Correlation of Dynamic Contrast-Enhanced MR Imaging (DCE-MRI) and Histopathology in Osteosarcoma Response to Neoadjuvant Chemotherapy

Muhammad Phetrus Johan
Hasanuddin University
M. Ruksal Saleh
Hasanuddin University
Mirza Ariandi (Mirzaariandi@gmail.com)
Hasanuddin University

Research Article

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Abstract

Background To evaluate the *dynamic contrast-enhanced MRI (DCE-MRI)* parameters for monitoring the neoadjuvant chemotherapy (NAC) response in osteosarcoma and correlate the parameters of histopathology specimens.

Methods Patients with pathologically confirmed as osteosarcoma had three cycles of NAC administered. Dynamic MRI were performed on all patients before and after chemotherapy. Semi-quantitative and quantitative parameters were compared between the good response group *(TNR ≥ 90 percent)* and poor response group *(TNR < 90 percent)* using the histology response as the reference standard *(tumor necrosis rate).* The Mann-Whitney U test was used to assess the differences in *DCE-MRI* parameters before and after *NAC*.

Results 15 patients were enrolled in this study of whom 3 patients lack of preoperative imaging examination, 2 patients inoperable to asess *tumor necrosis rate* and 1 had an allergy to a contrast agent. DCE-MRI of n = 9 patients were subsequently used for this study. Prior to chemotherapy, there were no statistically significant differences between the good response group and poor response group in *TTP, AUC, MAX Slope, Ktrans, Kep, and Ve* (P < 0.05). Following the completion of chemotherapy, the *TTP, AUC, MAX Slope, Kep and Ktrans* were significantly difference between the good response group and poor response group (P < 0.05). The Ve did not show significant difference between the two groups after the chemotherapy (P = 0,121).

Conclusion *DCE-MRI* has effectively monitor the response to NAC during osteosarcoma treatment cycle.

1 Introduction

Over the last few decades, the approach to management of osteosarcoma has evolved over time. The advances in multi-modality therapy strategy for osteosarcoma are to stimulate later tumor resection by causing tumor necrosis and decreasing the size of the primary tumor. Since the introduction of combining preoperative and postoperative chemotherapy with vigorous surgery has increaseed survival rates from 20–60% − 70% compared to surgery alone [1–4].

Because the degree of necrosis had a better survival, many studies have shown that one of the most significant outcome indicators is the histological response to preoperative chemotherapy [5–8]. Currently, the gold standard for evaluating chemotherapy response is histological assessment of tumor necrosis rate in the resected tumor and it significantly associated with the survival rate [9–13]. However, tumor necrosis rate is only observable after surgery, which suggests during the course of chemotherapy requires repeated surgery to decide the suitable chemotherapy regimen and cycle, but also it's difficult to assess histologic response inopperable's patients. In addition, chemotherapy resistance limits the effectiveness of chemotherapy [14]. It is important to monitor tumor response to chemotherapy. To address this issue, numerous imaging evaluation could be performed before surgery to evaluate medication response following NAC completion, such as magnetic resonance imaging *(MRI)* [15].

Radiological alterations can be detected by *diffusion-weighted imaging (DWI)*, thallium-201 scintigraphy, *dynamic magnetic resonance imaging (DCE-MRI)*, and positron emission tomography with computed tomography (PET/CT) [1, 16–19].

Dynamic contrast-enhanced MR imaging (DCE-MRI) is a noninvasive approach for identifying properties of tissue microvasculature that could be linked to tumor angiogenesis, such as interstitial volume, capillary permeability and tissue perfusion [20, 21]. Additionally, It has also been applied to estimate the histological improvement for osteosarcoma chemotherapy [1, 22, 23]. *DCE-MRI* has mostly been utilized to predict therapy response in breast cancer and brain tumors [24, 25].

Few studies have examined the effectiveness of *DCE-MRI* in predicting chemotherapy outcome of osteosarcoma using pharmacokinetic characteristics. Therefore, it is important to assess the roles of *DCE-MRI* parameters in patients of osteosarcoma before and after neoadjuvant chemotherapy and correlate the parameters with histopathology specimens. The aim of this study was to assess whether the parameters of the *DCE-MRI* are able to predict the neoadjuvant chemotherapy effects on osteosarcoma patients.

2 Materials And Methods

2.1 Patients

All patient's osteosarcoma were diagnosed by histologic examination which included in this study. The following are the exclusion criteria in this study: had a secondary osteosarcoma, already received chemotherapy and had contraindication to contrast agent. Enrolled patients had *DCE-MRI* imaging typically performed before of chemotherapy and additional *DCE-MRI* performed after the third cycle of chemotherapy. After obtaining informed consent from the patient or parent, all patients recieved thrapeutic precedures approved by the hospital's Institutional Review Board. Preoperative chemotherapy consisted of three cycles of doxorubicin (60 mg/m2), cisplatin (120 mg/m2), and high dose methotrexate (10–12 g/m2) with or without ifosfamide (14 g/m2) [19]. All medication were given intravenously over 6 week. All patients underwent definitive surgery immediately following the post-chemotherapy imaging examination and the analysis of intraoperative specimens were done in the same plane as the *DCE-MRI*. The intervals between the end of the first cycle of chemotherapy, the end of the third cycle and surgery were around 8 weeks.

2.2 DCE-MRI evaluation

DCE-MRI examination were performed before and after chemotherapy to assess the tumor microvasculature characteristics prior to definitive surgery. GE Healthcare's 3-Telsa was used for *DCE-MRI* images. Having chosen the only section that most clearly displayed the tumor, we obtained 30 sequence axial T1W turbo spin echo (T1-WTSE) images (TR/TE = 777/9.2 msec, 256 phase encodings, 4-mm thickness, 42-37.8 mm field of view, matrix size 320x224, 4 acquisitions) over a 5-min-Ute period before, during, and after a bolus injection of 0.1 mmol/kg gadopentetate dimeglumine (Omniscan) at a rate of 2

ml/sec via a size 20 intravenous line into the antecubital vein followed by a saline flush. The next investigations were conducted in the same plane and same slice position as the initial examination.

DCE-derived parameters were analyzed by musculoskeletal radiologists who can assess clinical and biopsy features. The radiologists were blinded to the treatment outcome during the data analysis procedure.

Regions of interest (ROI) were then drawn manually in the pre-chemotherapy and post-chemotherapy images by calculating pharmacokinetic *DCE-MRI* parameters in the tumours. ROIs that were drawn in the tumors were used to defining the visually solid section of the tumours with excluding cystic, necrotic, and hemorrhagic portions.

Following the completion of all sequences, all dynamic images were then sent to mean curve platform for post-processing. Then ROIs of approximately 5 cm^2 were chosen and circled with a cursor manually on the screen. The ROIs that had been selected were plotted automatically on images that had been taken in the same sequence. ROIs which was placed on the most enhancing section was used for analysis. In cases of post-chemotherapy MR images, The ROIs were placed over the same region that the pre-chemotherapy MR imaging had shown to contain tumors.

DCE-MRI parameters were involve with semiquantitative and quantitative analysis together with ROI in various locations, particularly the suspected limited section in *DWI-ADC* imaging.

The calculated semiquantitative parameters were: time to peak *(TTP)*, area under curve *(AUC)*, and maximum slope of enhancement *(MAX Slope)*. ROI was set at the most enhancing area of the tumor in each slice manually. The ROI area was set, color-coded *MAX Slope* and time-intensity curves were created. These time-intensity curves were used to calculate the time to peak *(TTP)*. ROI with the gratest *MAX Slope* value was chosen for peak enhancement and *TTP* values of the tumor.

The following quantitative parameters were measured the *Ktrans* (the volume transfer constant of Gd-DTPA), *Ve* (the extracellular volume fraction of the imaged tissue) and *Kep* (rate constant). After the highest enhancing portion of the lesion was defined, then generated output maps were automatically measured. In order to review the corresponding values of *Ktrans, Kep* and *Ve* for further analysis, three distinct ROIs covering the entire tumor (with the exeption of peripheral fat, blood vessels and artifacts) were defined separately based on the *Ktrans* maps. These ROIs included the other adjacent up and down slices. All ROI sizes were documented.

2.3 Histologic evaluation

Histologic evaluation of the surgical resection specimen was assessed after definitive surgery. Prior to resection, all of the patients had *DCE-MRI* evaluation and the en bloc specimens were collected in the same plane as the *DCE-MRI* scan.

The specimens of resected tumour were examined by experienced pathologists. Patients were classified based on their pathological response (good response and poor response). Poor responds were those who had less than 50% necrosis, which corresponded to Huvos grades 1 and 2. Good respond tumors showed more than 90% necrosis and reffered to grades 3 and 4 [26]. The grade 3 and 4 responses were found to be associated with increased long-term survival [27].

2.4 Statistical analysis

This study uses Statistical Product and Service Solutions (SPSS) version 25 for the statistical analysis. Descriptive statistical test is performed to describe the characteristics of research subjects and the frequency of osteosarcoma, and to determine data distribution. Statistical analysis before and after completion of the NAC was done using Mann–Whitney U test. This to determine the correlation between *DCE MRI* parameters findings with its histopathological of osteosarcoma. *DCE-MRI* parameters according to histological response were regarded statistically significant if the p value < 0.05.

3 Results

15 patients were diagnosed with osteosarcoma and undergoing neoadjuvant chemotherapy (NAC) between January 2020 and January 2022. 3 patients had lack of preoperative imaging examination, 2 patients were in an inoperable condition after neoadjuvant chemotherapy and 1 patient had an allergy to a contrast agent. *Dynamic contrast-enhanced MR imaging (DCE-MRI)* was used in the study both before and after the preoperative chemotherapy.

A total of 9 patients (6 men and 3 women) were available for imaging data processing and further analysis of the study. The age of the patients in this study ranged from 11 to 20 years with a median of 15 years. 9 patients had bone tumor cases; 5 in the femur, 2 in the tibia, and 2 in the fibula. There were 3 patients in the responder group (34%) and 6 patients in poor-responder group (66%). Based on histological evaluation of tumor necrosis rate showed that 6 patients responded poorly (four grade I and two grade II) and 3 patients responded well (two grade III and one grade IV). All 9 patients underwent surgery: 6 patients was performed limb salvage surgery while the other 3 patients underwent amputation (A summary of demographic information of the patients is shown in Table 1).

Table 1
Patient characteristics.

Variable	Value
Gender, n (%)	
Male	6 (66%)
Female	3 (34%)
Age (years)	
Range	11–20
Median	15,1
Primary sites, **n (%)**	
Femur	5 (56%)
Tibia	2 (22%)
Fibula	2 (22%)
Type of surgery	
Limb Salvage	6 (66%)
Amputation	3 (34%)
Histologic response, n (%)	
Good response (> 90% tumor necrosis rate)	3 (34%)
Poor response (< 90% tumor necrosis rate)	6 (66%)

DCE-MRI parameters comparisons of the good response group and poor response group before and after the completion of NAC are shown in Tables 2 and Table 3. Table 2 shows comparisons of *DCE-MRI* parameters between good response group and poor response group before NAC. The values of *TTP*, *AUC*, *MAX Slope*, *Ktrans*, *Kep*, and *Ve* did not show any significant differences between the good response group and poor response group ($P < 0.05$).

Table 2
The values of *DCE-MRI* parameters in good response and poor response group before neoadjuvant chemotherapy.

Parameters	Good Response	Poor Response	*P valuea*	Mean Differences
TTP	42.8	41.4667	1.000	0.00
AUC-TC	0.924	0.767	0.381	2.00
MAX Slope	1.402	1.198	0.714	1.00
Ktrans	0.793	0.623	0.095	3.50
Kep	0.846	0.728	0.167	3.00
Ve	0.49	0.497	0.548	-1.00
No significant difference of TTP, AUC-TC, MAX Slope, Ktrans, Kep, and Ve score between good and poor response in pre-chemothreapy group				

a Mann–Whitney U test

Table 3
The values of DCE-MR parameters in good response and poor response group after neoadjuvant chemotherapy

Parameters	Good Response	Poor Response	*P valuea*	Mean Differences
TTP	85.6	53.5	0.039	4.0
AUC-TC	0.364	0.756	0.02	-4.50
MAX Slope	0.453	1.011	0.02	-4.50
Ktrans	0.184	0.568	0.02	-4.50
Kep	0.28	0.687	0.02	-4.50
Ve	0.399	0.452	0.121	-3.00
Significant difference of AUC-TC, MAX Slope, Kep, TTP, and Ktrans scores between good and poor responses in post-chemothreapy group				

a Mann–Whitney U test

Table 3 showed the values of DCE-MRI parameters in good response group and poor response group after the completion of NAC. The *TTP, AUC*, *MAX Slope*, *Kep* and *Ktrans* differed significantly between the two groups after completion of NAC ($P < 0.05$). The *Kep* and *Ktrans* values of the good response group were significantly lower than that of the poor response group ($P = 0.02$). In assessment of treatment response to *AUC* and *MAX Slope* values were significantly lower in the good response group than in the poor response group ($P = 0.02$). The *TTP* values of the good response group were significantly higher than in the poor response group ($P = 0.039$). The *Ve* did not show significant difference between the two groups after the NAC (P = 0,121).

Based on the graph trend in Fig. 1, *TTP, AUC*, *MAX Slope*, *Kep* and *Ktrans* of the good responder group differ significantly after the completion of NAC. However, the changes in the poor responder group were not significant between before and after chemotherapy.

4 Discussion

DCE-MRI is a widely used imaging method reflecting vascular perfusion and endothelial permeability of tumor microcirculation, which are regarded as the most important factors in assessment of chemotherapy response. The *DCE-MRI* parameters has not been a consensus regarding adequate semi quantitative and quantitative parameters representing treatment response. Until now, several researches have supported the effectiveness of *DCE-MRI* become an accepted non-invasive in assessing tumor necrosis and biomarker for the response of treatment in osteosarcoma [1].

In this study, the role of semi-quantitative and quantitative parameters derived from *DCE-MRI* data for prediction of treatment response to chemotherapy in patients osteosarcoma was investigated. Our semi-quantitative and quantitative parameters showed that there was significant difference in chemotherapy response between the good response and poor response groups after chemotherapy. These result consistent with previous study that semi-quantitative and quantitative parameters values of *DCE-MRI* are correlated each other [4].

The results from quantitative analysis of *DCE-MRI* in response assessment of chemothreapy in osteosarcoma were consistent with those of several previous studies [28–36]. The pre-chemotherapy *Ktrans* and *Kep* values did not differ significantly between good and poor responders. Our finding is in agreement with studies on Zhang et al study in 19 patients of osteosarcoma that has reported that *Ktrans* and *Kep* pre chemotherapy showed no significant differences between the good respond groups and poor respond groups [28]. The *Ktrans* and *Kep* values are closely associated with the degree of tumor microcirculation and angiogenesis. Tumor neovascularization leads to increased permeability and perfusion, which means higher *Ktrans* and *Kep* values compared with normal blood vessels [29]. Several studies found that there was significant relationship between tumors with high *Ktrans* values pre chemotherapy have better treatment response compared with those with low *Ktrans* values, because the chemotherapeutic drugs are delivered more effectively, and the radiosensitivity is higher [30–33]. However, the other study found contrary in *Ktrans* pre-chemotherapy values and therapy response in squamous cell carcinoma of head and neck, oral cancer and rectal cancer [32, 36, 38].

We also found that the *Ktrans* value in the good respond group showed a significant decrease after chemotherapy, a finding that corresponded well with those of previous studies, Guo et al. showed that there was a significantly difference between responders and non-responders in *Ktrans* and *Kep* at week 9 in osteosarcoma [1]. Other studies, Zhang et al. reported in comparison to the non-responder group, the *Ktrans* and *Kep* values in the responder group significantly lower after chemotherapy [28]. Kim et al. attributed the contrasting changes and ratios of *Ktrans* after chemotheraphy to a larger fibrotic area in

good responders, but a substantial, residual, viable tumor area in poor responders [36]. Other study explained the decrease of Ktrans value by lower microvessel density after chemotherapy [37].

The findings of the study showed that *Ktrans* and *Kep* after chemotherapy were correlated significantly with histologic response. Good treatment responders had lower *Ktrans* and *Kep* values post chemotherapy compared with poor responders. Most research supported the associations of *DCE-MRI* parameters for the predictive potential of chemotherapy treatment response. Zhang et al. elucidate a similar relationship that following the end of treatment, responders had significantly lower *Ktrans* and *Kep* values than non-responders [28]. In a research by Giesel et al. non-responders showed an increase in *Kep* values throughout chemotherapy while responders showed a drop in *Kep* values [38]. This outcomes might be attributed to a reduction in microvascular density and permeability brought on by cytostatic and anti-angiogenic vascular disrupting effect.

The change in the *Ve* value is clinically important for determining how well a tumor responds to treatment [34]. However, Zhang et al. revealed no significant change Ve after complete of chemotherapy [28]. These results are consistent with the findings of our study. The *Ve* value represents the extracellular space which mean the motion space of water molecules, and is affected by blood flow. Increased blood flow can increase the contrast agent getting into the extracelullar space, so *Ve* cannot be used alone to evaluate the blood perfusion and extracelullar space. which the microvasculature structure of the tumor could alter following chemotherapy. However, there was no significant change in extracellular space. This may be caused by increased necrosis of tumor cells during chemotherapy, which results in an increase in extracellular space.

Semi quantitative *DCE-MRI* parameters that consist of the change in slope value and *AUC* in the good respond group showed a significant decrease after complete chemotherapy and *TTP* showed a significant increase in good response group after complete chemotherapy. Our results correspond to previous studies [2] that significantly longer *TTP* in good responders compared to poor-responders after NAC. It means decreased blood perfusion leads to slower in-flow of contrast in the tumor after NAC.

The result *Max slope* compared to the poor responders following the end of NAC, good responders showed a considerably greater slope (67% reduction) than poor responders (7% reduction). Others study revelead that predict good histologic response with reduction in slope > 60% reduction whereas < 60% was predictive of poor response [23, 29, 41].

The results of this study are the same as previous research that in the good respond group showed a significant decrease *AUC* after complete chemotherapy compared with poor respond grup [41–43]. Early response to chemotherapy causes the neoangiogenic arteries' vascular permeability to diminish, which lowers the pace of enhancement. Before and after the first treatment cycle, *DCE-MRI* parameters was examined by Johansen et al. in patients (n = 24) scheduled for NAC. *AUC* decreased in patients who had a clinical therapeutic response after just one cycle of NAC [41]. Sharma et al. study showed that *IAUC* was an important indicator of chemotherapeutic response following two cycles of NACT and *IAUC* showed an early change in responding patients [42]. *DCE* characteristics were assessed one week following induction

chemotherapy by Powel et al. They evaluated the changes of *Ktrans* and *IAUC60* between non-responders and responders in their cohort. *Ktrans* and *IAUC* significantly decreased in the responders group after therapy compared to before, falling by around 50% [43].

Our investigation was limited by the fact that all *DCE-MRI* characteristics for each patient were collected from a single, two dimensional slice across the tumor. Even if the positioning of the slices was carefully chosen based on earlier tests, variations in slice orientation and position could lead to greater variety in the outcomes of subsequent tests. Second, the relatively small sample size may limit the capacity to identify significant differences. Third, measurement inaccuracy may result from the delineation of the interest region being impacted by the radiologist's subjective assessment.

In summary, *DCE-MRI* can distinguish between patients who respond and those who do not during the NAC course of osteosarcoma using semi-quantitative and quantitative measures. To prevent ineffective NAC in poor responders, the DCE0MRI may be promising noninvasive prognostic markers for osteosarcoma. Therefore, additional research with a bigger sample size is necessary to confirm the utility of *DCE-MRI* in evaluating the effectiveness of chemotherapy in osteosarcoma.

Abbreviations

AUC	Area under curve
DCE-MRI	Dynamic contrast-enhanced MRI
DWI	Diffusion-weighted imaging
NAC	Neoadjuvant chemotherapy
ROI	Regions of interest
TNR	Tumor necrosis rate
TTP	Time to peak

Declarations

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Author contributions Muhammad Phetrus Johan and Mirza Ariandi performed manuscript draft writing, conceptualization, and resources. Ruksal Saleh and Mirza Ariandi performed a critical review and editing of the manuscript. All authors have checked the final version of the manuscript.

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Competing interests The authors declared no conflict of interest

Data availability

The datasets generated during and/or analysed during the current study are available in the Google Drive repository [https://docs.google.com/spreadsheets/d/1ZhueJEjCekHrVItRgXyhuy3mqpyFjgVZ/edit?usp=sharing&ouid=111867796410534422680&rtpof=true&sd=true]

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Figures

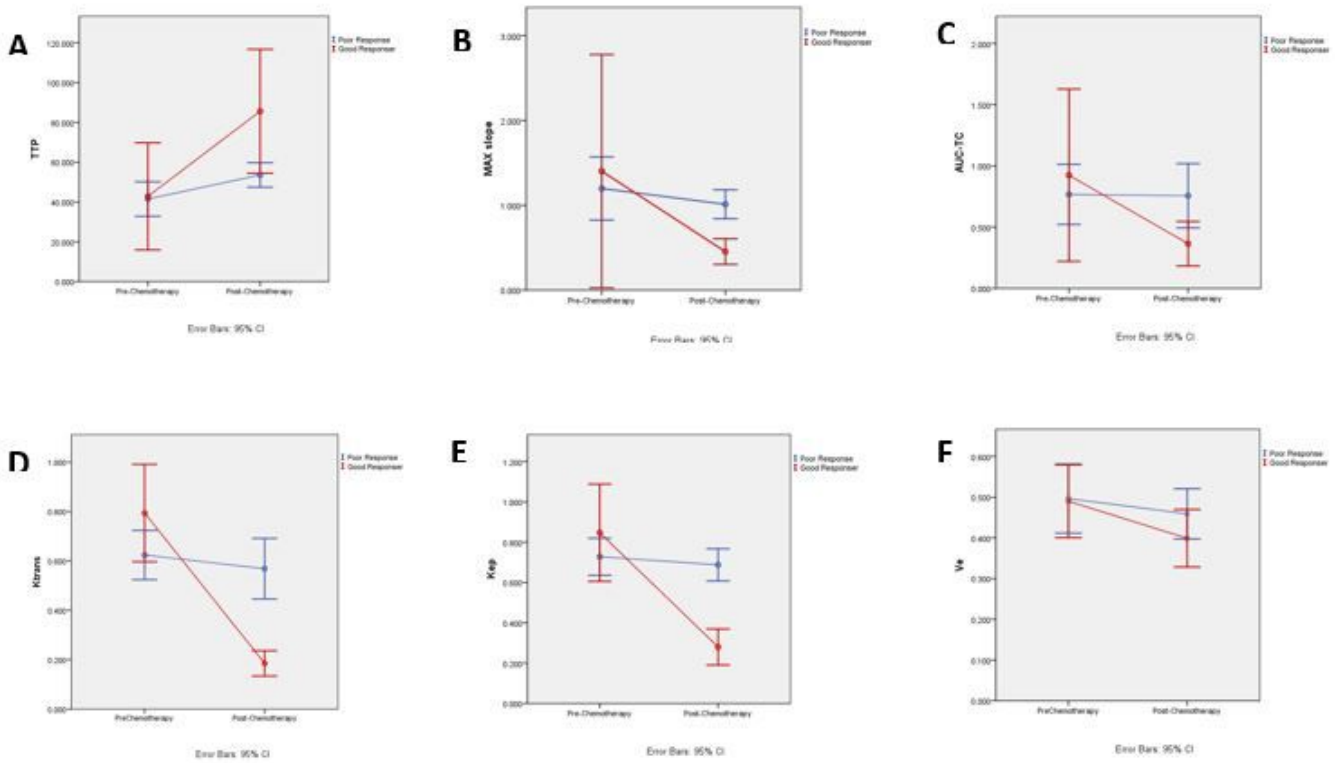

Figure 1

Changes in *TTP* (**A**), *MAX slope* (**B**), *AUC* (**C**), *Ktrans* (**D**), *Kep* (**E**) and *Ve* (**F**) between before and after chemotherapy in patients with good (red) and poor (blue) response. Median values were connected by straight lines.