Time to intrahepatic progression (TTIP) was defined as the time from the first TACE to progression of the intrahepatic disease. Median OS, PFS as well as TTIP were calculated for all included patients ($N = 30$). In addition to that, Kaplan-Meier analysis in patients who received cross-sectional imaging ($N = 25$) was performed for each tumor response assessment method, stratifying the patient collective in R and NR. The differences (R vs. NR) were assessed using the log-rank test. A P-Value ≤ 0.05 was considered to indicate statistically significant differences. The median OS and the 95% confidence interval (CI) for R and NR were calculated for every method. The predictive value of each radiological technique was assessed using Cox proportional hazard ratios (HR). This was followed by a univariate and multivariate analysis. First, a univariate Cox regression model was used to evaluate the association of overall survival with clinical factors assessed on baseline: gender, age, Eastern Cooperative Oncology Group (ECOG) performance score, status post (s/p) surgical resection of the primary tumor, s/p surgical resection of liver tumors, radiation of the primary tumor, number of lines of chemotherapy, tumor burden, presence of extrahepatic disease, synchronous diagnosis of primary tumor and liver metastases as well as the time between diagnosis and intraarterial therapy of liver metastases. In the second step, adjusted hazard ratios for all radiological measurements were estimated from the Cox regression model which simultaneously included the respective radiological method as well as clinical factors that were found to be significantly predictive of overall patient survival ($P < 0.05$) [23]. The agreement of manual measurements between the radiological readers was assessed using a linear regression analysis in order to investigate the correlation of results. Pearson's correlation coefficient (R^2) was calculated. All statistical computations were performed using the commercial statistical software GraphPad Prism (Version 6, San Diego, California, USA) and SPSS (IBM, Version 22.0, Armonk, NY, USA).

3. Results

3.1. Therapy, toxicity and survival outcome

Table 3 gives an overview of the treatment history and provides information on the frequency of the procedures. All patients received cTACE as the initial therapy and 2 patients crossed over therapy to receive Yttrium90 radioembolization. The majority of patients had undergone surgery of the primary tumor (77%, histopathologically tumor-free margins in 10 patients), as well as 3 or more lines of systemic chemotherapy (80%), with a maximum of 15 cycles in one patient. A total of 21 patients (70%) received radiation treatment of the primary lesions before cTACE. A total of 77 cTACE sessions (100%) were

technically successful. As for peri-procedurally recorded adverse events, right upper quadrant pain was the single most frequently reported adverse event, which occurred in a total of 11 cases (14%). Overall, occurrence of adverse events in the analyzed patient cohort was relatively low (45%) and no Grade III and IV adverse events were reported. However, one patient demonstrated post-procedural infarction and subsequent necrosis of the tumor-bearing liver segment 6, which did not require any additional interventions. As for the 30-day mortality, one such event was recorded in a patient with significant extra-hepatic tumor burden (extensive metastases to the brain and lungs), but the cause of death was not related to the cTACE procedure (pleural effusion with subsequent multi-organ failure). Table 4 summarizes the reported adverse events. Median OS of the entire population was 21.2 months (95% CI, 13.4–28.9 months) (Fig. 2A). The progression-free survival of the entire cohort was 6.3 months (95% CI, 4.4–8.2 months). A total of 13 patients (43%) demonstrated intra-hepatic progression of the disease and the TTIP was 7.0 months (95% CI, 3.9–10.0 months). As for the univariate analysis of prognostically relevant parameters in this patient cohort, radiation therapy of the primary malignancy was the only statistically significant factor to improve survival outcome (HR 0.2 [95% CI, 0.1–2.3]; $P = 0.007$). Patients who underwent radiation of the primary malignancy ($N = 21$) showed a significantly higher median OS (21.4 months [95% CI, 15.5–27.3]) as compared to those who did not receive such treatment ($N = 9$; median OS, 9.6 months [95% CI, 8.2–10.9], Fig. 2B). In addition, a trend towards improved prognosis was observed for patients who underwent surgical resection of the metastatic liver disease prior to TACE (HR, 0.3 [0.1–1.2], $P = 0.081$) as well as in those who underwent surgical resection of the primary tumor (HR, 0.2, [0.1–2.0], $P = 0.185$). However, both parameters did not achieve statistical significance.

3.2. MR imaging analysis

A total of 25 dominant targeted lesions were assessed using all five image analysis methods (RECIST, vRECIST, EASL, mRECIST, and qEASL). The agreement between the radiological readers was good for RECIST ($R^2 = 0.94$) as well as for the mRECIST ($R^2 = 0.81$). Relatively low values were achieved for EASL measurements ($R^2 = 0.69$). When using RECIST measurements, 1 patient (4%) had PR, 20 patients (80%) showed SD and 3 patients (16%) demonstrated PD. When using vRECIST, 2 patients (8%) had PR while 16 patients (64%) had SD and 7 patients (28%) PD. Because of the poor stratification in both anatomic techniques, no comparative survival analysis between R and NR was performed for RECIST and vRECIST. When stratifying according to the enhancement-based EASL guideline, 2 patients (8%) showed CR and 9 patients (36%) had PR while 7 patients (28%) demonstrated SD and 7 patients (28%) had PD. The mRECIST measurements identified 2 patients (8%) as CR and 10 patients (40%) as PR while 10 patients (40%) had SD and 3 patients (12%) showed PD. According to qEASL, no patient was identified as CR and 12 patients (48%) were identified as PR while 4 patients (16%) were identified to have SD and 9 patients (36%) had PD. The results from the uni- and multivariate analysis are presented in Table 5. In summary, assessing tumor response of STS metastases using anatomic response criteria did not allow a meaningful stratification between R and NR. All enhancement based techniques showed a clear stratification between R and NR. However, qEASL was the only technique to demonstrate a statistically significant separation between R and NR using the univariate analysis (HR, 0.4 [95% CI, 0.1–1.1); $P = 0.026$). When using the multivariate

analysis, both mRECIST and qEASL provided a statistically significant separation between R and NR ($P = 0.019$ and $P = 0.006$, respectively) while demonstrating marked survival benefits in those patients who did respond to therapy (Fig. 3A–C).

4. Discussion

The main finding of this study identified enhancement-based imaging biomarkers (mRECIST and qEASL) as reliable and advantageous early predictors of patient survival after cTACE in patients with STS metastases to the liver. While achieving a high response rate of up to 48%, the use of cTACE for salvage therapy has demonstrated an adequate level of periprocedural safety in a cohort of patients with significant comorbidities.

The ultimate purpose for imaging biomarkers of tumor response to therapy is the early identification of non-responders [24]. This principle is all the more important in patients with a short life expectancy that undergo cTACE treatment as salvage therapy. In this setting, imaging-based tumor assessment techniques should facilitate clinical decision on whether or not to retreat a non-responder [25]. The diagnostic accuracy and reproducibility of such techniques represents a fundamental precondition for a clinically meaningful use of these instruments. The demonstrated failure of anatomic, size-based measurements to identify non-responders in this study is of great importance primarily because these techniques are still widely used in clinical practice [10,12,26]. Specifically, neither RECIST nor vRECIST were able to reflect the anti-tumoral effects of intraarterial therapy which promptly causes tumor necrosis without affecting the overall lesions size on early post-procedural CT and MR imaging. The benefits of enhancement-based assessment techniques are supported by the herein presented results and must therefore be emphasized. However, it is also true that the most commonly used enhancement-based methods (EASL, mRECIST) have been primarily designed to simplify the assessment of hepatocellular carcinoma lesions before and after intraarterial therapies [16]. A direct translation of these techniques onto metastatic STS lesions might prove inaccurate, as demonstrated in the case of the EASL technique. This can be mainly explained by the nature of manual, diameter-based measurements. These methods assume that 3D response to treatment occurs in a symmetrical, spherical manner. However, most liver tumors are prone to asymmetry and frequently demonstrate inhomogeneous patterns of necrosis [24]. This is particularly the case in patients with STS metastases because most of these patients present for cTACE after several lines of systemic chemotherapy and usually exhibit central necrosis as well as remaining rim and segmental enhancement with scattered foci of viable tumor tissue [13]. A whole-tumor analysis using a segmentation-based 3D quantitative assessment technique can thus be advantageous in overcoming the limitations of manual analysis of the enhancing tumor portions, which was also confirmed for qEASL as the single most predictive image assessment technique in this study.

The 3D quantitative technique used in this study has several methodological strengths: First, this approach is based on a semi-automatic tumor segmentation, which enables a reproducible, radio-pathologically validated and accurate volumetric lesion assessment [18–21]. Furthermore, as opposed to fully automated segmentation techniques, a semi-automatic brings the dual benefit of fast, software-based segmentation while allowing for a

radiological reader to make adjustments, if necessary [19]. In addition, the use of an enhancement-based, 3D quantitative technique allows for this system to be used across several imaging modalities, such as ceMRI, multi-detector as well as cone-beam computed tomography (CBCT).

The herein presented patient population represents the largest so far reported single-institution experience with STS metastases to the liver treated with TACE. The reported median OS of 21.2 months is in agreement with previous publications [7,10,12]; however, a comparison of OS, PFS and TTIP rates between different reports is highly inaccurate primarily because of the histological heterogeneity of the included tumor types. Our cohort was mainly composed of patients with leiomyosarcoma lesions whereas other studies reported more heterogeneous collectives with a variety of different histological sarcoma types [10,12]. An additional, important finding of this study was the positive effect of radiation therapy of primary lesions on the overall survival outcome in treated patients. Currently, several ongoing clinical trials are investigating the role of radiation therapy in the management of STS patients and there is growing evidence in support of this therapeutic option [8,27–29]. However, our patient collective was not specifically selected under the premise of investigating the role of this treatment modality and it is imperative to view the presented result with caution, unless confirmed with a dedicated randomized trial. As for tumor response, no consistent data is available with criteria-dependent response rates ranging from 13% to 60% [8,10–12,30]. Overall, our study has some limitations: First, the retrospective character of this analysis prevented us from a thorough analysis of changes in laboratory parameters of liver function after therapy in all patients. Second, our study protocol did not include the assessment of multiple target lesions. However, several recent reports did not confirm the benefits of a multi-lesion assessment in the setting of intraarterial therapies [15]. Specifically, semi-automated 3D analysis offers a higher diagnostic accuracy and improved reproducibility of measurements making it less susceptible to reader bias, thus making multiple lesion analysis unnecessary. From a technical standpoint, the single-lesion approach can be explained by the therapeutic principle of cTACE as this modality is being applied for treatment in a lesion-by-lesion fashion. Thus selecting a dominant, i.e. largest treated lesion for the assessment of treatment response might very well be enough to correctly evaluate the effects of therapy. While offering the largest so far reported cohort of sarcoma patients treated with TACE, the sample size of the current study is fairly small and the overall statistical strength of the results can be seen as limited.

5. Conclusion

In summary, the use of cTACE for the treatment of metastatic STS can be seen as a safe and reliable salvage therapy option in patients with an otherwise dismal prognosis. The demonstrated benefits of enhancement-based tumor response analysis in identifying non-responders after cTACE should be taken into account when designing clinical outcome studies for metastatic STS in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

mSTS	metastatic soft-tissue sarcoma
qEASL	quantitative European Association for the Study of the Liver
RECIST	Response Evaluation Criteria in Solid Tumors

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejrad.2014.11.034.

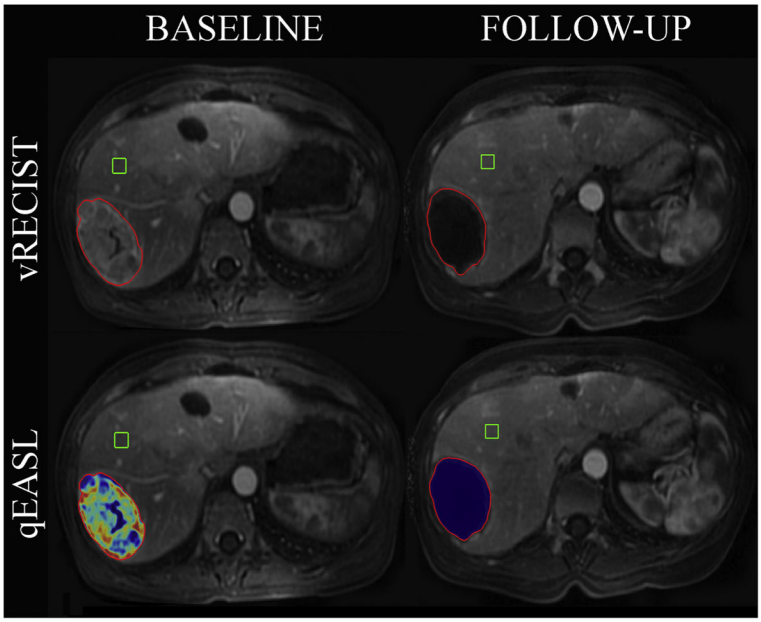

Fig. 1. 3D quantitative assessment technique

The left column represents baseline imaging and right column represents the follow-up imaging post TACE. The upper row demonstrated the minimal changes of tumor volume according to the segmentation-based volumetric method (volumetric (v) RECIST). The lower row illustrates the dramatic changes in a lesion enhancement due to therapy, measured using the quantitative (q) EASL approach.

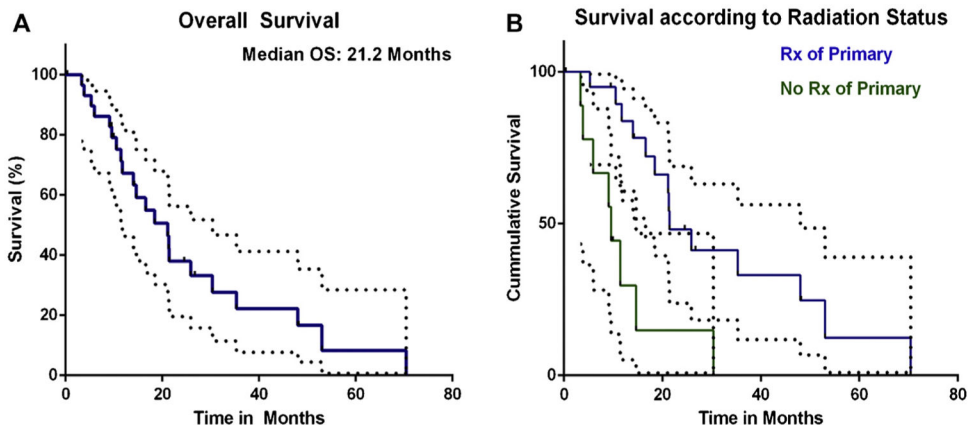

Fig. 2. Survival analysis

A illustrates the overall survival of the entire patient cohort (***N*** = 30) and (B) demonstrates the survival differences according to radiation treatment of the primary tumor.

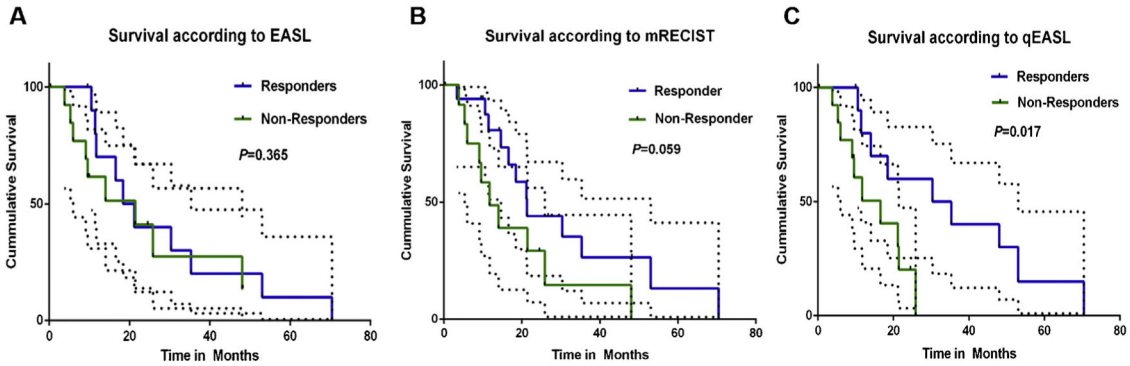

Fig. 3.

Comparison of survival between responders and non-responders, stratified accroding to enhnacmenet based techniques in ***N*** = 25 patients who received contrast-enhanced imaging both on baseline and follow-up. The ***P***-values resulted from the univariate analysis before the inclusion of additonally predictive prognostic markers.

Table 1

Baseline patient characteristics.

Parameter		*N* (%)
Demographics		
Age, years	<65	24 (80)
	≥65	6 (20)
Sex	Male	11 (37)
	Female	19 (63)
Race	White	26 (86)
	African American	2 (7)
	Other	2 (7)
ECOG performance status	0	9 (30)
	≥1	21 (70)
Bilirubin, mg/dL	Median	0.5
	Range	0.2–1.0
Albumin, g/dL	Median	4.1
	Range	2.9–4.7
Prothrombin time (INR)	Median	1.0
	Range	0.9–1.2
Child-pugh class	A	30 (100%)
Tumor characteristics		
Tumor burden, %	<50	22 (73)
	≥50	8 (27)
Synchronous disease	Yes	9 (30)
	No	21 (70)
Extra-hepatic metastases	Yes	19 (63)
	No	11 (37)
Tumor location	Bilobar	24 (80)
	Unilobar	6 (20)
Tumor multiplicity	Single Lesion	3 (10)
	2–5 Lesions	8 (27)
	>5 Lesions	19 (63)
Primary site	Retroperitoneum	9 (30)
	Uterus	8 (27)
	GI tract	4 (13)
	Other:	9 (30)
Histological type	Leiomyosarcoma	
	Angiosarcoma	25 (84)
	Fibrosarcoma	3 (10)
	Chondrosarcoma	1 (3)
		1 (3)

ECOG, Eastern Cooperative Oncology Group.

Table 2

Definitions of tumor response.

Evaluation method	Class	Subclasses of tumor response
RECIST	R	CR: complete disappearance of tumor
		PR: ≥30% decrease
	NR	SD: criteria of PR/PD not met
		PD: ≥ 20% increase
vRECIST	R	CR: complete disappearance of tumor
		PR: ≥65% decrease
EASL	NR	SD: criteria of PR/PD not met
		PD: ≥73% increase
mRECIST	R	CR: complete disappearance of enhancement
		PR: ≥50% decrease
qEASL	NR	SD: criteria of PR/PD not met
		PD: ≥ 20% increase
	R	CR: complete disappearance of enhancement
		PR: ≥30% decrease
	NR	SD: criteria of PR/PD not met
		PD: ≥ 20% increase
	R	CR: complete disappearance of enhancement
		PR: ≥65% decrease
	NR	SD: criteria of PR/PD not met
		PD: ≥73% increase

CR, Complete response; PR, Partial Response; SD, stable disease; PD, progressive disease.

Table 3

Treatment history.

Parameter		N (%)
Previous systemic chemotherapy, lines	None	3 (10)
	1–2	3 (10)
	3–5	15 (50)
	>5	9 (30)
Previous resection of the primary tumor	Yes	23 (77)
	No	7 (23)
Previous radiation of the primary tumor	Yes	21 (70)
	No	9 (30)
Previous hepatic resection	Yes	8 (27)
	No	22 (73)
Interval from STS diagnosis to	Median	25.6
first IAT, months	Range	0.9–136
Interval from STS diagnosis to	Median	8.5
Metastases, months	Range	0–132
Interval from diagnosis of	Median	10.1
Metastases to first IAT, months	Range	0.9–39
TACE frequency	Sessions, overall	77
	Mean/Patient	2.6
	Range	1–9
	TACE	75 (97)
	Radioembolization	4 (3)
Patients with crossover of IAT	Yes	2 (7)
	No	28 (93)

STS, Soft-tissue sarcoma.

IAT, Intraarterial therapy.

TACE, Transarterial chemoembolization.

Table 4

Recorded toxicity.

Toxicity	Grade I	Grade II	Grade III	Grade IV
Pain	8	3	0	0
Fatigue	6	2	0	0
Nausea	4	4	0	0
Vomiting	3	2	0	0
Facial Edema	2	0	0	0
Fever	0	1	0	0

Table 5

Method	N (%)	Overall Survival		Univariate analysis		Multivariate analysis	
		Median	95% CI	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
EASL							
R	11 (44)	21.4 mo	4.6–38.3	0.7 (0.3–1.9)	0.55	0.6	0.31
NR	14 (56)	18.4 mo	11.3–25.6	1.0		1.0	
mRECIST							
R	12 (48)	21.2 mo	2.6–39.7	0.4 (0.1–1.1)	0.068	0.3 (0.1–0.8)	0.019
NR	13 (52)	11.7 mo	5.1–18.4	1.0		1.0	
qEASL							
R	12 (48)	30.4 mo	4.2–56.6	0.3 (0.1–0.9)	0.026	0.2 (0.1–0.6)	0.006
NR	13 (52)	16.6 mo	6.5–26.7	1.0		1.0	