rosy setiawati <rosy-s@fk.unair.ac.id>

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1 message

Heliyon <em@editorialmanager.com> Wed, Oct 28, 2020 at 5:18 PM
Reply-To: Heliyon <info@heliyon.com>
To: Rosy Setiawati <rosy-s@fk.unair.ac.id>

CC: "Suanarta Suanarta" natamind@gmail.com, "Paulus Rahardjo" paulus.r.rahardjo@gmail.com, "Filippo Del Grande" filippo.delgrande@eoc.ch, "Giuseppe Guglielmi" giuseppe.guglielmi@unifg.it

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Correlation of Quantitative Diffusion Weighted MR Imaging between Benign, Malignant Chondrogenic and Malignant Non-Chondrogenic Bone Tumors with Histopathologic Type

Dear PhD Setiawati,

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Decision on submission HELIYON-D-20-08013R1 to Heliyon

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Heliyon <em@editorialmanager.com> Fri, Jan 15, 2021 at 5:27 PM
Reply-To: Heliyon <info@heliyon.com>
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Ms. No.: HELIYON-D-20-08013R1
Title: Correlation of Quantitative Diffusion Weighted MR Imaging between Benign, Malignant Chondrogenic and Malignant Non-Chondrogenic Bone Tumors with Histopathologic Type
Journal: Heliyon

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Kind regards,

Tommaso D'Angelo, M.D.
Associate Editor - Clinical Research
Heliyon

Editor and Reviewer comments:

Reviewer #2:

Methods:
ok

Results:
ok

Interpretation:
ok. I would suggest to add in discussion section the use of DWI imaging for the assessment of response to therapy of bone lesions.

References:
ok. I would suggest to cite the following paper: (doi: 10.1016/j.acra.2014.05.021)

Other comments:

Table 2 --- there is a mistake in the following sentence "The Distribution of mean ADC values and standar(t) deviation based on the
269 histopathological type bone tumor". Fix it.
In TABLES and FIGURES abbreviations are missing, add it.

*****

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Decision on submission HELIYON-D-20-08013R2 to Heliyon

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Heliyon <em@editorialmanager.com> Thu, Feb 18, 2021 at 5:29 PM
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Ms. No.: HELIYON-D-20-08013R2
Title: Correlation of Quantitative Diffusion Weighted MR Imaging between Benign, Malignant Chondrogenic and Malignant Non-Chondrogenic Bone Tumors with Histopathologic Type
Journal: Heliyon

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5 - Wrote the paper.
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Reviewer #3:
Interesting study. Written well.
I only have one observation:
Please define all abbreviations at first use in Abstract (ADC??)

Methods:adequate.

Results: It seems adequate.

Interpretation: adequate.

*****

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Correlation of Quantitative Diffusion Weighted MR Imaging between Benign, Malignant Chondrogenic and Malignant Non-Chondrogenic Bone Tumors with Histopathologic Type

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Abstract:

Objectives: This study aims to determine the diffusion on weighted imaging which may help in providing characterization of Apparent Diffusion Coefficient (ADC) values in benign, malignant chondrogenic and malignant non-chondrogenic bone tumors.

Material and Methods: A retrospective study with 84 samples was conducted from October 2017 to December 2019. The samples consisted of 44 males and 40 females; the age range of 10 to 73 years (mean age of 32.7 years old). A Diffusion-weighted Magnetic Resonance (MR) utilizes a single-shot echo-planar imaging sequence technique with the 3T MR Scanner. We classified the types of tumors into benign, malignant chondrogenic and malignant non-chondrogenic bone tumors. The mean of ADC values from the area with lowest ADC values was selected for statistical analysis. ADC values were compared between benign, malignant chondrogenic and malignant non-chondrogenic bone tumors. Therefore, Receiver Operating Curve (ROC) analysis was done to determine optimal cut-off values. The correlation of ADC values between benign, malignant chondrogenic and malignant non-chondrogenic bone tumor with histopathologic type was also evaluated.

Results: The mean of ADC values from the area of benign, malignant chondrogenic and malignant non-chondrogenic bone tumor were 1.55×10^{-3} mm2/s, 1.84×10^{-3} mm2/s and 1.12×10^{-3} mm2/s respectively. As a matter of fact, there was a significant difference between benign and malignant bone tumor with cut-off value of 1.15×10^{-3} mm^2/s and had a sensitivity of 82%, and a specificity of 92.3%. Moreover, a significant correlation was also found between ADC values with the histopathology type of bone tumors.

Conclusion: The ADC values of benign and malignant (chondrogenic and non-chondrogenic groups) bone tumors are different. Thus, the measurement of ADC values improves the accuracy of the diagnosis of bone tumors.

Keywords: Apparent Diffusion Coefficient, Bone tumors, Diffusion Weighted Imaging

Correlation of Quantitative Diffusion Weighted MR Imaging between Benign, Malignant Chondrogenic and Malignant Non-Chondrogenic Bone Tumors with Histopathologic Type

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Introduction

MR imaging is the method of choice to detect, characterize, and to asses extension of bone tumors (Costa et al, 2011). Conventional MR imaging sequences have limited value in differentiating benign to malignant bone tumors, especially owing to their low specificity (Subhawong et al., 2012; Costa et al, 2011; Gielen et al., 2004). Advanced MR imaging techniques such as Diffusion Weighted Images (DWI) is applied to bone and soft tissue tumors to increase the ability to discriminate between benign and malignant bone tumors (Del Grande et al, 2017; Lee at al., 2016; Wang et al., 2014; Razek et al, 2012; Oka et al., 2011; Nagata et al., 2008).

Diffusion-weighted imaging (DWI) is a well-established non contrast MR technique based on Brownian motion of water molecules (Costa et al., 2011; Wang et al., 2014) that was originally applied to neuroimaging and is nowadays a well-established technique body MRI as well (Wang et al., 2014). DWI can be considered a proxy of malignancy through the detection of tissue cellularity (Marini et al., 2007). Apparent Diffusion Coefficient (ADC) is

the quantitative value of DWI and has been shown to potentially play a role to differentiate benign and malignant bone and soft tissue tumor (Schnapauff et al., 2009; Koh et al., 2007) and predicts the aggressiveness and potential response before starting a treatment (Ahlawat et al., 2015; Bley et al., 2009;) High ADC values represent low cellularity tissues whereas low ADC values represent high cellularity tissues (Schnapauff et al., 2009).

The aim of this study was to analyze correlation of quantitative DWI between benign, malignant chondrogenic and malignant non-chondrogenic bone tumors with histopathologic findings

Materials and Methods

Population

This retrospective study was approved by the regional ethics committee and all participants signed an informed consent.

From the October 1st 2017 to December 31th 2019, 84 consecutive patients were included (44 males and 40 females with an age range between 10 to 73 years and average age ± 32.702 years). The inclusion criteria were the followings: patients with bone tumor with complete bone tumor MRI protocol including DWI sequence. Exclusion criteria were the followings: non diagnostic DWI images and patients with previous chemotherapy or radiotherapy. All bone tumors were confirmed by pathology (50 surgical biopsies and 34 percutaneous core or fine needle biopsies).

MRI Protocol

All the examinations were performed on MRI 3 Tesla (Siemens Magnetom Skyra, Siemens AG Germany) using different RF coil depending of the location of the tumor. The field of view (FOV), slice thickness and matrix were adapted to the different body regions.

The following sequences were performed on every patient; axial, sagittal and coronal T1-weighted (repetition time (TR) 672-863/echo time (TE) 9-20 ms), coronal short time inversion recovery (STIR) (TR 4000/TE 82ms) and axial T2-weighted fat saturated (TR 4040/TE 60 ms) sequences

DWI with ADC maps were performed in the axial plane with b values of 50 and 800 s/mm^2 before intravenous contrast medium administration, using a spine echo, single shot echo planar technique. The parameters where TR (4430-6640 ms), TE (55-76 ms), FOV 200 – 325 mm^2, matrix size (voxel) of 115 × 128, thickness of 5-6 mm with an interslice gap of 1.5 mm and average of 1-2.

Image Interpretation

In our study, DWI images were evaluated independently using Siemens PACS workstation by two radiologists with 10 years and 20 years experience who were impartial in regard to the clinical and other radiological information. Moreover, the corresponding of ADC map to the average diffusion images was attained. Area within the lesion showed a high signal on DWI corresponding with low signal ADC maps are characterized as diffusion-limited areas. As a matter of fact, within the most restricted area of the ADC map including the areas of enhancing tumor with the lowest ADC, the circular or elliptical region of interest (ROI) was placed. It was determined by visual inspection which was assumed to have corresponded to the largest amount of cellular tissue and attempted to include the largest area of tumor within the ROI, with a minimum area of 10 mm^2 and a maximum of 55 mm^2. The mean ADC values were obtained (**Figure 1)(Figure 2**). When tissue heterogeneity were found, at least three measurements were conducted by each observer in the most restricted area, then the mean ADC value of the three measurements was recorded. The position of the

ROI was always examined thoroughly in regard to conventional MRI. The mean ADC values from the area with lowest ADC values were selected for statistical analysis.

Statistical Analysis

Data analysis was performed using SPSS 23 statistics software. For statistical analysis, bone tumors were divided into benign, malignant non-chondroid, and malignant chondroid matrix, according to pathology reports. We applied receiver operating curve (ROC) analysis to determine the optimal minimum and mean cut-off of ADC values to differentiate benign, malignant chondroid tumor, and malignant non-chondroid tumor. Mann-Whitney test was used to evaluate differences in ADC values between bone tumors. Chi-square was used to assess the correlation between bone tumor DWI and ADC values with histopathological types. Inter-reader agreement of both observer was calculated with kappa test. Intraclass correlation coefficient (ICC) with $P > 0.75$ was considered as a good agreement.

Result

The ICCs for inter-observer agreement between the two readers was good with the kappa coefficient value of (k) = 0.003 (*p=0.000*) at a significance level of 5%. The variability between ADC measurements was larger by using single ROI for measurement than using multiple small ROIs.

In fact, the most common age group presupposed for both benign and malignant bone tumors was 11 to 20 years as same as 31 cases or 36.49%. Furthermore, it was followed by 51 to 60 years or 18 cases with a percentage of 21.4%. Minimal number of cases were discovered in the age group of 0 to 10 years and >60 years with each 1.2% in one case. Thus, mean age of presentation was 32.7 years. In this study, a number of affected males were

obtained as 44 or 52.3% and total number of affected females were 40 or 47.6% with the ratio 1.1:1 of M:F.

From 84 bone tumors, 41 tumors were located in the femur, 17 in the tibia, 8 in the humerus, 6 in the radius, 4 in the sacrum, 3 in the iliac wing, 2 in the acetabulum, 2 in the pedis and manus , as well as 1 in the ulna(**Table 1**).

Minimum ADC values, mean ADC values and p-values for benign bone tumor , malignant non-chondroid tumor, malignant chondroid tumor, and respectively are shown in the **Table 2**. ADC value ranged from 0,82 × 10^{-3} mm^2/s to 2,88 x 10^{-3} mm^2/s for benign tumor, from 0.78 × 10^{-3} mm^2/s to 1,67 × 10^{-3} mm^2/s for malignant non-chondroid tumor, and from 1,22 × 10^{-3} mm^2/s to 2,38 × 10^{-3} mm^2/s for malignant chondroid tumor. Mean ADC values 1.55 × 10^{-3} mm^2/s for benign tumor, 1,12 × 10^{-3} mm^2/s for malignant non-chondroid tumor, and 1.84 × 10^{-3} mm^2/s for malignant chondroid tumor (**Table 3**).

According to the ROC analysis for differentiation between malignant and benign bone tumor, the cut-off of ADC values of 1.15 × 10^{-3} mm2/s had a sensitivity of 82%, specificity of 92.3%, and AUC (area under curve) of 0.166 (**Figure 1**). Cut-off difference of the ADC value between benign and malignant bone tumor is significant (p-value = 0.000 ($p<\alpha$)). There is a significant relationship between ADC values with the histopathology type (p=0.000) (**Table 3 and 4**).

Discussion

Our study indicates that mean ADC value supports the discrimination between benign, malignant chondrogenic tumor, and malignant non-chondrogenic bone tumors. Malignant chondrogenic bone tumors showed significantly higher mean ADC values compared to malignant non-chondroid tumor and such chondrogenic tumors should considered separately in the assessment with ADC values.

DWI is a non-contrast advanced MR technique increasingly used in body imaging (Dietrich et al., 2010). ADC represent the quantitative value of DWI and helps to differentiate high cellular from low cellular tumors (Türkbey et al., 2012). Several studies which have utilized the qualitative DWI MRI techniques and quantitative ADC. Bone tumors with unrestricted diffusion showed high ADC values representing the presence of hypocellular and damaged cell membrane integrity which allows greater water diffusion whereas bone tumors with restricted diffusion showed low ADC values, representing high cellularity and intact cell membrane integrity with limited diffusion of water molecules (Bley et al., 2009). As such low ADC values are presumed to correlated with malignancy, in other hand high ADC values are presumed to correlated with benign bone tumors (Ahlawat et al., 2018; Surov at al., 2015). However, ADC values can vary considerably among different studies depends on tissue type (Padhani et al., 2009; Matsushima at al., 2007), measurement techniques (minimum vs mean ADC values) (Ahlawat et al., 2018) and MRI characteristics (Sasaki et al., 2008). For instance, cystic degeneration, chondroid matrix, and myxoid matrix can results in false negative of high ADC values whereas tumor with high fibrovascular tissue can results in false positive of low ADC values (Rosari et al., 2020.; Ahlawat et al., 2018; Pekcevik et al., 2013; Yakushiji et al., 2009; Hayashida et al., 2006). DWI MRI is also used for monitoring therapeutic responses and a high ADC values after therapy shows a good therapeutic response. This response was likely related to necrosis or cellular lysis because of radiotherapy as well as chemotherapy, which leads to increases tissue water diffusivity, resulting in restricted diffusion area in the tumor, thus lowering signal intensity on high b value images with corresponding increases in ADC values. Because cell death in response to treatment precedes changes in lesion size, changes in DW-MRI may act as an effective, early biomarker of response to therapy (Gaeta et al., 2014; Thoeny et al., 2010).

Comment [DRS1]: I added this statement to reveal the use of DWI imaging for the assessment of response to therapy of bone lesions

Our results showed malignant chondroid tumors had the highest ADC values among malignant tumors that 9.5% of the patients with histologic proven chondroblastic osteosarcoma had minimum ADC value higher than 1.18×10^{-3} mm^2/s and mean ADC value higher than 1.77×10^{-3} mm^2/s. 4.8 % of the patients with chondrosarcoma have minimum ADC values higher than 1.43×10^{-3} mm^2/s and mean ADC value higher than 1,96 $x \times 10^{-3}$ mm^2/s. 31% of the patients with histologic proven as non chondroblastic osteosarcoma had minimum ADC values lower than 0.78×10^{-3} mm^2/s and mean ADC values higher than 1,13 $x \times 10^{-3}$ mm^2/s (**Table 2**)(**Figure 2**). The studies of Rao et al; Shivani et al; Pekcevik et al; Hayashida et al; Yakushiji et al consistently obtained similar results (Rao at al., 2019; Ahlawat et al., 2018; Geneidi et al., 2016; Pekcevik et al., 2013; Neubauer et al., 2012; Ginat et al., 2012; Yakushiji et al., 2009; Hayashida et al., 2006).

We speculated that the water molecules are relatively free to spread inside the chondroid matrix compared to osteoid matrix, resulting in higher ADC values. This statement was supported by study conducted by Ahlawat S and Fayad LM (Ahlawat et al., 2018), noted that high water content of hyaline cartilage in chondrogenic lesions leads to overall high ADC values. This was similar to myxoid tumor that shows higher ADC values compared to non-myxoid tumors regardless malignant or benign etiology. By increasing osteoid matrix at expanses of chondroid matrix, there will be an increasing DWI restriction and decreasing ADC values. Similar results were reported by Nagata et al (Nagata et al., 2008). that recommended cartilaginous tumors with a chondroid matrix to be classified separately where both benign and malignant tumors with a chondroid matrix component have high ADC values and further studies need to be conducted to distinguish ADC values from benign and malignant tumors with the chondroid matrix. Jifei Wang et al (Wang et al., 2017). stated in their study that extracellular matrix cartilage with high water components and hyper-permeability may also produces higher ADC values.

For malignant non chondrogenic tumor, the minimum ADC values of malignant bone tumors was 0.78×10^{-3} mm^2/s that belonged to bone metastases and Non-Hodgkin lymphoma. These result was consistent with study by Pekcevik et al (Pekcevik et al., 2013). which obtained all bone metastases (n=5) below the cut-off value of ADC with a minimum ADC value of 0.67×10^{-3} mm^2/s and a maximum of 1.02×10^{-3} mm^2/s. Furthermore, study conducted by Cao, et al (Cao at al., 2017), metastasis (n=7) with a minimum ADC value of 0.79×10^{-3} mm^2/s and a maximum ADC value of 1.10×10^{-3} mm^2/s. In this study, Plasmacytoma (n=4) and Non-Hodgkin lymphoma (n=1) had ADC values below the cut-off (mean ADC value 1.29×10^{-3} mm^2/s and 0.78×10^{-3} mm^2/s) with DWI's interpretation of all restricted diffusions.

In our study, giant cell tumors have heterogeneous ADC values, that divided into three malignant giant cell tumors that had lower mean ADC values of 1.16×10^{-3} mm^2/s and 18 giant cell tumors with mean ADC value of 1.51×10^{-3} mm^2/s, respectively(**Table 2**)(**Figure 3**). This result is similar to Peckevik et al. and Nagata et al (Pekcevik et al., 2013; Nagata et al., 2008). Nagata et al. reported in their study that the lower ADC value found in malignant giant cell tumors might be related to their histology in the form of adequate vascularized network of round, oval, or spindle-shaped stromal cells and multinucleated giant cells which probably decrease the extracellular space and result in decreased ADC values (Nagata et al., 2008).

Our study has limitation that the distribution of samples of benign bone tumor were predominantly giant cell tumors, which tend to have lower ADC values, also influenced the result of cut-off value in differentiating malignant from benign bone tumor. This study needs to be continued with more control group in each subtype of tumor. From malignant bone tumor group, the evaluation of ADC value study in osteosarcoma subtypes is also needed to provide more specific result.

Conclusion

In differentiating malignant from benign bone tumors and tumor like lesions, DWI is considerably helpful. Despite some overlapping occurred, ADC values of benign and malignant bone tumors seem to be different, so that the measurement of ADC values enriches the accuracy of bone tumors diagnosis. Our study demonstrated a significant correlation between ADC values of benign, malignant chondrogenic and malignant non chondrogenic bone tumors with histopatologic type.

Declaration

Author contribution statement

Rosy Setiawati: Conceived and designed the analysis; Contributed data or analytic tools,; Perfomed the analysis; Wrote the paper .

Suarnata MS: Collected the data; Contributed data or analytic tools; Wrote the paper.

Paulus Rahardjo: Collected the data, Contributed data or analytic tools; Performed the analysis.

Del Grande Filippo: Conceived and designed the analysis; Performed the analysis; Wrote the paper.

Giuseppe Guglielmi: Conceived and designed the analysis; Contributed data or analytic tools, Perfomed the analysis; Wrote the paper.

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213 *Data availability statement*

214 Data included in article/supplementary material/referenced in article.

215 *Declaration of interest statement*

216 The authors declare no conflict of interest.

217 *Additional information*

218 No additional information is available for this paper

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Abbreviations:

ADC	: Apparent diffusion coefficient
DWI	: Diffusion weighted image
DW - MRI	: Diffusion weighted - magnetic resonance imaging
FOV	: Field of View
ICC	: Interclass correlation coefficient
MRI	: Magnetic resonance imaging
ROI	: Region of interest
ROC	: Receiver operating curve
STIR	: Short time inversion recovery
T1FSE	: T1 Fast spin echo
T2FRFSE	: T2 Fast relaxation fast spin echo
TR	: Time repetition

Comment [DRS2]: I added abbreviations as w

Table 1. The Location of Bone Tumor in the Study Subjects

Location	Frequency	Percentage (%)
Femur	41	48.8
Tibia	17	20.2
Humerus	8	9.5
Radius	6	7.1
Sacrum	4	4.8
Iliac wing	3	3.6
Acetabulum	2	2.4
Foot	1	1.2
Hand	1	1.2
Ulna	1	1.2
Total	**84**	**100**

Table 2. The Distribution of Mean ADC Values and Standart Deviation of Bone Tumors based on the Histopathology Type

Comment [DRS3]: I revised the previous sentences
From :
"The Distribution of mean ADC values and standa deviation based on the histopathological type bor tumor"
To :
"The Distribution of mean ADC values and standa deviation of bone tumors based on the histopathol type"

Group of Bone Tumor	Histopatology type	ADC values		
		Frequency	Mean	Percentage (%)
Benign tumor	Osteomyelitis	6	1.5767	7.1
	Giant Cell Tumor	18	1.5139	21.4
	Aneurysmal bone cyst	3	1.6767	3.6
Malignant Chondrogenic Tumor	Chondroblastic type Osteosarcoma	8	1.7763	9.5
	Chondrosarcoma	4	1.96	4,8
Malignant Non-Chondrogenic Tumor	Osteosarcoma	27	1.1278	32,1
	Metastatic bone disease	10	1.044	11.9
	Malignant Giant Cell Tumor	3	1.165	3.6
	Plasmacytoma	4	1.2933	4.8
	Non hodkin lymphoma	1	0.78	1.2

	Total	84		100

Table 3. The Correlation between ADC Values with The Degree of Histopathological Examination between Benign, Malignant Chondrogenic Tumor and Malignant Non-Chondrogenic Tumor.

Bone tumor	**Frequency**	**ADC values**			
		Minimum ($x10^{-3}$ mm^2/s)	**Maximum (10^{-3} mm^2/s)**	**Mean ($x10^{-3}$ mm^2/s)**	**SD**
Benign tumor	45	0.82	2.88	1.5459	0.572
Malignant Chondrogenic tumor	12	1.22	2.38	1.8375	0.381
Malignant Non-chondrogenic tumor	27	0.78	1.67	1.1158	0.151
p values	84				**0,000**

Table 4. Comparison of ADC Values of Benign and Malignant Lesions of Present Study with Other Studies

Studies	**The mean ADC values of malignant lesions (×10−3 mm^2/s)**	**The mean ADC values of benign lesions (×10−3 mm^2/s)**	**The cut-off ADC values (×10−3 mm2/s)**	**The cut-off sensitivity of ADC (%)**	**The cut-off specificity of ADC (%)**
Present study	1,48 ± 0,45	1,55 ± 0.41	1.15	82	92.3
Rao et al[28]	1.092 ± 0.497	1.62 ± 0.596	1.31	73.3	77.1
Pekcevik et al[22]	1.02 ± 1.0	1.99 ± 0.57	1.37	77.8	82.4
Wang et al [9]	0.87 ± 0.20	1.17 ± 0.36	1.10	89.7	84.5

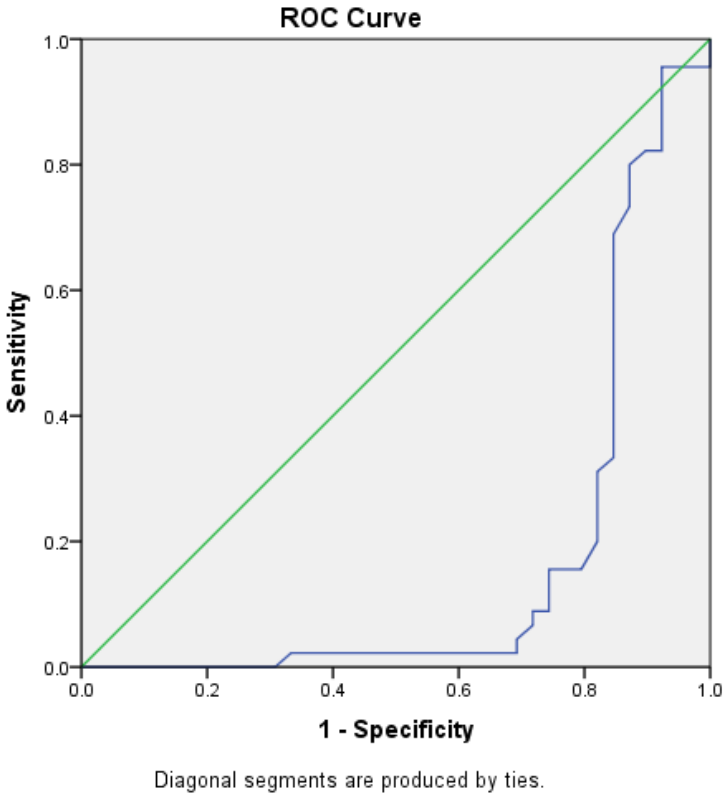

Figure 1: Receiver operating curve (ROC) curve of mean minimum apparent diffusion coefficient value for differentiation malignant and benign bone tumors. The area under the ROC curve is 0.166 (95% confidence interval 0.548-0.919)

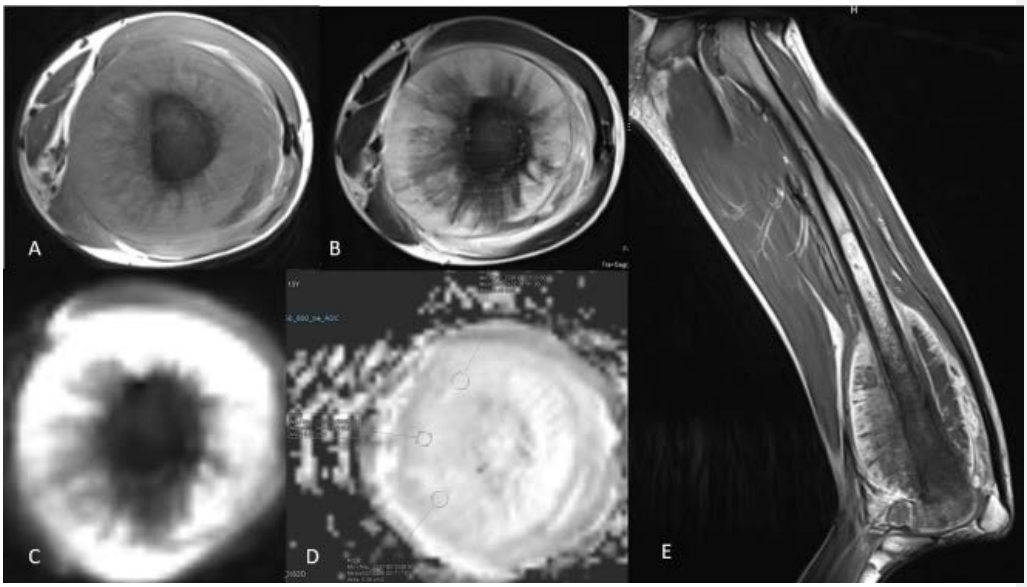

Figure 2. A 14-year-old male patient with chondroblastic type of osteosarcoma distal left femur. On MRI examination showed solid mass which appears isointense on axial T1 FSE (A), slight hyperintense on axial T2 FSE (B) and coronal T1 TSE fatsat with contrast showed contrast enhancement (E). Restricted diffusion area on DWI and slight hypointense on ADC maps (C, D) with mean ADC value of 2.27 x 10^{-3} mm^2/s.

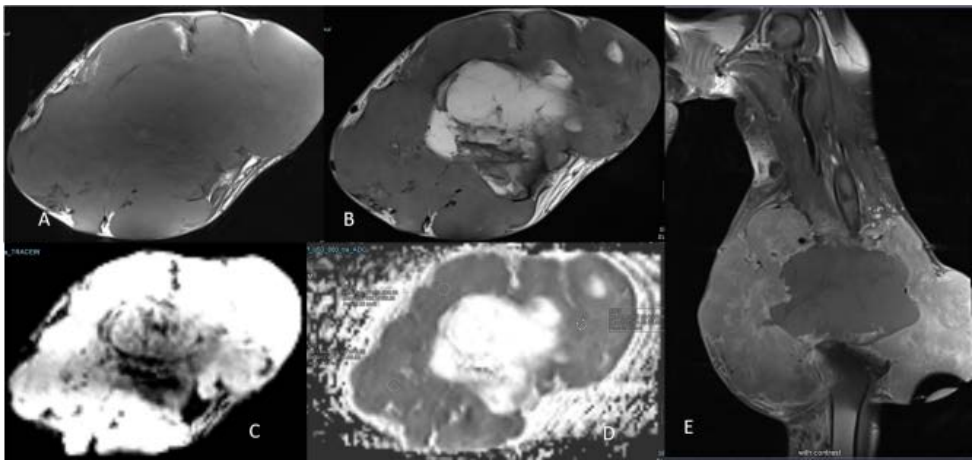

Figure 3. A 31-year-old woman with GCT in the distal left femur. MRI examination showed isointense solid mass with a central necrotic on axial T1 FSE and T2 FRFSE (B), and coronal T1 TSE fatsat with contrast showed contrast enhancement in the solid component part(E). Solid tumor component showed peripheral restrictive diffusion area on DWI and hypointense on ADC maps (C, D) with mean ADC value of 1.10 x 10^{-3} mm^2/s.

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