

Role of Time Intensity Curve in Dynamic Contrast MRI Evaluation of Soft Tissue Tumor

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A B S T R A C T

Introduction: Soft tissue tumors are commonly encountered in the oncologic practice and cause major concern to the patients as well as treating clinicians regarding its nature whether it is benign or malignant. Purpose of this study was whether dynamic contrast enhanced MRI is useful for differentiating benign and malignant lesions with use of time intensity curves or not.

Material and methods: The study population consisted of 32 consecutive patients having soft tissue mass, referred for Magnetic resonance imaging. The study group consisted of 21 male and 11 female patients, between the age of 12 to 72 years (mean age 39 years; Median age, 40 years). After routine MR examination dynamic contrast MRI was done with gradient echo sequence – 3D FLASH (Fast Low Angle Shot) technique. Images are analyzed by independently by two viewers. The dynamic contrast MRI data were analyzed with Mean Curve software available with the MR workstation. The images were visually analyzed for enhancement and circular region of interest were kept over the most enhancing part of the tumor. For comparison the region of interest were also kept over an adjacent uninvolved muscle.

Results: The study population consisted of 32 consecutive patients having soft tissue mass, referred for Magnetic resonance imaging. Among 13 benign tumors, 11 showed either type 2 or 1 curve and only 2 lesions showed type 3/4/5 curve. Among 19 malignant lesions 17 showed either of the three curve types 3, 4 /5 and 2 of them showed type 2 curve. Based on these type I & II curves were designated as benign type and type III, IV & V curves were designated as malignant types. Thus when the type I and II curves were taken as benign types and type III, IV & V curves were taken as malignant types the sensitivity and specificity approached 84.6% and 89.5% respectively. There were two cases in benign and two cases in malignant group showed a false positive and false negative for malignancy.

Conclusion: Time intensity curves when combined with routine MRI can improve the diagnostic performance in the prediction of malignancy. Type III, IV & V curves are predictors of malignancy and type IV is more specific.

Key words: Soft Tissue Tumor, Magnetic Resonance Imaging, Dynamic Contrast MRI, Time Intensity Curve, Benign Tumor, Malignant Tumor

INTRODUCTION

Among various imaging modalities available MRI is considered to be the modality of choice for imaging of soft tissue tumors because of its inherent soft tissue contrast and multiplanar imaging capability. Dynamic contrast enhanced MRI is physiologic imaging method which can monitor tumor enhancement in vivo and give information regarding tumor vasculature and interstitial space volume. Time intensity curve is one of the parameter in Dynamic contrast enhanced MRI which can predict tumor nature in vivo.

Soft-tissue neoplasms are defined as mesenchymal proliferations occurring in the extraskelatal, nonepithelial tissues of the body, other than viscera, coverings of the brain, and lymphoreticular system. Soft tissue sarcomas accounts

for 1 % of malignant soft tissue tumors⁴

Classification of soft tissue tumors

There are several comprehensive classification systems available in the literature. The one prescribed by the World Health Organization (WHO) classifies soft tissue tumors according to the tissue type they produce, including fat, fibrous tissue, and neurovascular tissue.¹ Each of the tissue categories are subclassified into benign, malignant and in some tissues intermediate groups.² The entire classification is more voluminous and most frequent tumors are illustrated below

WHO Classification of Soft-Tissue Neoplasms³

- Tumors of adipose tissue:**
Lipomas, liposarcoma

2. **Tumors and tumor-like lesions of fibrous tissue:**
Nodular fasciitis, Fibromatoses, Superficial fibromatoses, Deep fibromatoses, Fibrosarcoma
3. **Tumors of smooth muscle:**
Leiomyoma, Leiomyosarcoma
4. **Vascular TUMORS**
Hemangioma, Lymphangioma, Hemangioendothelioma, Angiosarcoma
5. **Fibrohistiocytic tumors**
Fibrous histiocytoma, Dermatofibrosarcoma protuberans, Malignant fibrous histiocytoma
6. **Chondro osseous tumors:**
Mesenchymal chondrosarcoma, Soft tissue chondroma, Extra skeletal osteosarcoma
7. **Tumours of skeletal muscle:**
Rhabdomyoma, Rhabdomyosarcoma
8. **Tumours of uncertain histogenesis:**
Synovial sarcoma, Alveolar soft-part sarcoma, Epithelioid sarcoma
9. **Peripheral nerve tumors (classified separately)**
Neurofibroma, Schwannoma, Granular cell tumor, Malignant peripheral nerve sheath tumors

There are several studies in the literature to evaluate the role of dynamic contrast MRI in oncologic imaging. A study done on breast lesions done by Buadu et al states that steepest slope of the time intensity curve is correlated with microvessel density and thereby invasive tumors.⁵

Teifke et al found that benign tumors have more uniform distribution of microvessels. They found that malignant breast tumors have higher ratio of microvessels in tumor periphery than center. This leads to high enhancement ratio of the periphery of malignant tumors⁶

Benign lesions are usually less than 5 cm in diameter, have well defined margin and homogenous signal intensity.⁷

Initially most of the studies using dynamic contrast enhanced MRI were done on breast cancer to differentiate benign and malignant lesions as well as to assess the response to chemotherapy.

Dynamic contrast MRI in Soft Tissue Tumors

Van Rijswijk et al. had done a study on 140 patients with soft tissue lesion, to evaluate the static and dynamic contrast enhanced MRI parameters for predicting malignancy. They concluded that the dynamic MR imaging improved the differentiation of malignant tumors from benign lesions⁸

In their study they found that there were 5 types of time intensity curves (TIC).

Types of Time intensity curves observed in soft tissue tumors:

Type I : No enhancement

Type II : Gradual enhancement

Type III : Initial rapid enhancement followed by plateau

Type IV : Initial rapid enhancement followed by washout

Type V : Initial rapid enhancement followed by sustained late enhancement

Above mentioned 5 types of Time intensity Curve shown Figure-1

In their study, they analyzed several parameters like tumor size, margin, peritumoral edema, signal intensity, invasion

of adjacent structures as well as dynamic contrast study to predict malignancy in soft tissue tumors. In their study they found that the Time intensity curve can predict malignancy in soft tissue tumors with P value of <.001 and inter observer agreement of 0.70. They conclude that time intensity curve can improve the diagnostic performance of MR imaging of soft tissue neoplasms

Tacikowska conducted a study on Dynamic MRI in soft tissue tumors and found that the tissue enhancement rate can be used to differentiate sarcomas from non-malignant lesions⁹

The purpose of this study was to study whether dynamic contrast enhanced MRI is useful for differentiating benign and malignant lesions with use of time intensity curves or not and to assess the diagnostic accuracy of time intensity curves in differentiating benign and malignant soft tissue tumors

MATERIAL AND METHODS

The Prospective study consisted of 32 consecutive patients having soft tissue mass, referred for Magnetic resonance imaging. The study group consisted of 21 male and 11 female patients, between the age of 12 to 72 years (mean age 39 years; Median age, 40 years).

The indications for MRI in these patients include assessment of local extent and characterization of the soft tissue mass. Obvious benign lesions like subcutaneous lipoma were excluded. Patients with benign lesions but atypical features and indeterminate lesions have undergone MRI with dynamic contrast. Two patients with giant cell tumour were also included in the study who were operated previously for giant cell tumour of the lower end of radius and later presented with soft tissue mass near the wrist.

Standard of reference was Histopathological results of the operated specimen. Histopathological confirmations were obtained for 31 patients aspiration cytopathology for 1 patient. Subjects were followed up for a period of 6 months.

Inclusion Criteria

1. All patients with soft tissue mass
2. Age between 7 to 70 years.

Exclusion Criteria

1. Mass near a moving structures like diaphragm
2. Patients with contraindication for MRI like patients having pacemaker, cochlear implants etc.
3. Claustrophobic patients.
4. Patients who underwent any chemotherapy or radiotherapy

Patient Preparation: No specific preparation needed.

Methods:

MR Imaging Protocol

All patients were studied with Philips 1.5 Tesla MR imaging units (archeiva)

Standard imaging sequences were obtained in two perpendicular planes with at least one in the axial plane.

Following imaging sequences were routinely used for the study.

1. T1 weighted Spin Echo (TR 400-600, TE 10-20)

2. T2 weighted fast spin echo (TR 2000- 4000, TE 80-120)
3. STIR (TR 4000-6000, TE60-100, IT 100-150msec)
4. T1 weighted with fat suppression (TR 400-700, TE 10-20)
5. Dynamic contrast enhanced MRI with Gradient echo sequence - 3D FLASH with Flip angle less than 90 degrees. (TR 29.2, TE 1.4 msec)
6. Axial Post contrast T1 weighted spin echo with fat suppression. (Static contrast enhanced MRI)

Field of view, matrix size, slice thickness and interslice gap were selected according to the size as well as location of the mass and the specific sequence. Choice of coils was also dependent on the specific anatomic site of the tumor.

The MR images were obtained in three planes with at least one in the axial plane. For lesions in sides of the body coronal plane was preferred whereas for those lesion located in anterior or posterior location sagittal plane was preferred.

Dynamic contrast MR imaging

After routine MR examination dynamic contrast MRI was done with gradient echo sequence – 3D FLASH (Fast Low Angle Shot) technique. There were totally 15 series of images taken over 5 minutes. The contrast was injected after first series. Fourteen series were taken during and after contrast injection. Pre contrast series was subtracted from the rest of the series during evaluation. The contrast used was Gadolinium with a dose of 0.05 mmol/kg bodyweight. The contrast was injected with hand via 18G IV cannula through antecubital vein at rate of 3-5 ml per minute. The contrast was followed by a 20 ml of saline flush.

Image analysis

The images obtained with nonenhanced MRI were analyzed with regards to the site, lesion size, tumor margin, Signal homogeneity in T1 & T2 and any neurovascular invasion. In case of extremity lesions the specific compartment of the lesion and its infiltration into adjacent compartment were evaluated.

Among various parameters in the unenhanced MRI we took mainly tumor margin and signal homogeneity to characterize the lesion.

Tumor with well defined margin with preservation of fat plane around the lesion was considered as having well defined margin and classified as benign lesion. Lesions having irregular and ill defined margin involving at least part of the circumference of the lesion was considered as having ill defined margin and classified as malignant lesion. Likewise tumors with homogenous signal intensity on T1 & T2 were classified as benign. Whereas lesions with inhomogeneous signal intensity in T1, T2 or both were classified as malignant. The dynamic contrast MRI data were analyzed with Mean Curve software available with the MR workstation. Time intensity curve depicts the signal changes in tissue in relation to time in a graphic form with time in the X axis and signal intensity in the Y axis.

The images were visually analyzed for enhancement and circular region of interest were kept over the most enhancing part of the tumor. For comparison the region of interest were also kept over an adjacent uninvolved muscle. Time intensity curve were obtained for each lesion and types of curves were

analyzed. The curves were classified into five types based on its early (first 2 minutes) and delayed enhancement. The patients were followed up and Histopathological confirmation was obtained.

STATISTICAL ANALYSIS

The frequency distribution of the above mentioned MR parameters (Tumor Margin, Signal homogeneity & Time intensity curve type) in the histopathologically proven benign group was compared with that of the malignant tumor group by using χ^2 test and P value was calculated.

The P value of <0.05 is considered as significant difference between two groups.

Sensitivity, specificity, Positive Predictive value & Negative Predictive value of each parameter were analyzed and compared.

RESULTS

Nineteen malignant lesions and 13 benign lesions made the basis of study. All malignant and 12 of the benign lesions were confirmed histopathologically and fine needle aspiration cytology for one benign lesion. The confirmed cases were 18 different pathological types of tumor / lesions and includes 11 types of malignant and 7 types of benign tumors.

Distribution of Non enhanced MRI parameters

frequency distribution of tumor margin & signal heterogeneity and their correlation with final diagnosis (malignant or benign). Among 18 lesions with well defined margin 11(61%) were benign and 7 (39%) were malignant. In the ill defined margin group 12 (86%) were malignant and 2 (14%) were benign.

Types of curves seen in the study

During the study 5 types of curve were seen. Among 5 types type II curve was most common and type I was the least common. Type I was seen in only one patient with lipoma.

Among 13 benign tumors, 11 showed either type 2 or 1 curve and only 2 lesions showed type 3/4/5 curve. Among 19 malignant lesions 17 showed either of the three curve types 3, 4 /5 and 2 of them showed type 2 curve. Based on these type I & II curves were designated as benign type and type III, IV & V curves were designated as malignant types. Above mentioned Distribution of TIC among the benign and malignant lesions in our study were shown in the Table 1.

Thus when the type I and II curves were taken as benign types and type III, IV & V curves were taken as malignant types the sensitivity and specificity approached 84.6 % and 89.5 % respectively. There were two cases in benign and two cases in malignant group showed a false positive and false negative for malignancy.

Histo pathologically proven case of malignant pleomorphic

	Benign	Malignant	
TIC 1&2	11	2	13
TIC 3,4,5	2	17	19
	13	19	

Table-1: Distribution of TICs among benign and malignant lesions

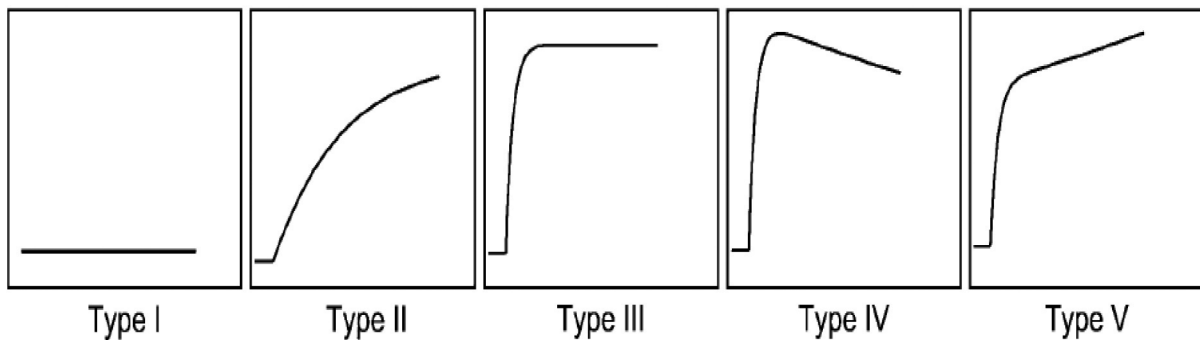


Figure-1: Shows 5 types of Time intensity curves in dynamic contrast enhanced MRI of Soft tissue tumours.

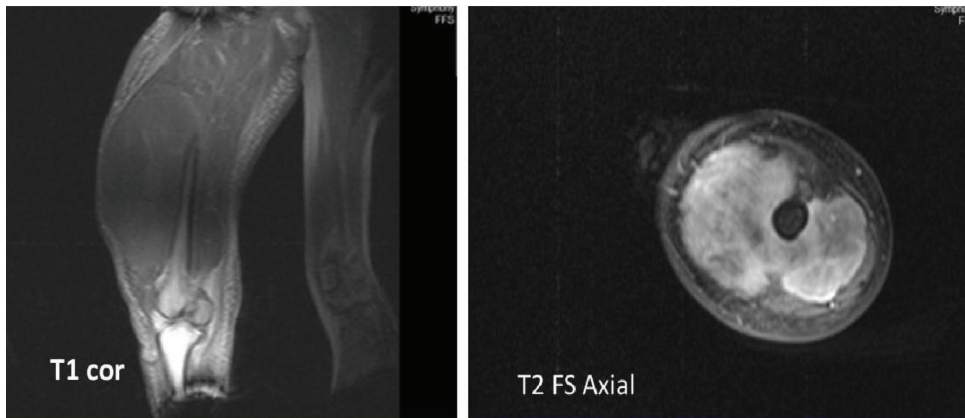


Figure-2: Shows large T1 hypointense & T2 heterointense lesion in the lateral aspect of the thigh. Part of the lesion shows ill defined border.

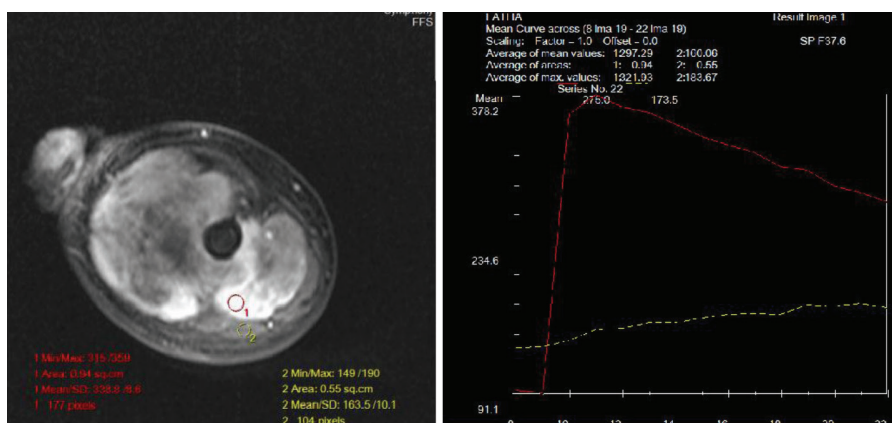


Figure-3: Dynamic contrast enhanced MRI with TIC analysis shows heterogeneous enhancement. The time intensity curve shows rapid initial enhancement and delayed washout. Type 4 curve. HPE: Malignant pleomorphic sarcoma.

sarcoma shown in the image (Figure 2 and Figure 3). T1 hypointense and T2 heterointense signal mass with illdefined margin noted in the lateral aspect of thigh (Figure 2). Dynamic contrast MRI shows heterogenous enhancing mass noted on contrast. Time intensity curve analysis for this tumour shows rapid enhancement and delayed washout and it corresponding to Type 4 Time intensity curve (Figure 3).

DISCUSSION

Non contrast MRI parameters taken in our study were tumor margin and signal heterogeneity of the lesion. When irregular margin of the tumor is used as criteria for malignant tumor it showed a sensitivity of 85% and specificity of 63% with P value 0.02.

Signal heterogeneity could be due to various causes like tumor hemorrhage, liquefaction, necrosis and indicate the lesion as malignant. When signal heterogeneity of the lesion is considered as a criteria the sensitivity is 69% and specificity is 79% with P value of 0.01. The low sensitivity could be due to the fact that malignant lesions show necrosis, hemorrhage only after they attained a large size.

Both of these parameters were useful because their P values are < 0.05. These results are consistent with the study done by van Rijswijk et al. They studied 67 benign and 73 malignant soft tissue tumor and found that various MRI parameters are useful for predicting malignant lesions and tumor margin & signal heterogeneity are among them. They found P value of 0.003 for tumor signal intensity and 0.007 for tumor margin

and adjacent soft tissue edema.⁸ But their sensitivity and specificity are low and less than 80%.

While using Time intensity curves the sensitivity and specificity were 85% and 89% respectively. Thus when dynamic contrast enhanced MRI is added to routine MRI it improved the diagnostic accuracy.

One research study on 100 patients of breast lesions (64 malignant, 36 benign) concluded that On TIC, TTP (time to peak) has been the only discriminating factor. When threshold for carcinoma has been set at $TTP \leq 2$ min, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy have been 36, 100, 100, 43, and 57% respectively. On relative TIC, accuracy of TTP has increased to 89%. Area under the ROC curve for TTP has improved from 0.77 for TIC to 0.86 for relative TIC ($p < 0.05$). WO ratio (Washout ratio) has become a second discriminating factor on relative TIC with more washout in malignant lesions ($WO = 41 \pm 32$) than benign lesions ($WO = 11 \pm 19$) ($p < 0.05$). PE (peak enhancement) and S (initial enhancement slope) were not statistically significant on TIC or relative TIC¹⁰

Mohamed Ahmed Youssefa et al, study of 27 breast mass lesions, DCE-MRI time signal intensity curve revealed 3 lesions showed progressive raising curve (type I curve), by histopathology the 3 lesions were benign. 9 lesions showed plateau curve (type II curve), all the 9 lesions were benign. 15 lesions showed rapid wash out (type III curve) all proved by histopathology as malignant. This is comparable with many studies that reported the importance of the curve shape in differentiating between malignant and benign lesions.¹¹

Lavini Cristina et al, in this article evaluated all the literature which makes use of TIC shape analysis in tissues other than breast, discuss the results, highlight the possible shortcomings, and suggest directions for future research and concluded in that article we could find agreement that a prevalence of a rapidly growing, rapidly washing out TIC shape remains consistently a mirror of malignancy in tumors and of activity in rheumatoid arthritis, the latter being a pathology where TIC shape analysis seems to be particularly successful.¹²

Dynamic contrast enhanced MRI has improved the diagnostic performance of MRI in our patients when compared with non enhanced MR parameters alone. There were some differences in the occurrence of type of time intensity curve in benign and malignant groups.

Malignant lesions generally show more contrast enhancement than benign lesions. But few benign lesions like vascular lesions may show high contrast enhancement and mimic malignant lesions. Likewise few malignant lesions like necrotic mass may show lesser contrast enhancement thus necessitating other methods to better characterize the lesion. Dynamic contrast MRI by using time intensity curves allows to predict the enhancement kinetics in early and delayed phase semi quantitatively.

Malignant tumors have leaky vascular channels and low interstitial space and thereby shows steep enhancement in early phase and plateau or washout in the late phase. Benign lesions having slow perfusion and wide interstitial space will show late enhancement. Zhang, Y. et. al study of Dynamic contrast MRI in 45 patients

with soft tissue tumour concluded that The preliminary findings suggested that semiquantitative and quantitative parameters of DCE-MRI enabled differentiation between benign and malignant soft-tissue tumors. The values of TTP (Time to peak) were lower, while those of MAX Conc, AUC-TC (area under curve of time concentration curve) and MAX Slope were higher, for malignant soft-tissue tumors than for benign tumors.¹³

Park MY et al, Dynamic contrast MRI study in 13 soft tissue tumours concluded that The steepest slope and early relative enhancement has potential for differentiating benign from malignant soft tissue tumors. Short length DCE-MRI protocols may be adequate for the purpose, compared to the longer length protocols.¹⁴

In our study malignant tumors (17/19) showed type III and IV curves more commonly. Type V curve was seen in only 2 patients. Two lesions which showed type III curve were finally proven to be benign lesions. One lesion was angiomyxoma and the other one was granulomatous lesion. The probable explanation for this fast enhancement is relatively increased vascularity in some inflammatory lesions. No benign lesions showed type IV or V curve. Thus when only type IV & type V were considered the test becomes more specific but the sensitivity will be considerably low. But type V curve occurs only in 2 patients. So type IV curve could be considered more specific for malignant lesions. This is consistent with the result of the study on breast tumor by Katharina et al. In their study they concluded that Type III curve of the breast tumors is the strong indicator of malignancy.¹⁵ This curve having fast initial enhancement and washout phase is similar to the type IV curve of our study.

Two lesions which showed type II curve were finally turned out to be malignant. Both were histologically proven spindle cell tumor. Few malignant tumors show relatively low vascularity in the early stage due to biological variations. This could be the reason for slow enhancement of the lesion with benign type of curve.

As reported by Konec et al., there is some overlap of tumor vascularity exists between benign and malignant tumors which will cause false negative and false positive results during dynamic contrast enhanced MRI¹⁶

Advantages

1. The study is simple and available with most MR systems
2. Requires only 5 -6 minutes extratime.
3. When added to the routine MRI it will improve the diagnostic performance
4. In addition time intensity curves will guide the site of biopsy for better diagnostic yield.
5. Time intensity curves can be used for assessing the response to chemotherapy thereby useful in follow up.

Limitations

1. There is some overlap between the vascularity of the benign and malignant lesions which is the cause for false positive and false negative results.
2. Cases included in the study were only referral cases. So true incidence and frequency of the tumors could not be calculated.
3. The study group was a heterogeneous group consisting

- of different types of soft tissue tumors.
4. In our study only limited number of benign lesions were studied. But when real incidence is considered benign lesions are 100 times more common than malignant lesions.
 5. Only 32 patients were included in the study. This sample size may be small when the vast types of tumor of soft tissue are considered. So findings in this study need further confirmation with large study.

CONCLUSION

Time intensity curves when combined with routine MRI can improve the diagnostic performance in the prediction of malignancy in soft tissue tumors. Type III, IV & V curves are predictors of malignancy and type IV is more specific. Dynamic contrast enhanced MRI has a potential role in evaluating the response to chemotherapy and guiding the biopsy.

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