Multimodality imaging in bone and soft tissue tumours: deciphering quantitative data
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Chapter 4

Relative wash-in rate on dynamic contrast-enhanced MRI as a new prognostic biomarker on event-free survival in 82 patients with osteosarcoma; a multicentre study

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Abstract

Background: Decreased perfusion of osteosarcoma in dynamic contrast-enhanced (DCE) MRI has been described to reflect a good histological response to neoadjuvant chemotherapy. *Purpose:* In this study, we aim to explore the potential of the relative wash-in rate as a prognostic factor for event-free survival (EFS). *Methods:* Skeletal high-grade osteosarcoma patients, treated in two tertiary referral centres between 2005 and 2022, were retrospectively included. The relative wash-in rate (rWIR) was determined with DCE-MRI before the start of neoadjuvant chemotherapy, and after, or during the second cycle of chemotherapy (pre-resection). A previously determined cut-off was used to categorize patients, where rWIR <2.3 was considered poor and rWIR ≥2.3 a good radiological response. EFS was defined as the time from resection to the first event: local recurrence, new metastases, or tumour-related death. EFS was estimated using Kaplan–Meier's methodology. Multivariate Cox proportional hazard model was used to estimate the effect of histological response and rWIR on EFS, adjusted for traditional prognostic factors. *Results:* Eighty-two patients (median age: 17 years; IQR: 14–28) were included. The median follow-up duration was 11.8 years (95% CI: 11.0–12.7). During follow-up 33 events occurred. Poor histological response was not significantly associated with EFS (HR: 1.8; 95% CI: 0.9–3.8), whereas a poor radiological response was associated with a worse EFS (HR: 2.4; 95% CI: 1.1–5.0). In a subpopulation without initial metastases, the binary assessment of rWIR approached statistical significance (HR: 2.3; 95% CI: 1.0–5.2), whereas its continuous evaluation demonstrated a significant association between higher rWIR and improved EFS (HR: 0.7; 95% CI: 0.5–0.9), underlining the effect of response to chemotherapy. The 2- and 5-year EFS for patients with a rWIR ≥2.3 were 85% and 75% versus 55% and 50% for patients with a rWIR <2.3. *Conclusion:* The predicted poor response with DCE-MRI (rWIR <2.3) is associated with shorter EFS even when adjusted for known clinical covariates and shows similar results to histological response evaluation. rWIR is a potential tool for future response-based individualized healthcare in osteosarcoma patients before surgical resection.

Introduction

Osteosarcoma is a malignant bone tumour that generally affects children and adolescents, with a second peak at >40 years of age. Neoadjuvant chemotherapy (NAC) followed by tumour resection is key in curative treatment.[1–3] The gold standard for evaluating response to NAC in osteosarcoma patients relies on the histological assessment according to the modified Huvos classification.[4,5] This method has limitations, including the examination of only one slab of tumour tissue, high inter-observer variability, the use of a binary cut-off (≥10% viable tumour cells indicate poor response), and the inability to assess response before resection. These limitations partially cause the lack of clinical implications of histological response assessment in current clinical guidelines as they only become apparent after surgical resection.[6] Consequently, there is a need for a non-invasive prognostic biomarker able to accurately predict chemotherapy treatment response before surgery. Dynamic contrast-enhanced (DCE-)MRI is an imaging sequence capable of visualizing and quantifying various tumour properties such as tissue perfusion and capillary permeability.[7,8] In a previous study, the relative wash-in rate (rWIR) was described to correlate with histological response. The rWIR, derived from the baseline imaging's maximum slope of contrast enhancement (wash-in rate) divided by the post-NAC wash-in rate observed on DCE-MRI time-intensity curves, reflects alterations in tumour perfusion before and after NAC.[9] Utilizing this technique, the response to NAC can be predicted before tumour resection. Association between response assessment before tumour resection and prognosis could thus potentially provide tools for treatment personalization. Previous studies identified age, tumour size, the presence of metastases at presentation, histological response to chemotherapy, and local recurrence (LR) as risk factors for EFS in osteosarcoma patients treated with curative intent.[10-14] The aim of this multicentre retrospective study is to explore the potential of the rWIR as a prognostic factor for clinical outcome and determine its added value to known prognostic factors.

Materials and Methods

Design, setting, and participants

This multicentre observational retrospective cohort study was conducted between 2005 and 2022 at the Leiden University Medical Center (LUMC) and the Ghent University Hospital (GUH). The study was approved by the ethical review board in both centres, and the need for informed consent was waived due to the retrospective nature of this study (protocol and approval codes: B19.050, BC-09111, and G18.065/SH/gk). Patients with histologically proven skeletal high-grade osteosarcoma and treated with curative intent consisting of chemotherapy and tumour resection were included. All
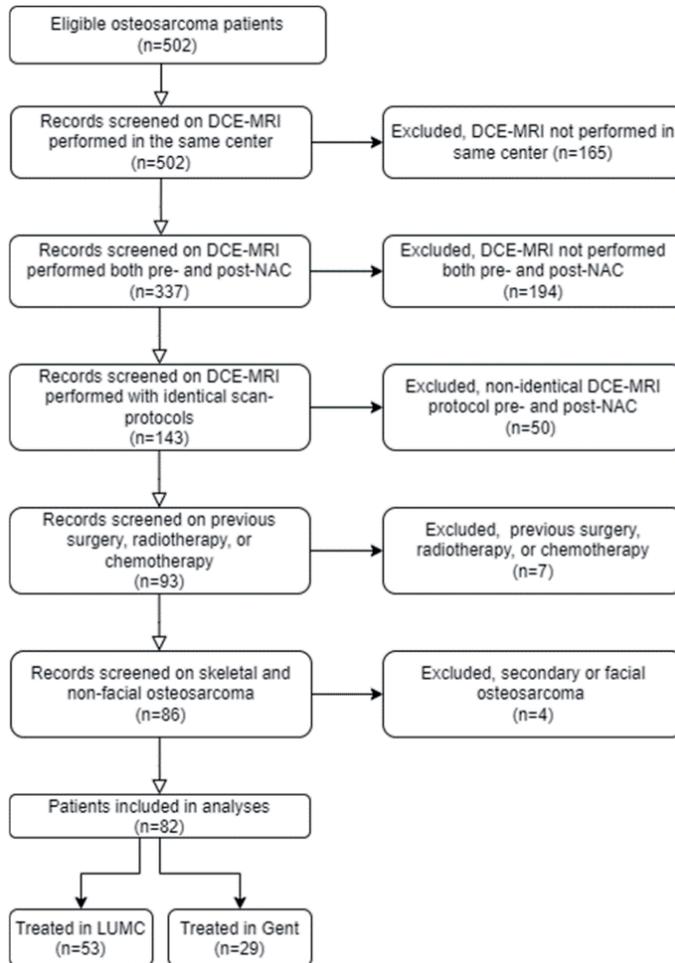
Figure 1 | Flowchart of patient selection. DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; NAC = neoadjuvant chemotherapy

participants underwent DCE-MRI both before and after NAC, using the same scan protocol. Exclusion criteria included patients with secondary osteosarcoma, craniofacial lesions, pre- and post-NAC MRI performed in different centres, a history of previous chemotherapy, and tumour resection or concomitant radiotherapy at the same site. Among 502 initially enrolled patients, 420 were excluded, resulting in a total study population of 82 patients (Figure 1). Of these, 53 were treated at the LUMC and 29 at the GUH. The entire study population of 82 patients was previously studied.[9,10] The first study provided an overview of survival and prognostic factors in 402 patients with skeletal high-grade osteosarcoma, including 53 patients from the current cohort.[10] The second study described the development of the biomarker rWIR, predicting the

histological response to NAC in 85 osteosarcoma patients, including 82 patients from the current cohort.[9] In this study, we report the potential of the rWIR as a prognostic factor for survival outcomes and determine its added value to known prognostic factors.

rWIR and selection of prognostic variables

DCE-MRIs, and the corresponding rWIR, were processed in a blinded and independent manner by G.M.K. (4 years of experience) for LUMC patients and T.V.D.B. (4 years of experience) for GUH patients, and rWIR was determined for all included patients. Previous research reported an intraclass correlation coefficient of 0.81 for rWIR in neoadjuvant-treated osteosarcoma, suggesting good repeatability. The rWIR was calculated by dividing the maximum slope of contrast enhancement on the time–intensity curves (wash-in rate) from baseline imaging by the wash-in rate post-NAC. Details can be found in a previous study by Kalisvaart and VanDenBerghe et al.[9] A prior study by Evenhuis et al.[10] identified prognostic factors for survival in 402 patients treated for a skeletal high-grade osteosarcoma. Age groups, tumour sizes, poor histopathological responses, and metastases at presentation were found to be independent prognostic factors influencing EFS in a multivariate Cox proportional hazard model and were also used in the current analysis.[10] For the current study, patient records were reviewed by the local investigator to obtain demographics, treatment details, and clinical outcomes. Baseline variables included sex, age group (children: 0–<16 years; adolescents and young adults [AYA]: 16–<40 years; older adults: ≥40 years), tumor location, tumor size (≤8 cm or >8 cm), metastases at presentation, histological response according to the Huvos classification (poor response: ≥10% viable tumour cells; good response: 90% response) and rWIR.[4,9] The rWIR was analysed both as a dichotomous variable (rWIR <2.3 indicated a poor radiological response, and rWIR ≥2.3 indicated a good radiological response) and as a continuous variable to evaluate the potential of rWIR to overcome the limitation of the arbitrary threshold for poor response originating from the 10% viable cells threshold in the Huvos classification. EFS was defined as the time from resection to the first event that consisted of LR, new metastases, or tumour-related death. In patients with metastatic disease at presentation, the next consecutive event was considered for EFS.

Follow-up

Patients were monitored at the outpatient clinic for local control and disease progression. Follow-up protocols varied by centre but generally included physical examinations and imaging modalities including computerized tomography (CT), MRI, and radiography.

Statistical analysis

A multivariate Cox proportional hazard regression model was estimated to study the effect of risk factors on EFS. The model included age group, histological response to

chemotherapy, tumour size, and metastases at presentation. A second model included the same prognostic factors but replaced histological response with rWIR. The rWIR was used as a categorical parameter (rWIR <2.3 indicated a poor radiological response) and afterwards as a continuous parameter. The proportional hazard assumption was tested by using the weighted residuals.[15] This analysis was also conducted on a subpopulation that excluded patients with baseline metastases. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were reported. To evaluate the additional value of rWIR, a comparison between two nested Cox models on the same data set with and without rWIR were compared using a likelihood ratio test.[16] EFS was estimated by employing the Kaplan–Meier (KM) methodology. The median follow-up time was computed using the reversed Kaplan–Meier methodology.[17] The combining batches (ComBat) harmonization method was used to reduce centre-specific effects for the rWIR conform the previous study by Kalisvaart and VanDenBerghe et al.[9] Analysis was performed with rWIR after ComBat harmonization and repeated with data without harmonization. Statistical analyses were performed using the SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and R-studio software version 4.2.1. The level of significance was set at a p-value of < 0.05.

Results

Participants and baseline characteristics

The cohort consisted of 50 males (61%) and 32 females (39%), with a median age of 17.4 years (interquartile range [IQR]: 13.7–27.7). Respectively, 7/43 patients (16%) with a poor and 5/39 patients (13%) with a good histological response had metastases at presentation (Table 1). The median follow-up time was 11.8 years (95% CI: 11.0–12.7). A total of 33 events were observed during the follow-up. The histological and radiological responses were classified as poor in 43 (52%) and 41 (50%) patients, respectively. In 18 patients (22%), histological and radiological response classifications were discordant. LR was observed in nine patients (11%). All patients with LR underwent re-resection, without additional chemo- or radiotherapy. The development of metastases during follow-up was observed in 31 patients (38%) that were treated with metastasectomy alone (n = 16, 52%), metastasectomy and chemotherapy (n = 5, 17%), metastasectomy and radiotherapy (n = 3, 10%), chemotherapy (n = 3, 10%), and metastasectomy, chemotherapy, and radiotherapy (n = 1, 3%), and 3 patients (10%) were not treated due to poor prognosis.

Characteristics	N Total (%)	LUMC	GUH	p-Value
Total	82	53 (65)	29 (35)	
Sex				0.20
Male	50 (61)	35 (66)	15 (52)	
Female	32 (39)	18 (34)	14 (48)	
Age group				0.16
Children (0–<16 yrs)	35 (43)	19 (36)	16 (55)	
AYA (16–<40 yrs)	35 (43)	24 (45)	11 (38)	
Older adults (≥40 yrs)	12 (15)	10 (19)	2 (7)	
Location tumour	86			0.10
Lower extremity	68 (83)	41 (77)	27 (93)	
Upper extremity	7 (9)	5 (9)	2 (7)	
Axial skeleton	7 (9)	7 (13)	0	
Tumour size				0.92
Small (≤8 cm)	39 (48)	25 (47)	14 (48)	
Large (>8 cm)	43 (52)	28 (53)	15 (52)	
Metastases at presentation				0.98
No	70 (85)	46 (87)	24 (83)	
Yes	12 (12)	7 (13)	5 (17)	
Preoperative CTx treatment	81	52	29	0.17
1 MAP or 2 AP completed	4 (5)	4 (8)	0 (0)	
2 MAP or 3 AP completed	71 (87)	43 (83)	28 (97)	
>2 MAP or >3 AP completed	6 (7)	5 (10)	1 (3)	
Histological response to CTx				0.20
Poor (≥10% viable tumour cells)	43 (52)	25 (47)	18 (62)	
Good (<10% viable tumour cells)	39 (39)	28 (53)	11 (38)	
Radiological response to CTx				0.49
Poor response (rWIR <2.3)	41 (50)	28 (53)	13 (45)	
Good response (rWIR ≥2.3)	41 (50)	25 (47)	16 (55)	
Local recurrence				0.38
No	73 (89)	46 (78)	27 (93)	
Yes	9 (11)	7 (13)	2 (7)	
Metastases during follow-up				0.06
No	51 (62)	29 (55)	22 (76)	
Yes	31 (38)	24 (45)	7 (24)	

Table 1 | *Characteristics of the overall cohort. AYA = adolescents and young adults; yrs = years; MAP = Methotrexate, Adriamycin, and Cisplatin; AP = Adriamycin and Cisplatin; CTx = chemotherapy; and rWIR = relative wash-in rate.*

Factors	HR	95% CI	Factors	HR	95% CI	Factors	HR	95% CI
Age Group			Age group			Age Group		
Children	Ref		Children	Ref		Children	Ref	
AYA	1.36	0.61–3.03	AYA	1.43	0.64–3.22	AYA	1.32	0.59–2.98
Older adults	1.26	0.45–3.55	Older adults	1.55	0.55–4.41	Older adults	1.41	0.50–3.97
Tumour size			Tumour size			Tumour size		
Small ≤ 8 cm			Small ≤ 8 cm			Small ≤ 8 cm		
Large > 8 cm	0.90	0.46–2.00	Large > 8 cm	0.97	0.47–2.00	Large > 8 cm	0.96	0.46–2.01
Histological response to CTx			DCE-MRI response (binary) to CTx			DCE-MRI response	0.78	0.60–1.01
Good response (<10% viable tum. cells)			Good response (rWIR ≥2.3)			(continuous) to CTx		
Poor response (≥10% viable tum. cells)	1.82	0.86–3.84	Poor response (rWIR <2.3)	2.39	1.14–5.01			
Metastases at presentation			Metastases at presentation			Metastases at presentation		
No			No			No		
Yes	2.29	0.90–5.83	Yes	2.31	0.90–5.92	Yes	1.85	0.70–4.94

Table 2 | *Hazard ratios (HRs) along with the 95% confidence intervals using multivariate Cox regression models for EFS in a study population (n = 82), with prognostic factors including histological response (left), rWIR as a binary variable (middle), and rWIR as a continuous variable (right) as the prognostic factors. HR = hazard ratio; ref = reference category; 95% CI = 95% confidence interval; CTx = chemotherapy; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; AYA = adolescents and young adults; and rWIR = relative wash-in rate.*

Factors	HR	95% CI	Factors	HR	95% CI	Factors	HR	95% CI
Age group			Age group			Age group		
Children	Ref		Children	Ref		Children	Ref	
AYA	1.43	0.59–3.46	AYA	1.46	0.61–3.53	AYA	1.28	0.53–3.13
Older adults	2.11	0.66–6.79	Older adults	2.30	0.74–7.21	Older adults	2.02	0.63–6.50
Tumour size			Tumour size			Tumour size		
Small ≤ 8 cm			Small ≤ 8 cm			Small ≤ 8 cm		
Large > 8 cm	1.26	0.55–2.92	Large > 8 cm	1.33	0.60–2.97	Large > 8 cm	1.23	0.54–2.80
Histological response to CTx			DCE-MRI response (binary) to CTx			DCE-MRI response (continuous) to CTx	0.69	0.50–0.94
Good responder (<10% viable cells)			Good responder (rWIR ≥2.3)					
Poor responder (≥10% viable cells)	1.98	0.84–4.67	Poor responder (rWIR <2.3)	2.28	1.00–5.19			

Table 3 | *Hazard ratios (HRs) along with the 95% confidence intervals using multivariate Cox regression models for EFS with prognostic factors including histological response (left), rWIR as a binary variable (middle), and rWIR as a continuous variable (right) as the prognostic factors in a subpopulation of 70 patients without metastases at presentation. HR = hazard ratio; ref = reference category; 95% CI = 95% confidence interval; CTx = chemotherapy; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; AYA = adolescents and young adults; and rWIR = relative wash-in rate.*

Chapter 4

Prognostic factors' effect on EFS

In the first model (histological response included), none of the variables were significantly associated with EFS. Histological response (HR: 1.8; 95% CI: 0.9–3.8; reference category: good responder) and metastases at presentation (HR: 2.3; 95% CI: 0.9–5.8; reference category: no metastases) were the most influential factors, though not significant (Table 2). In the second model, the rWIR was used instead of the histological response to chemotherapy. The rWIR <2.3 was significantly associated with worse EFS (HR: 2.4; 95% CI: 1.1–5.0; reference category: rWIR >2.3), and other factors did not show a significant association. Repeating the analysis in the none ComBat harmonization cohort showed that rWIR <2.3 was still associated with EFS (HR: 2.8; 95% CI: 1.3–5.9). In the third model, the rWIR as a continuous variable was incorporated. None of the included variables were significantly associated with EFS. The rWIR as a continuous variable (HR 0.8, 95% CI 0.6–1.0) and metastases at presentation (HR 1.9, 95% CI 0.7–4.9) were the most influential variables. A further subpopulation analysis, including 70 patients (85% of the total pupolation) without metastases at presentation, revealed that rWIR as a binary variable nearly approached significance for the association with EFS (HR: 2.3; 95% CI: 1.0–5.2) (Table 3). rWIR as a continuous variable was significantly associated with EFS (HR: 0.7; 95% CI: 0.5–0.9). Thus, an increase in the continuous rWIR (and a decrease in wash-in rate during NAC) resulted in an increased EFS. The proportional hazard assumption for each covariate was not violated. Analysis of deviance suggests that adding rWIR to the multivariate Cox model leads to an improved fit over the model (p = 0.07), although not significant.

Event-free survival

The 2- and 5-year EFS for patients with a rWIR of ≥2.3 (a good response) were 85% (95% CI: 74–96) and 75% (95% CI: 62–89) versus 55% (95% CI: 40–70) and 50% (95% CI: 35–66) for patients with a rWIR of <2.3 (a poor response) (Figure 2). Among 70 patients without metastases at presentation, 24 (35%) experienced an event. The 2- and 5-year EFS for patients with a rWIR of ≥ 2.3 (a good response) were 89% (95% CI: 79–99) and 77% (95% CI: 63–91) versus 61% (95% CI: 44–78) and 55% (95% CI: 38–72) for patients with a rWIR of <2.3 (a poor response) (Figure 3). The 2- and 5-year recurrence-free survival for patients with a rWIR of ≥2.3 were 98% (95% CI: 93–100) and 98% (95% CI: 93–100) versus 87% (95% CI: 77–97) and 82% (95% CI: 69–94) for patients with a rWIR of <2.3. The 2- and 5-year metastasis-free survival for patients with a rWIR ≥ of 2.3 were 85% (95% CI: 75–96) and 75% (95% CI: 61–88) versus 57% (95% CI: 41–72) and 52% (95% CI: 36–67) for patients with a rWIR of <2.3.
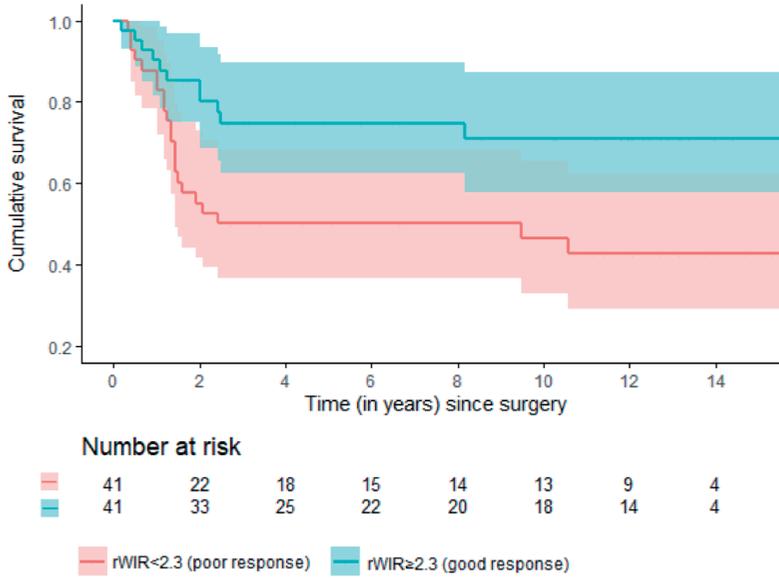
Figure 2 | Estimated event-free survival among good and poor responders based on the rWIR with a cut-off of 2.3.
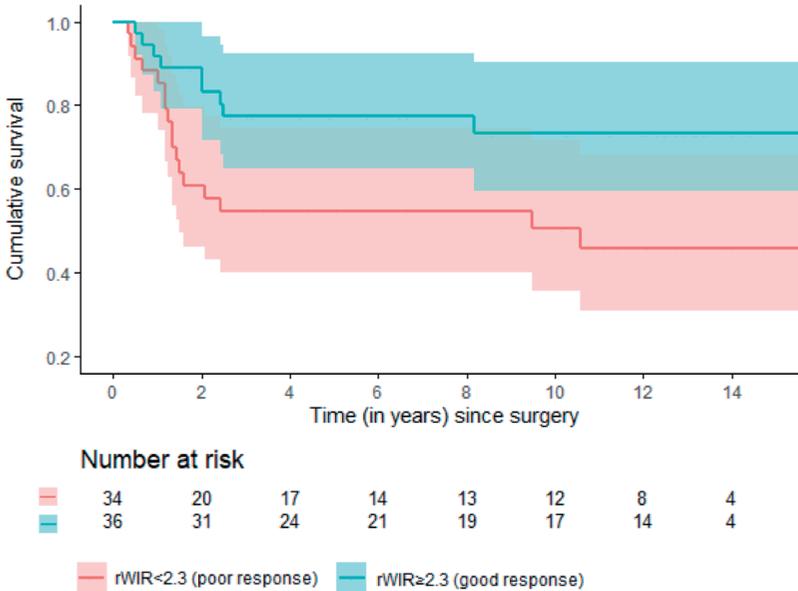

Figure 3 | Estimated event-free survival among good and poor responders based on the rWIR with a cut-off of 2.3 in a subpopulation of 70 patients without metastases at presentation.

Discussion

In this multicentre study, rWIR, as determined using pre- and post-NAC DCE-MRI, was found to be associated with EFS in patients with osteosarcoma. To the best of our knowledge, this is the first study to date on the prognostic value of rWIR for EFS. Results show that a previously determined cut-off of rWIR < 2.3 is associated with poor EFS when adjusted for age group, tumour size, and metastases at presentation. Furthermore, the continuous rWIR was significantly associated with EFS in a subpopulation without metastases at presentation. Our findings suggest rWIR might have value for response stratification in patients at diagnosis, as rWIR can be determined before resection and used as a continuous variable in survival prediction. This contrasts with the traditionally used histological response, which is a binary cut-off, and in our population was not significantly associated with EFS.

The link between DCE-MRI-based perfusion characteristics and histological responses has been described extensively in literature.[7,18] Guo et al. and Hao et al. found that several features, describing tissue permeability and perfusion, were correlated with histologic responses.[7,19] Standardized optimal methods to use perfusion characteristics, specifically the derived time–intensity curve, for histological response prediction were recently identified.[9] The determination of the association with biological changes in tumour tissues allows a more explainable association of this imaging characteristic with survival outcomes in the current study.

Although in this study the use of pre- and post-NAC DCE-MRI was investigated to predict clinical outcome of osteosarcoma patients, there are other functional imaging techniques such as PET/CT and DWI that have been described for predicting the response to chemotherapy.[7,20,21] These studies typically predict the histological response instead of survival. Studies evaluating quantitative, texture-based imaging features (radiomics) for predicting treatment response and survival have not yet resulted in widely accepted and implemented prognostic imaging biomarkers.[22-26] Interpretation of results in radiomics studies is often complicated by a lack of correcting methods for other prognostic factors, such as the presence of metastases or age and complexity of radiomics models. Furthermore, implementation is challenging, since specific software, quality control, and adherence to standardized study protocols are needed to assure reliable results and reproducibility of the results.[27,28] In this regard, the rWIR is a practical and explainable biomarker that is associated with clinical outcome when adjusted for most important covariates. Moreover, it facilitates a deeper understanding of tumour behaviour during treatment, providing radiologists and oncologists with a comprehensive tool for analysis and interpretation.

A limitation of this study is that it included patients previously described in the study deciphering the association between rWIR and histological response. Ideally, a different cohort should have been included. However, the model, which was used to identify rWIR, was not trained using survival data, causing the current study to provide valuable added information on patient stratification. Additionally, T1-mapping was not available in this study, preventing the use of Tofts features from the analyses.[29] DCE-MRI features based on the Tofts-model, such as differences in relative extravascular extracellular space and influx volume transfer constant, have been shown to be prognostic factors for EFS and overall survival (OS).[7,19] However, limited cohort sizes, arbitrary cut-offs for radiological response classification, and a lack of correction for other prognostic factors limit the interpretability of studies on the topic. Future studies should determine if Tofts modelling strengthens the prognostic value of DCE-MRI characteristics for patient stratification.

The rWIR holds potential for the early evaluation of NAC treatment response and EFS prediction in a non-invasive way before tumour resection. Moreover, patients with a poor radiological response to NAC experienced recurrences more often and seemed to have a shorter recurrence-free survival. Once further investigated and validated in larger sample sizes, this method could allow for standardized response monitoring in studies on neoadjuvant therapies, for example, in the development of new chemotherapy regimens. This, in turn, might contribute to individualized therapies and decision making. It involves the potential to either avoid or intensify ineffective chemotherapy cycles. Additionally, it might justify a more invasive surgical or adjuvant radiotherapy treatment in patients with predicted poor prognosis, aiming to prevent local recurrences and improve survival outcomes.

Conclusions

The rWIR is associated with EFS and is a valuable addition to other prognostic parameters. Future prospective studies on response monitoring and EFS prediction should be compared to the performance of rWIR.

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Chapter 4