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Applications And Challenges Of DWI In Bone Lesions- Our Experience

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I. INTRODUCTION

Diagnosis of bone tumors is a challenge.Radiography and bone scintigraphy are the initial imaging examinations.The application of **STAMPS** namely-**S** for Site,**T** for Transitional zone,**A** for Age and Aggressive nature,**M** for matrix mineralisation, **P** for Periosteal reaction and S for Soft tissue changes helps in analysing imaging findings of bone tumors and diagnose certain tumors and may suggest that a lesion may be benign or malignant. Sometimes it can narrow down differentials with suggestion further cross-sectional imaging.

CT,MRI,PET/ PET-CT are available imaging modalities with specific added advantages in each of these modalities. MRI is most sensitive for evaluation of bone lesions particularly in defining their composition, changes in bone marrow and defining the extent of lesion, relationship with adjacent structures and skip lesions. DWI is a promising non enhanced functional MR imaging technique for bone lesions. We have studied to evaluate the significance of diffusion weighted imaging in benign and malignant lesions with histopathologic correlation.

II. MATERIAL AND METHODS:

The study was conducted in the department of Radiology and Imageology at Nizam's Institute of Medical Sciences after approval by the Institutional Ethics Committee. This is a prospective study, conducted over a period of 17 months (March 2019-September 2020). Sixty patients were included in the study, who were referred for MRI with clinical suspicion of bone lesions from orthopaedic department.

Inclusion criteria:

All patients referred to MRI who were diagnosed with bone lesions on radiograph and computed tomography,conventional MRI. Lesion size greater or equal to 1 cm,in order to ensure an accurate measurement of the ADC values within a region of interest [ROI]) were included.

Exclusion criteria:

Outofthe initial 60 that were registered 5 were excluded from the study as they did not have histopathological follow up.

Equipment and technique used:

The study was performed using 3T MRI Siemens Magnetom Skyra (48 Channel Machine) with 18 channel body coils.

MR imaging protocol

In 3T MRI, T1 weighted axials and coronals,T2 weighted axials and coronals, fat suppressed T2 coronals and axials followed by DWI with 3 b values(50,400 and 800) and ADC mapping.

Image acquisition:

T1-weighted (TR/TE 960/9, SL 5–6 mm) and fat suppressed (FS) T2-weighted sequences (TR/TE 3600–4280/70, SL 5–6 mm) in the axial and coronal planes were obtained.

DWI was performed in the axial, coronal/ sagittal plane using a spin-echo, single-shot echo-planar imaging (EPI) sequence. The following parameters were used for DWI: TR = 760 ms, TE = 80 ms, NEX = 2, gradient strength = 25 mT/m, FOV = 180–250 mm^2, matrix size = 256 × 256pixels, section thickness = 5 mm, interslice gap = 1 mm, section levels = 30; a partial Fourier transform and EPI factor = 88 was used. The *b-values*used were 50, 400, and 800 s/mm^2. ADC maps were calculated using a mono-exponential fit with in line software.

Image analysis:

1. Lesion characterisation is initially done on conventional MR imaging.
2. The lesion was determined on DWI and ADC map by using the conventional MR images as a guide.
3. Signal intensity of the lesion on DWIs (b 50,400 and 800) is determined: either +hypointense (free diffusion) or hyperintense (restricted diffusion) subjectively by visual comparison with the adjacent (normal) bone.
4. Quantitatively measurements of the *apparent diffusion coefficient* (ADC) were made using electronic cursor on the ADC map in different regions of interest (ROI) of the bone lesion, are put specifically in the solid areas of tumor and which is showing diffusion restriction preferably, avoiding cystic/necrotic areasto prevent under estimation of the cellularity of the tumor.
5. Only lesions more than 1cm are considered for ADC evaluation as the ROI for each lesion to be placed at least 3 times.
6. All ROIs put are almost identical size and shape.
7.Then followed by calculation of mean ADC value of lesion from maximum and minimum ADC values in different regions of lesion derived from ROIs.
8. The ADC values are expressed in x $10^{-3}mm^2/s$.
9. All the cases underwent biopsy and were confirmed by HPE which is gold standardfor confirmation of diagnosis of bone lesions except few benign stable lesions which were followed up byscan after 6 months(e.g.-osteochondroma).

Statistical analysis:

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software, version 21. Chi Square test was done to assess the % outcome of Diffusion weighted imaging and Histopathological diagnosis. ADC values between the two groups (Benign and malignant bone tumors) and between (infection and malignant bone tumors) were compared using the student t test.

Receiver operating characteristic (ROC) curves were performed and area under curve (AUC) was calculated to seek the best cut-off values of mean ADC. Sensitivity and specificity were calculated when employing the cut-off mean ADC values. AUC of >0.5 was considered statistically significant. A $p<0.05$ was considered statistically significant and $p<0.001$ was considered highly significant.

OBSERVATION

The study included 55patients who were referred to our department of Radio-diagnosis who were diagnosed with bone lesions on radiography /computed tomography and conventional MRI. DWI were done in all and ADC was calculated. Images were analysed and imaging diagnosis was correlated with HPE.

We observed larger number of males (n=35, 63.3%) than females (n=20, 36.6%) with male to female ratio being1.7:1. Maximum were in the age group of 10-30 years of age group (Table-1).

Table -1: Showing mean age of each bone lesion in the study

BONE LESIONS	NO	MEAN AGE	M: F	PERCENTAGE	DWI	ADC
SBC	2	17	2:0	3.6	NO	2.9
ABC	2	16.5	0:2	3.6	NO	2.5
GCT	10	32.2	8:2	20	YES	1.3
GCT WITH ABC	3	35	3:0	5.4	YES	2.3
CMF	1	8	1:0	1.8	YES	1.9
INTRA OSSEIUS SCHWANNOMA	1	43	1:0	1.8	YES	1.3
FD	1	23	1:0	1.8	NO	1.9
OSTEOCHONDROMA	2	10.5	1:1	3.6	PARTIAL	1.9
ENCHONDROMA	1	31	1:0	1.8	YES	1.8
CS	4	49	1:3	6.12	YES (allcases)	2
EWS	10	11.8	6:4	16.36	YES	0.7
OS	12	19.8	7:5	20.63	YES- (all cases)	0.8
METASTASES	3	39	1:2	3.6	YES	1.35
LYMPHOMA	1	7	1:0	1.8	PARTIAL	0.9
INFECTION	2	30.5	1:1	3.6	PARTIAL	2.5

[SBC-Simple bone cyst; ABC-Aneurysmal bone cyst; GCT-Giant cell tumour; CMF-Chondro-myxoid fibroma; FD-Fibrous dysplasia; CS-Chondrosarcoma; EWS-Ewings sarcoma]

Most commonly involved bones in our study areappendicular skeleton (50 cases) compared to axial skeleton (5) cases, with Femur(19 cases) being the most common site of involvement followed by tibia and humerus. In axial skeleton pelvic bones and vertebral bodies are showing equal involvement.In total 23 cases of benign bone tumors 15 cases (65 %) showed restriction on DWI ,4 cases show partly restriction due to inhomogeneity of the lesions and 4 cases show no restriction.

In total 30 cases of malignant bone tumors 29 cases showed restriction on DWI, 1 case showed partly restriction due to inhomogeneity of the lesions. Mean ADC values of benign lesions is $1.9\pm0.7x10^{-3}mm^2$ /s. Mean ADC values of malignant lesions is $1.2\pm0.5x10^{-3}mm^2/s$.Highest mean ADC value noted in benign bone tumors -ABC($3.13x10^{-3}mm^2/s$) and followed by SBC($2.9x10^{-3}$ mm^2/s). Lowest mean ADC value noted in benign bone tumor GCT ($0.7x10^{-3}$ mm^2/s). Among malignant lesions, Chondrosarcoma had highest ADC ($2.4x10^{-3}mm^2/s$) and Ewing's sarcoma had lowest ADC ($0.578x10^{-3}$ mm^2/s) values.

III. DISCUSSION

Incidence of benign tumors are much more common than primary malignant bone tumors. Since most of benign tumors are asymptomatic and are unrecognised. Hence the exact figure of benign tumors isunderestimated [1].Most of the primary bone tumors are diagnosed on radiographs with a systematic approach,STAMP. MRI is done to assess local extent andstaging. However, there are some benign and malignant tumors that show atypical radiological features and needs further evaluation. DWI MRI may be helpful in such critical situation.

DWI is a promising technique for lesion characterization throughout the body. In our study, most common benign tumor was GCT and malignant was OS followed by EWS and CS. Appendicular skeleton was involved in 50 and axial in 5.Most common bone was femur followed by tibiathis is similar to study done by Sunil K et al [2]. It was a study of 45 bone tumors and tumor like lesions. The most common boneinvolved was femur followed by tibia; benign lesions constituted 69% and malignant was 31%. Overall OS was the most common followed by osteochondroma, non-ossifying fibroma. Among the malignant tumors OS,followed by myeloma followed by EWS [2].

NidhiVermastudied 64 cases and the common tumors were chondrogenic followed by osteogenic, giant cell rich tumors,hematopoietic tumors,EWS, Fibrohistiocytic and metastatic tumors. Age varied from 3-70 yrs with mean age of 26 years,male and female ratio was 2.8:1 [3].We had similar experience. Out of 55,25 were benign lesions (23 benign tumors and 2 were infective etiology). GCT was the most common in benign tumor. Out of 30 malignant bone tumors maximum were OS followed by EWS and chondrosarcoma.According to Dorfman, in their study, OS was most frequent followed by CS, EWS, Chordomaand MHF. In age less than 20 years, OS was most common,followed by EWS.CS was the most common bone lesion in persons older than 50years [4].

Increased ADC value represent an increase in extracellular water or loss of cell membrane integrity, whereas decreased ADC values represents decrease extracellular water content or increase in cell numbers or size. Malignant tumor tends to have lower ADC and benign tumors have higher ADC.In our study with total 23 benign bone tumor cases, 65% (15 cases) showed diffusion restriction,4 showed partly restriction and 4 showed

no restriction.Simple bone cyst and aneurysmal bone cysts have mean average ADC of $3.13x10^{-3}$ mm^2/s and $2.9x10^{-3}$ mm^2/s respectively. These were the benign bone tumors that had the highest ADC values, they were hyperintense on both DW imaging and ADC map (Figure-1). Bone cysts (ABC, SBC) had higher ADC values than fibrous lesions (FD-$1.9x10^{-3}$ mm^2/s).

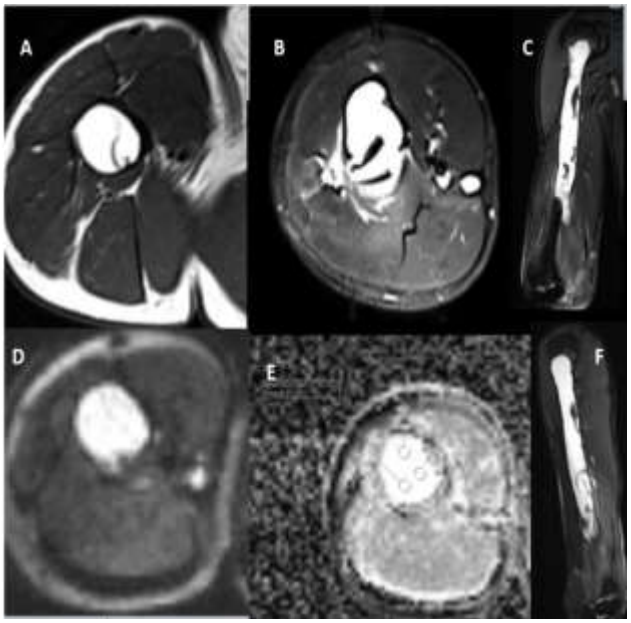

Figure- 1: A case of simple bone cyst with mid shaft fracture of right humerus in a 18 year old male patient: A-T2 Axial section shows hyperintense expansile lesion with fallen bone fragment within: B, C and F are STIR axial, coronal and sagittal showing hyperintense lesion with fallen bone fragment within involving proximal meta-diaphyseal region of right humerus and mid shaft displaced fracture.; D and E-Diffusion weighted imaging and ADC map axial sections showing hyperintense lesion with mean ADC value of $3.13x10^{-3}mm^2/s$. On HPE proven to be simple bone cyst

Osteochondroma,enchondroma also had high ADC value (Figures 2 and 3). This is similar to study done by Hayashida et al [5]. In their study of 20 bone tumors with high signal on T2W images were 8 -SBC,5-FD,7- CS and ADC value of these lesions were not different. Mean ADC of SBC $2.57\pm 0.13x10^{-3}mm^2/sec$ higher than FD and CS $2\pm 0.29x10^{-3}$ mm^2/sec and$2.29 \pm 0.14x10^{-3}$ mm^2/sec respectively [p value less than 0.05] [5].

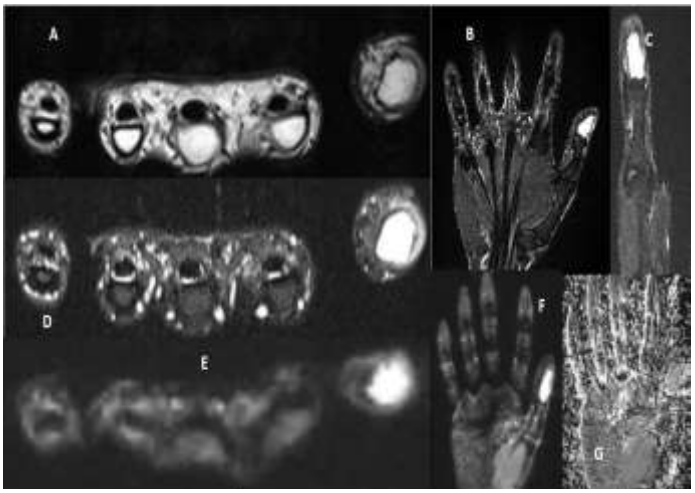

Figure- 2:A case of enchondroma involving distal phalanx of right hand in a 31 year old male patient : A-T2 Axial section shows hyperintense expansile lesion with thinning of cortex; B,C and D are STIR axial, coronal and sagittal showing hyperintense expansile lesion with thinning of cortex involving distal phalanx of right hand: E ,F and G -Diffusion weighted imaging (E,F-axial and coronal) is showing restriction and ADC map

coronal (G) sections show reversal with mean ADC value of 1.87 $x10^{-3}$ mm^2/s. On HPE proven to be enchondroma

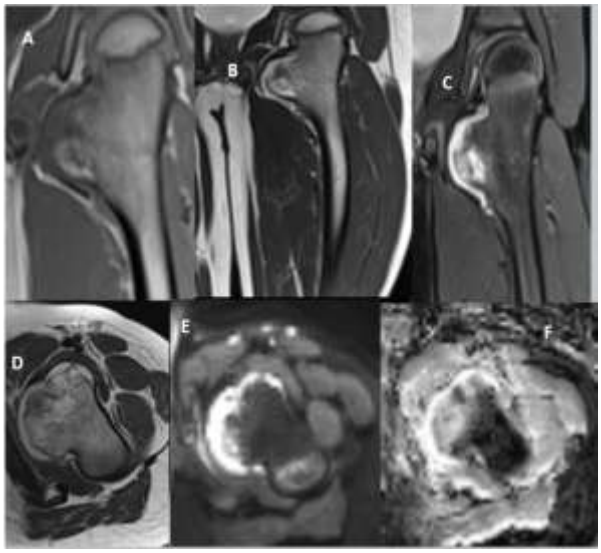

Figure- 3: A case of osteochondroma proximal metadiaphysis of left femur in 8 year old male patient ; A-T1 coronal section shows large bony outgrowth with medullary discontinuity and hypointense cartilage cap along medial aspect of lesion proximal meta-diaphysis of left femur; B, C and D -T2 and STIR coronal and T2 axial(D) sections shows large bony outgrowth with medullary continuity and hyperintense cartilage cap along medial aspect of lesion in proximal meta-diaphysis of left femur with adjacent marrow edema due to recent trauma; E and F -Diffusion weighted imaging axial section showing restriction of cartilage cap and ADC map axial sections showing no reversal with mean ADC value of $1.9x10^{-3}mm^2/s$

We had total 10 cases of GCT. They are large expansile altered signal intensity lesions in the form of T1 hypo T2/STIR heterogeneously hyperintensity and noted predominantly involving epi-metaphysis of long bones. On DWI they show restriction with mean ADC's variable ranging from$0.7x10^{-3}mm^2/s$ to $1.9x10^{-3}mm^2/s$(mean ADC's $-1.3x10^{-3}mm^2/s$). GCT show high signal in DWI and have low ADC(Figure-4).

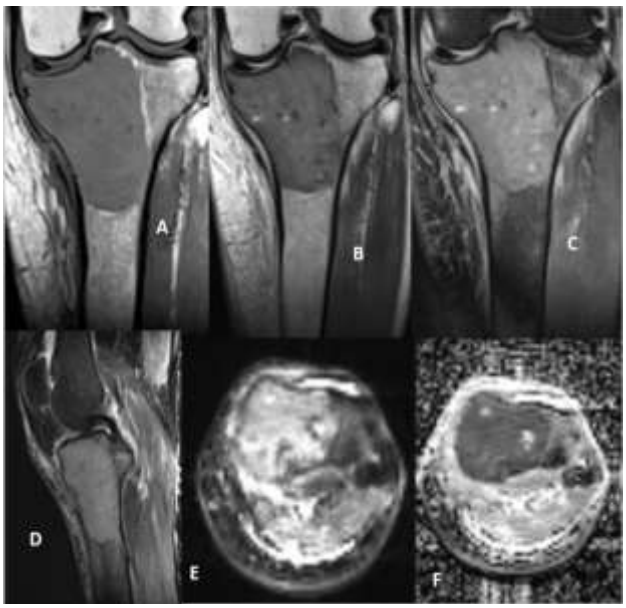

Figure- 4: A case of giant cell tumor involving proximal epi-metaphysis of left tibia in a 27 year old female patient: A and B -T1 and T2 coronal sections respectively shows altered signal intensity in the form of hypointensity involving proximal epi-metaphysis of left tibia causing thinning of cortex; C and D - STIR coronal and sagittal sections shows altered signal intensity in the form of hyperintensity involving proximal epi-metaphysis of left tibia causing thinning of cortex on lateral aspect; E and F -Diffusion weighted imaging axial

section showing partly restriction and ADC map axial sections showing reversal with mean ADC value of $0.8x10^{-3}$ mm^2/s

This is due to its histology of spindle cells and multinucleated giant cells [6]. Moderately vascularised network of round, oval spindle shaped cells and multinucleated giant cells probably decrease extracellular space and result in decrease ADC.ADC value is variable in giant cell tumor and cannot be taken as a reliable diagnostic marker.

In our series OS was the most common malignant tumor showing restricted diffusion and low ADC of $1.1\ x10^{-3}mm^2/sec$ in 11 cases (Figure-5) and one case was diagnosed as EWS on conventional MRI and HPE turned out to be OShaving ADC of $0.88x10^{-3}mm^2$. All these tumors are hypointense on T2WI and show restricted diffusion with low ADC as the lesions are hyper cellular with increased nuclear, cytoplasmic ratio, reduced intra and extracellular diffusion space.Yakushiji and Oka observed 17 of conventional OS had ADC of $0.84\pm0.15x10^{-3}mm^2/sec$ and Chondroblastic OS had $1.24 \pm0.10\ x10^{-3}mm^2/sec$ [7].

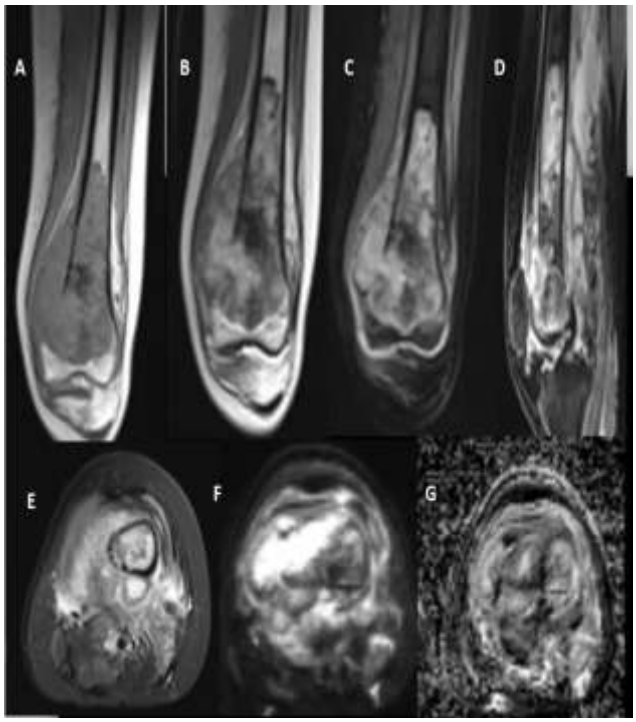

Figure-5: A case of osteosarcoma of distal end of femur in a 16 year old female patient; A-T1 coronal section showing heterogeneously hypointense lesion with few hypointense calcific foci within noted involving epi-metadiaphyseal region of distal right femur: B -T2 coronal showing heterogeneously hypointense lesion with few hypointense calcific foci within; C,D and E are STIR coronal, sagittal and axial sections showing heterogeneously hyperintense lesion with few hypointense calcific foci within ; there is cortical thinning and break on lateral aspect of the lesion with adjacent STIR hyperintense soft tissue component; F and G- Diffusion weighted imaging and ADC map axial sections showing lesion shows diffusion restriction with mean ADC value of $1.1\ x10^{-3}$ mm^2/s. On HPE proven to be osteosarcoma.

There were 10 cases of EWS and conventional MRI was correct in diagnosing 6 and 4 cases were thought to be OS,GCT,sacro-coccygeal teratoma and OM.However, the ADC were low in all cases with mean value of $0.578\ x10^{-3}mm^2/sec$ (Figure-6). In study by Anuradha Rao etal,EWS had lowest ADC value $0.7\ x10^{-3}mm^2/sec$ [8]. Pekcevik et al also had similar experience [9]. Small round cell tumors contain tissue with a relatively uniform population of small round cells, which have less extracellular space. Hence, they show high ADC value.

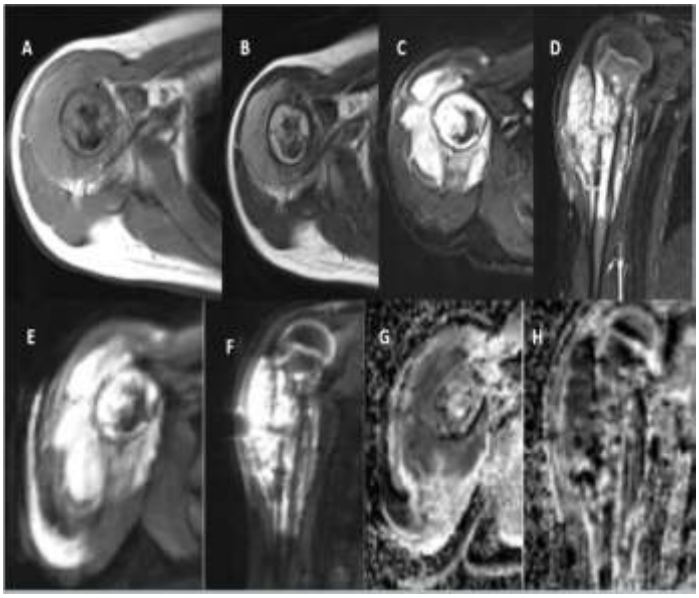

Figure-6: A case of Ewings sarcoma of proximal end of humerus in a 8 year old female patient ; A-T1 axial section showing heterogeneously hypointense lesion involving epimetadiaphyseal region of proximal end of humerus with marrow hypointensity and adjacent large soft tissue component: B -T2 coronal showing heterogeneously hyperintense lesion with marrow hyperintensity and adjacent large soft tissue component: C and D are STIR axial and coronal sections are showing heterogeneously hyperintense lesion with marrow hyperintensity, cortical thinning with adjacent STIR hyperintense large soft tissue component; F and G- Diffusion weighted imaging axial and coronal sections showing restriction and ADC map axial and coronal sections are showing reversal with mean ADC value of 0.7 $x10^{-3}mm^2/s$. On HPE prove to be Ewings sarcoma

Total 4 cases were Chondrosarcoma. They are large lobulated expansile altered signal intensity lesion in metadiaphysis of long bone and pelvis. Conventional MRI was diagnostic in all cases with sensitivity of 100%. On DWI there was restricted diffusion and mean ADC $1.9X10^{-3mm2}$/sec (Figure-7)due to presence of chondroid forming areas with myxoid matrix and high-water content.3 had ADC of 2.4-2.6 $X10^{-3}mm^2$/sec and one had very low ADC of 1.02 $X10^{-3}mm^2$/sec which on HPE proven to be high grade CS with dedifferentiation.Study by Yoshico etal showedthat CS had ADC similar to that of benign bone tumors. 7 out of 20 cases of bone tumors in their series had ADC of $2.29\pm0.14x10^{-3}mm^2$/sec. They also observed mean ADC of SBCwas higher than FD,CS the water content may explain the ADC value [10]. So, ADC is unreliable in diagnosis of chondrosarcoma.

In our study we had a case of primary bone lymphoma involving diaphyseal region of right femur with lamellated periosteal reaction with adjacent large soft tissue component and central necrosis, which was suspected as osteomyelitis based on radiograph, CT and conventional radiography. On DWI showed peripheral restriction of soft tissue component with mean ADC of $0.9 \times 10^{-3}mm^2/s$ with ROI at peripheral solid component (Figure-8).

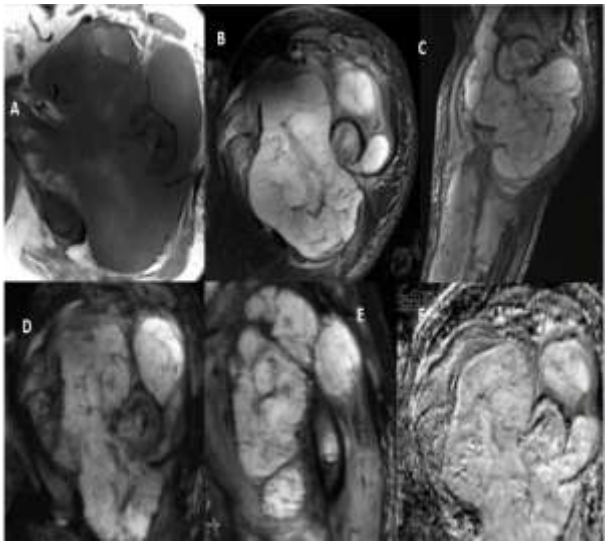

Figure- 7: A case of chondrosarcoma of proximal end of femur in a 54-year-old male patient ; A-T1 axial section showing large lobulated expansile hypointense lesion noted involving epi-metadiaphyseal region of proximal end of femur with marrow hypointensity; B and C -T2 axial and STIR coronal showing large lobulated expansile hyperintense lesion with marrow hyperintensity; D,E and F- Diffusion weighted imaging axial and coronal sections showing restriction and ADC map axial section is showing no reversal with mean ADC value of 2.5 x10-^{3}mm^{2}/s. On HPE proven to be chondrosarcoma.

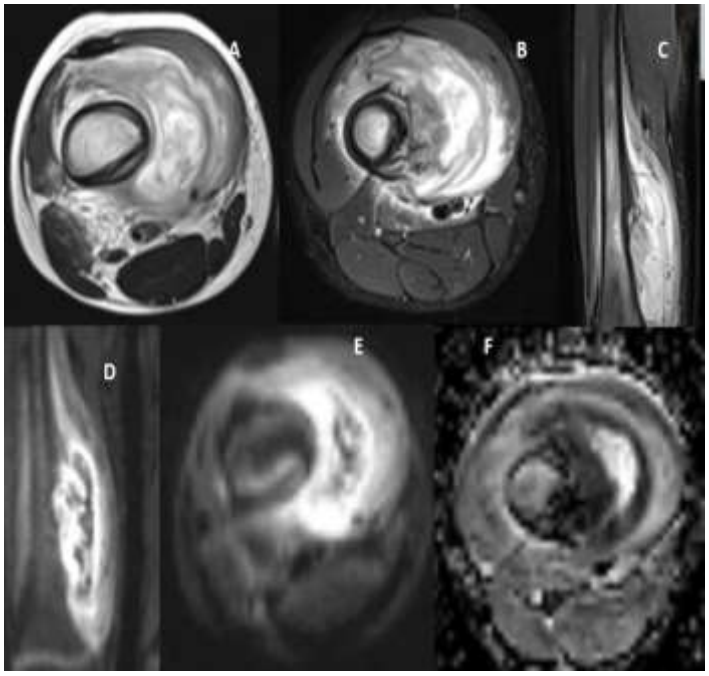

Figure- 8: A case of primary bone lymphoma involving distal diaphysis of femur in a 7-year-old male patient; A-T2 axial section showing lamellated and Codman's type of periosteal reaction along mid and distal diaphysis of left femur with adjacent large heterogeneously hypointense soft tissue component; B and C –STIR axial and coronal sections showing similar finding periosteal reaction along mid and distal diaphysis of left femur with adjacent large heterogeneously hyperintense soft tissue component-s/o necrosis in the centre of soft tissue component; D,E and F- Diffusion weighted imaging axial and coronal sections(D,E) showing restriction of the periphery of the soft tissue component and the necrosis in the centre. ADC map axial section is showing reversal with mean ADC value of 0.9x10^{-3} mm^{2}/s on DWI. On HPE proven to be primary bone lymphoma.

Nagata et alwho studied usefulness of the apparent diffusion coefficient for differential diagnosis states, malignant lymphomas showed characteristically low ADC values because of their high cellularity and nucleocytoplasmic ratio. Lymphomas have a high signal intensity on DW images and low ADC value (11).

We had only 3 cases of skeletal metastases. They were altered signal intensity lesions in the form of T1 hypo T2 heterogeneously hypointensity, STIR heterogeneously hyperintensity.Periosteal reaction was noted predominantly involving epi-metadiaphysis of long bones (humerus, femur). On conventional MRI both cases were correctly diagnosed with 100% sensitivity for diagnosis in known cases of carcinoma rectum and carcinoma cervix. On DWI shows restriction with one of the cases showing low mean ADC of $0.9x10^{-3}mm^2/s$ suggesting malignant lesion (Figure 9), another case with mean ADC $1.8x10^{-3}mm^2/s$.This is similar to study done by Padhani showed that 95th percentile for ADC values in bone metastases was $1.21x10^{-3}mm^2/sec$ and that using a cut off value of $0.77x\ 10^{-3}mm^2/sec$ resulted in a sensitivity of 85% and specificity of 90% differentiating marrowinfiltration from normal marrow (12).

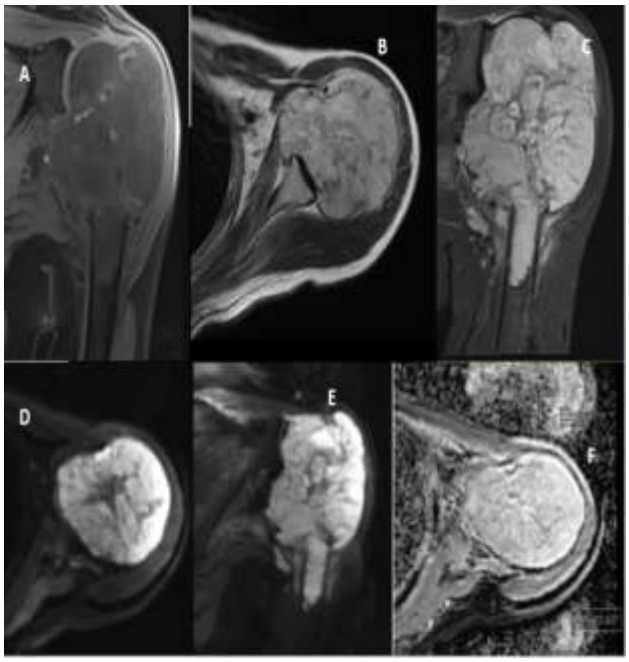

Figure-9: A case of bony metastasis to proximal epi-metaphysis humerus in a known case of Colo-rectal carcinoma (45 year old male patient); A-T1 axial section shows large expansile heterogeneously hypointense lesion with cortical break on postero-lateral aspect of lesion; B and C -T2 and STIR axial sections shows large expansile heterogeneously hyperintense lesion with cortical break on postero lateral aspect of lesion; D ,E and F -Diffusion weighted imaging axial and coronal sections showing restriction and ADC map axial sections showing reversal in part of lesion with mean ADC value of $1.8x10^{-3}$ mm^2/s. On HPE proven to be bony metastasis in a known case of Colo-rectal carcinoma

In total 2 infectious bone lesion cases, 50% (1 case) of them showed diffusion restriction,1 show partly restriction. Anuradha Rao et al statethat Osteomyelitis had lowest ADC values in benign lesions. There was significant difference in mean ADC values with respect to different benign lesions (9). However,in our study had 2 cases of osteomyelitis, which showed high ADC values ($2.5x10^{-3}mm^2/s$ and $1.9x10^{-3}mm^2/s$) respectively.

In our study p value of 0.001 for average mean ADC ($1.53X10^{-3}mm^2/sec$)to differentiate benign from malignant tumor is statistically significant. There is overlap of mean ADC of all benign lesions above ($1.53X10^{-3}mm^2/sec$ except GCT dueto its large giant cell contents.All malignant tumors had ADC below $1.53X10^{-3}mm^2/sec$. However, CS had high ADC due to its high mucin contents,myxoid matrix andlow collagen in the tumor.

IV. CONCLUSIONS

Malignant tumors are more common than benign due to underestimation of benign tumors. GCT is more common in benign and OS in malignant category. All benign bone tumors and tumor like lesions have high ADC except GCT due to the excess presence of spindle cells andmultinucleated giant cellsand less of extracellular space.All malignant tumors have low ADC and lowest in EWS andlymphoma due to small round cells having low extracellular space.CS have high ADC due to chondroid forming areas with myxoid matrix and high-water content. Hence DWI and ADC value should always be analysed along with conventional MRI sequences.The average mean ADC $1.53X10^{-3}mm^2/sec$ used to differentiate benign from malignant tumor was statistically significant in our series.

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