

Value of diffusion-weighted imaging for evaluating chemotherapy response in osteosarcoma: A meta-analysis

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Abstract. The histological examination of the tumor necrosis upon surgery remains the most reliable prognostic factor for osteosarcoma. However, the detection of more early prognostic factors is desirable in order to increase the survival rates and decrease the risk rates for iatrogenic toxicity. The purpose of the current systematic review and meta-analysis was to provide an up-to-date summary of the role of diffusion-weighted imaging (DWI) for the preoperative assessment of the chemotherapy response in osteosarcoma. Articles evaluating DWI for the preoperative assessment of the chemotherapy response of osteosarcoma were systematically searched for in four electronic literature databases. The mean difference in apparent diffusion coefficient (ADC) following neoadjuvant chemotherapy between good and poor histological responders was assessed in 5 studies. The mean difference in the ADC ratio (the percentage change in ADC between post-neoadjuvant and pre-neoadjuvant chemotherapy) reported in 3 studies was also assessed. Five articles with 106 patients fulfilled all of the inclusion criteria for the meta-analysis. Significant mean differences were found between good and poor responders in the ADC in the 5 studies ($P=0.03$) and the ADC ratio in the 3 studies ($P<0.00001$). The good responders demonstrated a higher ADC and a higher ADC ratio than the poor responders. DWI performed with ADC values was useful for predicting the chemotherapeutic response of osteosarcoma. This method may have promising potential as a preoperative non-invasive modality.

Introduction

Pre and postoperative chemotherapy in addition to surgery have significantly increased the survival rate for patients with osteosarcoma (1,2). However, over the last 20 years, attempts at more intense chemotherapeutic therapy using conventional

cancer agents have not improved the survival rate significantly. Furthermore, in spite of an aggressive surgical and chemotherapeutic treatment strategy, patients with unresectable primary osteosarcoma and those with distant metastases still have a poor prognosis (3-5). The prognosis strongly correlates with the tumor histological response to preoperative chemotherapy in osteosarcoma (6,7). However, this valuable standard criterion is available only following surgery, which means that histological evaluation of tumor necrosis during the course of chemotherapy requires repeated invasive biopsies. The quantitative evaluation of preoperative radiological changes using diffusion-weighted imaging (DWI), dynamic magnetic resonance imaging, thallium-201 scintigraphy and positron emission tomography with computed tomography (PET/CT) has been challenged (8-12). The operative treatment and neoadjuvant chemotherapy of suspected poor responders may then be intensified earlier, potentially increasing their survival rates and decreasing the risk rates of iatrogenic toxicity.

DWI is currently the only imaging method to non-invasively measure the local diffusion characteristics of water molecules *in vivo*. It is able to reflect the spatial composition and the functional status of water exchange among various tissues in pathophysiological states from the molecular level. The apparent diffusion coefficient (ADC) is used to measure water diffusion and has a decreasing tendency in highly cellular tissue. DWI has been used to classify the subtype of musculoskeletal tumors (13-16). As the signal of water diffusion is directly associated with the tumor cellularity, necrotic areas in the tumor increase a local diffusion signal. This phenomenon has been demonstrated in clinical and experimental practice (17-20). Although the ADC value on DWI may be a promising tool, due to the scant data currently available, there is no routine practice for DWI to predict the chemotherapeutic response of osteosarcoma.

The objective of the present study was to provide an up-to-date summary of the role of DWI for the preoperative assessment of the chemotherapy response of osteosarcoma. The mean difference of post-neoadjuvant chemotherapy ADC between good and poor histological responders of osteosarcoma was assessed using a systematic literature search and meta-analysis.

Materials and methods

Literature search. A systematic literature search was performed following the Preferred Reporting Items for

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Systematic Reviews and Meta-Analyses (PRISMA) statement (21). The main research question, consisting of the Target Population (including previous tests), Index Test, Comparator Test, Outcome and Study design (PICOS) strategy, was formulated into a search query. A combination of the terms ‘diffusion-weighted imaging’ and ‘osteosarcoma’ was searched without a time limitation, on four electric literature databases: MEDLINE, EMBASE, Web of Science and Cochrane Library.

Study selection. Two reviewers (TF and MJP) evaluated potentially relevant articles for eligibility. The decision of article inclusion or exclusion was hierarchical and firstly made on the basis of the article title, then of the article abstract and finally of the whole article. If either reviewer judged the article title and subsequently the article abstract to be potentially eligible, the two reviewers independently evaluated the whole article for eligibility using predetermined inclusion or exclusion criteria.

The inclusion criteria were i) articles published in English; ii) diffusion-weighted imaging was used to predict histological response following preoperative chemotherapy in osteosarcoma; iii) All ADC values or the mean ADC values were described; and iv) when parts of data were presented in more than one article, the most recent article was used.

Data extraction. The same investigators independently reviewed the included articles in consensus to extract study information for the meta-analysis.

Quality evaluation. The quality of study designs was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (22).

Meta-analysis. The mean difference in ADC value following neoadjuvant chemotherapy between good and poor histological responders was assessed in the 5 studies. Additionally, the ADC ratio was calculated by using the following formula to assess the relative change in the pre- and post-neoadjuvant chemotherapy ADC values of osteosarcomas: $\text{ADC ratio} = (\text{postchemotherapy ADC} - \text{prechemotherapy ADC}) / \text{prechemotherapy ADC} \times 100$. The mean difference in ADC ratio was correlated between good and poor histological responders in 3 of the 5 studies. Heterogeneity of the mean difference of each study was evaluated using the inconsistency index I-square (I^2) test as well as the χ^2 test. An $I^2 > 50\%$ and/or $P < 0.10$ was considered to be statistically significant. The Der Simonian and Laird random effect model was applied if significant heterogeneity between studies was observed, while a fixed effect model was used in the absence of significant between-study heterogeneity. Publication bias was estimated using funnel plot asymmetry tests. All meta-analysis was performed using Review Manager software, version 5 (Cochrane Collaboration, Oxford, UK). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Literature search and study selection. The PICOS main research question was P, patients with osteosarcoma treated by

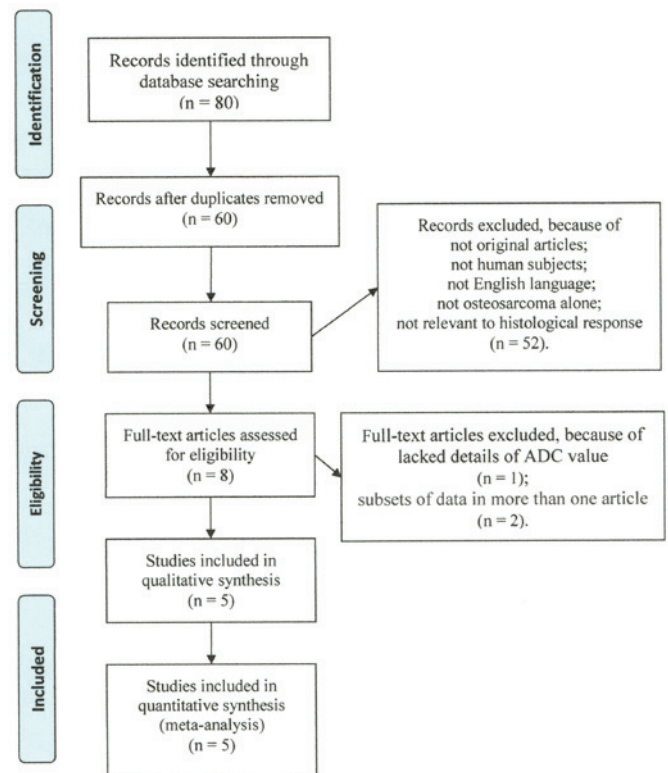


Figure 1. A flowchart of the study-selection procedure. ADC, apparent diffusion coefficient.

the combination of chemotherapy and surgery; I, preoperative DWI assessment for chemotherapy response; C, histological assessment for chemotherapy response; O, mean difference of ADC and ADC ratio; S, retrospective and prospective cohort studies. Using the predefined electric literature databases, we identified 80 potentially eligible articles, of which 72 were excluded due to duplication or after reviewing the article title and abstract. Subsequently, 3 articles were excluded after reviewing the whole article (23-25). Five articles with 106 patients who fulfilled all of the inclusion criteria were selected for the meta-analysis (Table I) (26-30). The detailed procedure of study selection and its exclusion reasons in the meta-analysis is presented in Fig. 1.

Study description and quality evaluation. Table II presents the clinical characteristics of the 5 studies included in the meta-analysis. All included studies fulfilled ≥ 5 ‘low’ answers in the 7 domains of the QUADAS-2 tool for methodological quality assessment. Common weaknesses concentrated on the domain of patient selection (Table III).

Meta-analysis. There was significant heterogeneity among the 5 studies in terms of the mean difference in ADC between good and poor responders ($P = 0.0004$ and $I^2 = 80\%$). Therefore, the random effect model was used. Significant mean differences were identified between good and poor responders in the ADC value (mean difference, 0.33; 95% CI, 0.04-0.63; $P = 0.03$). The good responders had a higher ADC value than the poor responders (Fig. 2A).

The mean difference in ADC ratio between good and poor responders was calculated with the fixed effects model, as

Table I. Summary of the studies included in the meta-analyses.

First author	Year	Journal	Country	N	Study design	Enrolment	(Refs.)
Baunin	2012	Skeletal radiol	France	14	Prospective	N/D	(26)
Byun	2013	J. Nucl med	Korea	27	Prospective	Consecutive	(27)
Oka	2010	Skeletal radiol	Japan	22	Retrospective	N/A	(28)
Uhl	2006	Pediatr radiol	Germany	8	Prospective	N/D	(29)
Wang	2013	PLoS One	China	35	Prospective	N/D	(30)

N/D, not documented; N/A, not available; N, number of patients.

Table II. Clinical characteristics of the patients included in the meta-analysis.

First author	Year	M/F	Age, years (mean/range)	Field, strength tesla	b-values, s/mm ²	Assessors	Blindness	(Refs.)
Baunin	2012	N/D	N/D	N/D	0, 900	2	N/D	(26)
Byun	2013	15/12	20.6/14-23	3.0	0, 800	2	N/D	(27)
Oka	2010	8/14	15.3/8-29	1.5	0, 1000	4	Blind	(28)
Uhl	2006	N/D	14.7/11-19	1.5	0, 700	2	Blind	(29)
Wang	2013	18/17	26.8/7-65	1.5	0, 700	2	N/D	(30)

N/D, not documented; M/F, male/female.

Table III. Quality assessment of diagnostic accuracy studies-2.

First author	Risk of bias				Applicability concerns			(Refs.)
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard	
Baunin	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	(26)
Byun	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	(27)
Oka	High risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	(28)
Uhl	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	(29)
Wang	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	(30)

there was no heterogeneity among the studies ($P=0.88$; $I^2=0\%$). There was a significant mean difference between the good and poor responders in the ADC ratio of the 3 studies (mean difference, 21.3; 95% CI, 12.2-30.5; $P<0.00001$) (Fig. 2B).

Publication bias was assessed using funnel plot asymmetry tests (Fig. 3). The plot of ADC meta-analysis among the 5 studies was asymmetric, indicating that there was some possible publication bias. However, the plots of ADC ratio meta-analysis was symmetric, suggesting a low risk of publication bias.

Discussion

Certain studies revealed that an increased ADC following neoadjuvant chemotherapy is associated with good histological

response (24,25,27,29,30). However, there have been conflicting results. Other studies have not identified a significant association between ADC value and tumor necrosis (23,26,28). Therefore, the predictive value of ADC remained undetermined. This meta-analysis focused on not only the ADC but also the ADC ratio for evaluating the chemotherapy response, which to the best of our knowledge had not previously been studied. The present study found that the good responders demonstrated a higher ADC and a higher ADC ratio than the poor responders.

The current study has several limitations. Firstly, only 3 articles with 44 patients were selected for the ADC ratio study. Further studies based on these promising results are warranted. Secondly, it was not possible to completely exclude potential bias, despite the following efforts. To minimize bias in the study selection and the data extraction, this study was

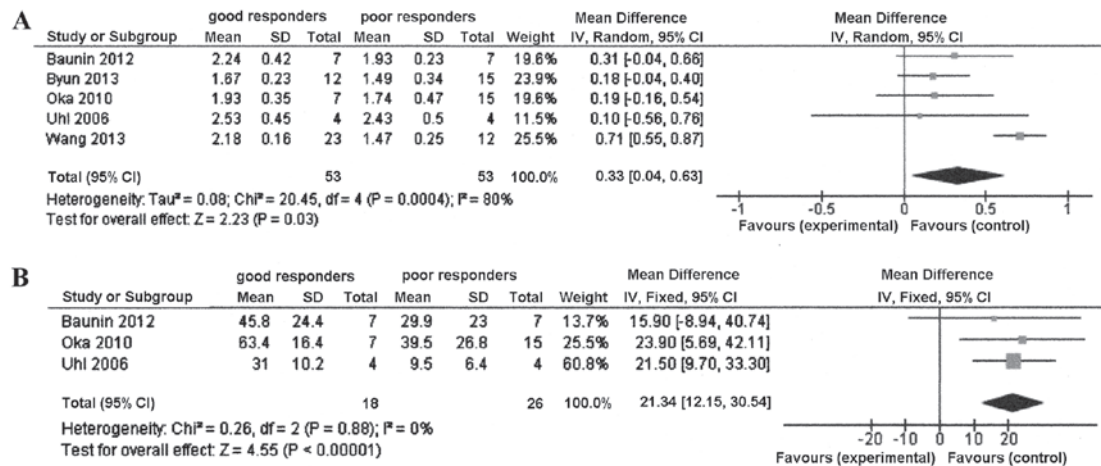


Figure 2. Forest plot showing outcomes of (A) the mean difference of ADC between good and poor responders in all 5 studies and (B) ADC ratio between good and poor responders in the 3 studies. Heterogeneity among studies was also evaluated using the χ^2 statistical test and the inconsistency index I^2 . ADC, apparent diffusion coefficient; SD, standard deviation; CI, confidence interval.

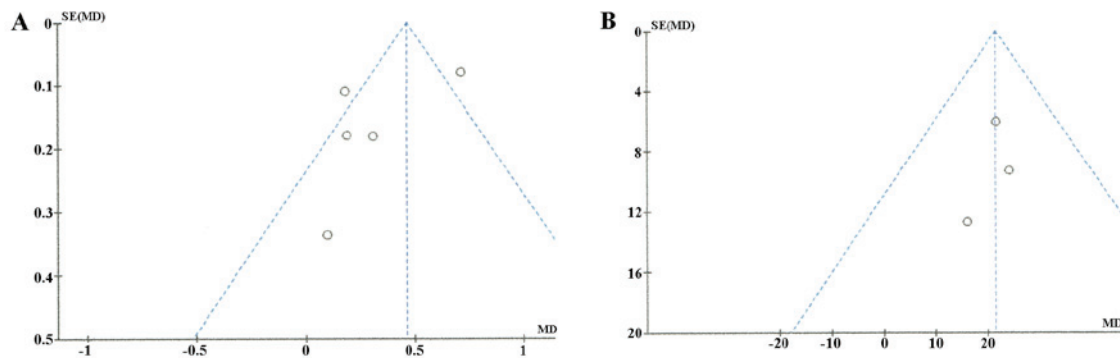


Figure 3. Funnel plot of the diagnostic odds ratios of (A) all 5 ADC articles and (B) the 3 ADC ratio articles. ADC, apparent diffusion coefficient.

performed blindly and independently. To be sure that all the selected articles were high-quality, only articles with a 'low' answer for the 7 domains in the QUADAS-2 quality assessment tool of ≥ 5 were selected. Publication bias was also assessed using a funnel plot, and there was some possible publication bias in the ADC meta-analysis among the 5 studies. Further prospective assessment of DWI to evaluate the chemotherapeutic response of osteosarcoma is required in order to exclude potential bias completely. Thirdly, significantly high heterogeneity of the diagnostic performance of DWI was found in the ADC meta-analysis among the 5 studies. This heterogeneity might be attributable to the methodological differences between the articles, such as the DWI acquisition technique, interpretation scheme or reference standard. For example, there was variation in the combinations of b-value and in the choice of region of interest among the 5 studies. Additional investigations with larger cohorts and the methodology of MR techniques that are both standardized and optimized are necessary to better characterize the benefit of this new technology for patients with osteosarcoma.

Recently, PET or PET/CT has become one of the most intensively-investigated imaging modalities for the monitoring of preoperative chemotherapy effects (12). Byun *et al* (27) reported the equivalent potential of PET/CT and DWI to predict the histologic response to neoadjuvant chemotherapy

in 28 patients with extremity osteosarcoma, using sequential imaging capture. The combination of PET/CT and DWI may yield varied biological information, such as changes in glucose metabolism and cellularity, which means that it has the potential to overcome the functional limitations of individual PET/CT and DWI. Several studies have suggested 40-60% of the standardized uptake value (SUV) ratio as the PET/CT cutoff point for a good response to neoadjuvant chemotherapy of osteosarcoma (12,27,31), but the optimal ADC cutoff point for good responders to neoadjuvant chemotherapy of osteosarcoma has yet to be reported. Furthermore, there is no standard means to measure ADC values. Further studies are required in order to obtain the standardized and optimized ADC values of DWI.

In conclusion, the present meta-analysis has demonstrated that the ADC and ADC ratio are useful for predicting the histologic response of patients to preoperative chemotherapy in osteosarcoma. This method may have promising potential as a preoperative non-invasive modality. For poor responders to preoperative chemotherapy, a more radical tumor resection should be performed and the postoperative chemotherapeutic regimen should be altered. For good responders, a minimally invasive surgical procedure can be selected with a low risk of local recurrence. These results have the potential to change the present therapeutic strategy for osteosarcoma based on the role of DWI prior to and following adjuvant chemotherapy.

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