Dynamic Contrasted MR Imaging in Differentiation of Recurrent Malignant Soft Tissue Tumor from Posttreatment Changes

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Objective: *To investigate dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) in term of differentiation recurrent malignant soft tissue tumor (MSTT) from post-treatment changes.*
Material and Method: *DCE-MRI was performed in consecutive patients in two-year periods to differentiate recurrent MSTT from post-treatment (surgery, radiotherapy, chemotherapy) changes. The steepest slope (SS) ratio between the artery and the lesion, sensitivity, and specificity were calculated.*
Results: *Thirty-five DCE-MRI studies were performed in 30 patients, which included 14 males and 16 females with an age range from 12 to 71 years (median 45.81 year). Thirteen were with recurrence and 22 were with post-treatment changes. The SS ratios were ranged from 0.66 to 29.15. The lesions with the SS ratio > 9.28 were all benign at follow up of at least two months, whereas those with SS ratio < 1.05 were all recurrent tumors proven by biopsy or surgery. Overlapping occurred when the SS ratios > 1.05 but < 9.28 in which the recurrence was 42.31%. The chance of having recurrence rather than post-treatment changes was approximately two and five times in patients with the ratio of 5.07 and 1.55, with the specificity of 54.55% and 90.91%, respectively.*
Conclusion: *The SS ratio between the artery and the lesion has limitations to differentiate recurrent MSTT from post-treatment changes. It is useful when the ratio is less than 1.05 (malignant) or more than 9.28 (benign). The chance of having recurrence rather than post-treatment changes was approximately two and five times in patients with the ratio of 5.07 and 1.55, respectively. The less value the ratio is, the more possibility to be recurrent tumor.*

Keywords: *Magnetic resonance (MR), Dynamic, Dynamic contrasted, Malignant, Soft tissue tumor, Recurrent*

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Malignant soft tissue tumors (MSTT) tend to have local recurrence after treatment[1-3] that includes surgery, radiotherapy, and chemotherapy. Early detection of local recurrence improves the patients' prognosis. Magnetic resonance imaging (MRI) is the modality well documented to evaluate MSTT after treatment. Occasionally problems exist in differentiation of recurrent tumor from post- treatment changes, which include granulation tissue, postoperative fibrosis, fluid collection, and post radiation reaction. Recurrent tumors usually show high signal intensity on T2-weighted (T2W) pulse sequence and enhancement after gadolinium administration. Unfortunately, post-treatment changes, in some instances, also show such characteristics[4,5]. Previous studies demonstrated that dynamic contrast enhanced MRI (DCE-MRI) help discriminate tissues of different vascularity[6-12]. Therefore, it was also used to differentiate recurrent tumor from post-treatment changes in several body parts such as breast, head and neck, along with those in the gynecological, genitourinary, gastrointestinal, and musculoskeletal systems with varying results[13-19].

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The authors conducted the present study to see how effective the DCE-MRI, by using ratio of the steepest slope (SS) of the artery and the lesion, can help differentiate MSTT from post-treatment changes.

Material and Method

The present study was approved by the Institutional Review Committee of Ramathibodi Hospital. The Ethic number is ID 10-51-55.

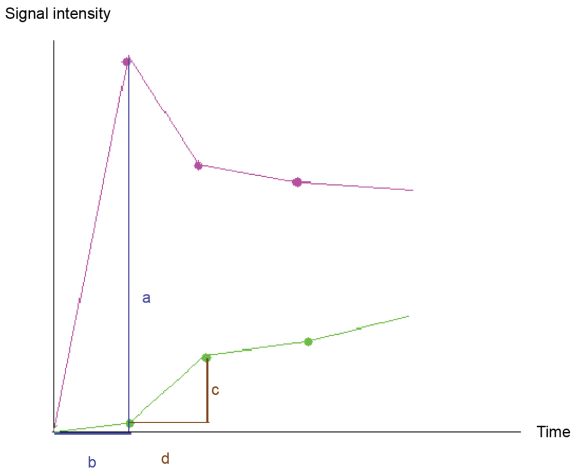
During the consecutive two years period, 36 patients who were treated for MSTT were sent to the Department of Radiology, Faculty of Medicine, Ramathibodi Hospital to perform 42 DCE-MRI to follow-up after treatment and to evaluate whether they had recurrent tumor. The treatments include surgery, radiotherapy and chemotherapy.

MRI was performed with 1.5 Tesla MR unit (Signa HDe MRi/CVi, General Electric [GE] Medical system, Milwaukee, WI) by using torso, body, cardiac or surface coils according to the site and size (area) of the suspected lesion. Static MRI was performed in axial, coronal and sagittal planes. Non-contrast study consisted of T1W (TR 400-600, TE 7.9-14.1 msec), T2W (TR 2580-5020, TE 42.8-86.9 msec), and T2W with fat suppression (T2FS) or STIR pulse sequence; the FOV used was 12 x 12 cm to 47.9 x 47.9 cm, matrix 256 x 160 to 320 x 224 and thickness of 2.0-12.0 mm. Dynamic studies were obtained following the preparation of intravenous line at the antecubital vein. The contrast agent used was 0.1 mmol/kg gadopentetate dimeglumine (Magnevist; Bayer-Schering, Berlin, Germany), given intravenously via the automatic injector (Spectris, Medrad, Warrendale, USA) at a rate of 3 ml/second and followed by 30-ml saline flush. The scanning technique was 3D-fast spoiled gradient-echo (FSPGR) using TR 4.6-8.8 msec, TE 1.4-4.2 msec, flip angle 10-15 degree, thickness 0.75-5.0 mm, FOV 12 x 12 cm to 47.9 x 47.9 cm and matrix 256 x 160 to 320 x 224. Sixteen phases of post contrast scan were performed with 25 seconds for each phase.

Image analysis

The images were analyzed by two radiologists (one musculoskeletal radiologist with 15-year experience and one second-year fellow in Body Imaging) with consensus agreement, without information about the original histopathologic findings or result of the clinical follow-up.

Post-contrast dynamic images were subtracted from the pre-contrast images by using subtraction function of software (Advantage workstation 4.0 ultra 60, GE medical system, Milwaukee, WI). The regions of interest (ROI) being round or ovoid in shape, not less than 2 mm^2 each, manually placed on the suspicious lesion, the artery, normal bone marrow, and normal-looking muscle in the same section in equal size. The criteria of suspicious lesion were a) hypersignal intensity on T2W, or b) thick rim, patchy, or nodular-like enhancement. The arterial perfusion slopes were created by the same software. The steepest slope (SS) of the suspicious lesion was compared to that of the artery, and the ratio was calculated (Fig. 1). Diagnosis of recurrent tumor was by histopathology (biopsy or excision); and of post-treatment changes was by biopsy, or clinical or imaging follow-up by not less than two months.



Ratio of SS of the artery and the lesion = a/b:c/d

Fig. 1 Time-signal intensity curve demonstrates how to calculate the ratio of SS of the artery and the lesion

Data were described using mean (or median where appropriated) and frequency for continuous and categorical data, respectively. Receive operating characteristic (ROC) curve analysis was applied to calibrate the cut-off point of SS ratio in classifying tumor recurrence. Statistical analysis was performed using STATA 11.0 (STATA Corp., College Station, Texas). P-value less than 0.05 was considered as statistical significant.

Results

Among the 36 patients with 42 DCE-MRI performed two patients lost follow-up, one patient was sent to radiotherapy before biopsy therefore there was no histology and three patients with 4 DCE-MRI were from another hospital who came here only for MRI

Table 1. Underlying diseases

Pathology	Number of patient
Liposarcoma	7
Rhabdomyosarcoma	5
Synovial sarcoma	3
Squamous cell CA	2
Malignant spindle cell tumor	2
PNET	2
Leiomyosarcoma	2
Malignant rhabdoid tumor	1
Malignant peripheral nerve sheath tumor	1
Malignant melanoma	1
Dermatofibrosarcoma protuberans	1
Malignant fibrous histiocytoma	1
Fibrosarcoma	1
Soft tissue osteosarcoma	1

evaluation, resulted in six patients and seven studies excluded. Finally, 30 patients, 14 males and 16 females with age range of 12 to 71 years (mean 45.81 year) with 35 DCE-MRI were included. The underlying diseases are shown in Table 1.

Thirteen DCE-MRI in 13 patients were proven pathologically as having recurrent tumor and 22 DCE-MRI in 17 patients had post-treatment changes. The median of SS ratios was 4.06 with a range of 0.66 to 29.15 (Table 2). The lesions with the SS ratio < 1.05 were all recurrent tumors (n = 2) (Fig. 2) whereas those with SS ratio > 9.28 were all benign at follow-up of at least 2 months (n = 7) (Fig. 3). Overlapping occurred when the SS ratios > 1.05 but < 9.28 (n = 26) in which the recurrence was found in 42.31%. The ROC curve analysis suggested two cut-off points that may be used for classifying recurrence from post-treatment changes (benign lesion) which were 5.07 and 1.55. The chance of having recurrence rather than post-treatment changes was approximately two and five times in patients with the ratio of 5.07 and 1.55, with specificity of 54.55% and 90.91%, respectively (Table 3). The 95% confidence interval (CI) was 0.64-0.94. The ROC area was 0.7937 with standard error of 0.0783 (Table 3, Fig. 4).

Table 2. Ratio of the SS of the artery and the lesion with clinical/imaging follow-up (arranged in order from minimal to maximal value)

Ratio of the SS of the artery and the lesion	Follow-up
0.6572	Recurrent tumor
1.0474	Recurrent tumor
1.069	Post treatment change
1.1633	Recurrent tumor
1.4628	Recurrent tumor
1.5223	Post treatment change
1.5352	Recurrent tumor
1.5477	Recurrent tumor
1.8841	Post treatment change
2.1098	Recurrent tumor
2.1829	Recurrent tumor
2.4545	Post treatment change
2.7317	Recurrent tumor
2.9086	Post treatment change
3.2414	Post treatment change
3.3473	Post treatment change
3.8267	Post treatment change
4.0637	Recurrent tumor
4.1724	Post treatment change
4.4665	Post treatment change
4.6544	Recurrent tumor
5.0709	Recurrent tumor
5.5154	Post treatment change
5.7943	Post treatment change
6.9668	Post treatment change
8.1347	Post treatment change
8.6785	Post treatment change
9.2766	Recurrent tumor
9.7231	Post treatment change
10.9283	Post treatment change
11.1428	Post treatment change
12.4819	Post treatment change
15.1856	Post treatment change
15.5465	Post treatment change
29.1481	Post treatment change

SS = steepest slope

Discussion

MRI is considered the best modality for tumor imaging; which includes detection, diagnosis, local staging, monitoring responses to varying treatment modality and follow-up[9]. At the time of follow-up, differentiation between recurrent tumor and post-treatment changes is a challenging task for MRI. In certain circumstances, the bright signal intensity on T2W images along with its configuration, or even the static contrast enhanced imaging, does not properly differentiate these two entities. This is because both the recurrence and post-treatment changes, when using static contrast enhanced imaging, will be enhanced in a similar way once the concentration of contrast medium has reached the equilibrium state between plasma and interstitial space[5].

Table 3. Cut-off point (SS ratio) to classify recurrence from posttreatment changes

Cut-off point	Sensitivity	Specificity	Classified	LR^+	LR^-
(≥ 8.1347)	92.31%	36.36%	57.14%	1.4505	0.2115
(≥ 6.9668)	92.31%	40.91%	60.00%	1.5621	0.1880
(≥ 5.7943)	92.31%	45.45%	62.86%	1.6923	0.1692
(≥ 5.5154)	92.31%	50.00%	65.71%	1.8462	0.1538
(≥ 5.0709)	92.31%	54.55%	68.57%	2.0308	0.1410
(≥ 1.5477)	46.15%	90.91%	74.29%	5.0769	0.5923
(≥ 1.5352)	38.46%	90.91%	71.43%	4.2308	0.6769
(≥ 1.5223)	30.77%	90.91%	68.57%	3.3846	0.7615
(≥ 1.4628)	30.77%	5.45%	71.43%	6.7692	0.7253
(≥ 1.1633)	23.08%	95.45%	68.57%	5.0769	0.8059

Obs	ROC area	Std. err.	Asymptotic normal (95% conf. interval)
35	0.7937	0.0783	0.64018-0.94723

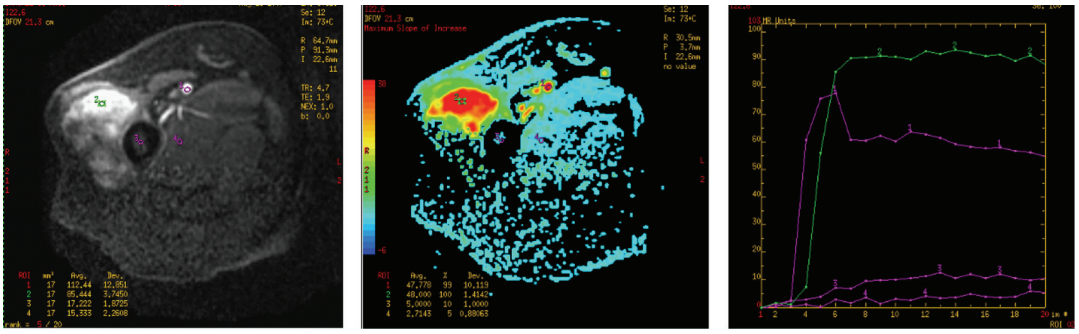


Fig. 2 Recurrent tumor. A 71-year-old female with high-grade pleomorphic rhabdomyosarcoma at the right thigh underwent wide excision without post-operative radiation. She developed palpable mass at the surgical bed, which was proved to be recurrent tumor (SS ratio = 1.0474, pink curve = artery, green curve = lesion)

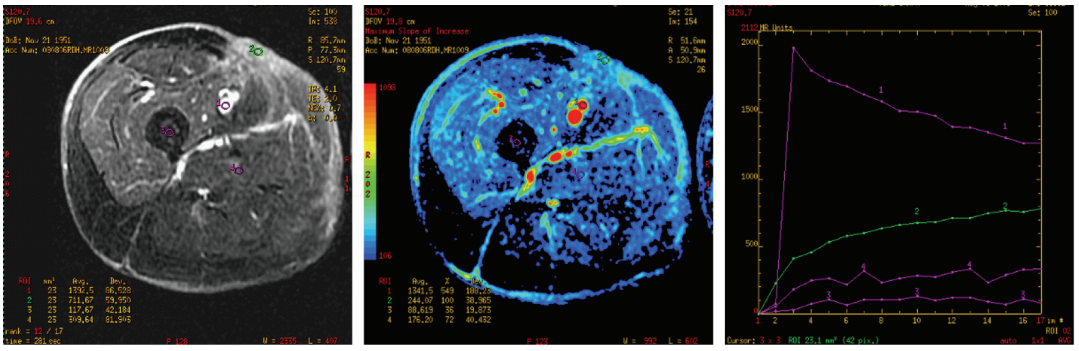
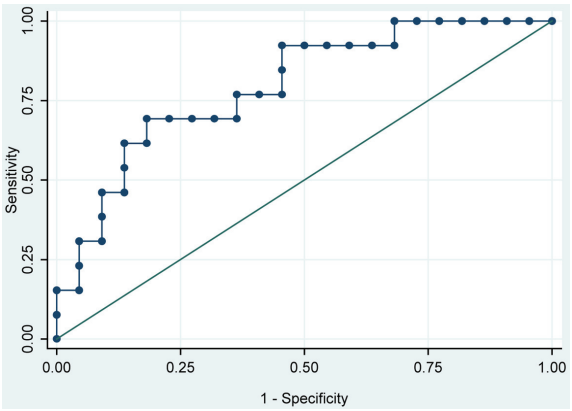


Fig. 3 Post-treatment changes. A 57-year-old male with malignant melanoma of the right thigh presented with metastasis at the right inguinal region. No evidence of local recurrence noted at the primary tumor site (SS ratio = 8.1347, pink curve = artery, green curve = lesion)



Area under ROC curve = 0.7937 ± 0.0783

Fig. 4 Calibrating the cut-off point of SS ratio for classifying tumor recurrence: The ROC curve analysis

Recurrent tumors have tumor angiogenesis resulting from many angiogenetic growth factors. They promote new capillary formation to supply the hypoxic and acidic parts of growing tumor by recruiting, activating and stimulating endothelial cells[20]. Gadopentetate dimeglumine, which is a low molecular weight gadolinium-containing compound, can rapidly diffuse in the extravascular extracellular space at a rate determined by the permeability of the microvessels and blood flow. DCE-MRI is therefore useful in this circumstance because it can provide information about tissue vascularization and perfusion[5,12,16,21,22]. Unfortunately, radiation therapy can induce neovascularization and consequently there will be increased perfusion in the irradiated area, where ingrowth of young granulation tissue can be observed microscopically[4,23]. These processes can cause increased steepness of the slope, resulted in differentiation of post-treatment changes from tumor recurrence being difficult if looking only at the steepness itself. In addition, post surgical status also can induce tissue reaction causing increased steepness of the slope as well. This was the reason why the authors tried to compare the slope of the lesions to those of the arteries, by using the arterial slope as the reference, in attempt to differentiate post-treatment changes from tumor recurrence.

Data from DCE-MRI have been presented in qualitative and quantitative analysis. In quantitative analysis, the measurements are maximum enhancement, rate of early enhancement, area under the curve, time to peak, and initial slope of increase. Vanel et al[4] and Rijswijk et al[12] reported that rapid initial enhancement by DCE-MRI related to recurrent malignant soft tissue tumor. Verstraete et al[24] studied the first-pass images that depicted tissue vascularization and perfusion using DCE-MRI. They reported that when using slope value of 45% per second, there was 77% specificity for malignant potential. The present study using SS ratio of the artery and the lesion found that the chance of having recurrence rather than post-treatment changes was approximately five times in patients with the ratio of 1.55 with specificity of 90.91%. However, wide range of overlapping existed, which corresponded to previous reports[24-26]. Recurrent tumor with relatively flat slope values within the range of benign lesions could be due to highly necrotic tumors, late tumor recurrences after radiation therapy or chemotherapy. The authors' findings therefore, suggested that the SS ratio provided information about the vascularization and perfusion of the lesion, but it was limited in differentiation benign from malignant lesion[24]. It would be better to use the SS ratio in conjunction with other imaging findings to narrow down the possibility.

The limitation of the present study was due to the fact that the MSTT can occur in any part of the body. The authors therefore had to use varying types of receptor coil while performing imaging, however, the authors tried to keep the imaging parameters close to the protocol as much as possible. In addition, the referenced artery in each case was different according to the body part studied. There may be some differences regarding the diameter of the artery and the velocity of blood flow. This was an unavoidable limitation. The authors performed the study by using the artery in the same axial image as the lesion in all cases. If there were more than one artery in one axial image, the authors reviewed the entire study and chose the artery that was most likely to supply the lesion.

In conclusion, the ratio of SS of the artery and the lesion has limitation to differentiate recurrent MSTT from post-treatment changes. It is useful when the ratio is less than 1.05 (malignant) or more than 9.28 (benign). The chance of having recurrence rather than post-treatment changes was approximately two and five times in patients with the ratio of 5.07 and 1.55, respectively. The less value the ratio is, the more possibility to be recurrent tumor.

Potential conflicts of interest

None.

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Dynamic contrast enhanced MRI ในการวินิจฉัยแยกระหว่างการกลับเป็นใหม่ของมะเร็งเนื้อเยื่ออ่อนกับการเปลี่ยนแปลงหลังการรักษา

สุภนีวรรณ เชาว์วิศิษฐ, ปัญจมาศ ไตรพรดีประเสริฐ, นิยตา จิตรภาษย์, อมรินทร์ ทักขิญเสถียร, อดิศักดิ์ นารถธนะรุ่ง, ธันย์ สุภัทรพันธุ์, พิมใจ ศิริวงศ์ไพรัช

วัตถุประสงค์: *เพื่อศึกษาว่า Dynamic contrast enhanced MRI (DCE-MRI คือ การตรวจด้วยเครื่องสร้างภาพจากคลื่นแม่เหล็กไฟฟ้าโดยวิธีการฉีดสารประกอบ gadopentetate dimeglumine ไปพร้อม ๆ กับการ scan) จะช่วยวินิจฉัยแยกระหว่างการกลับเป็นใหม่ของมะเร็งเนื้อเยื่ออ่อนกับการเปลี่ยนแปลงหลังการรักษาได้หรือไม่*

วัสดุและวิธีการ: *ได้ทำการตรวจด้วยวิธีการ DCE-MRI ในผู้ป่วยทุกคนที่มีข้อบ่งชี้เป็นระยะเวลาติดต่อกัน 2 ปี เพื่อวินิจฉัยแยกระหว่างการกลับเป็นใหม่ของมะเร็งเนื้อเยื่ออ่อนกับการเปลี่ยนแปลงหลังการรักษา (การผ่าตัด, รังสีรักษา, เคมีบำบัด) slope ที่ชันที่สุดของหลอดเลือดแดง และของรอยโรคต่อหนึ่งหน่วยเวลา (ซึ่งหมายถึงการที่เลือดเคลื่อนไหวในหลอดเลือดแดงและการที่เลือดเข้าไปเลี้ยงรอยโรคตามลำดับ) ได้ถูกนำมาคำนวณหาอัตราส่วน (Steepest slope ratio [SS ratio]), ความไว, ความจำเพาะ และค่าทางสถิติที่จะช่วยแยกทั้งสองภาวะออกจากกัน*

ผลการศึกษา: *มีการตรวจ DCE-MRI 35 ครั้ง ในผู้ป่วย 30 ราย (ชาย 14 คน หญิง 16 คน) ช่วงอายุ 12-71 ปี (ค่าเฉลี่ย 45.81 ปี) ที่สามารถติดตามผลได้ พบเป็นการกลับเป็นใหม่ของมะเร็งเนื้อเยื่ออ่อน 13 ครั้ง การเปลี่ยนแปลงหลังการรักษา 22 ครั้ง SS ratio มีค่า 0.66-29.15 รอยโรคที่มีค่า SS ratio น้อยกว่า 1.05 พบเป็นการกลับเป็นใหม่ของมะเร็งทั้งหมด ในขณะที่รอยโรคที่มีค่า SS ratio มากกว่า 9.28 พบเป็นการเปลี่ยนแปลงหลังการรักษาทั้งหมด ความคาบเกี่ยวเกิดขึ้นเมื่อค่า SS ratio มากกว่า 1.05 แต่น้อยกว่า 9.28 ซึ่งพบการกลับเป็นใหม่ของมะเร็งร้อยละ 42.31 โอกาสที่จะเป็นการกลับเป็นใหม่ของมะเร็งเปรียบเทียบกับการเปลี่ยนแปลงหลังการรักษาอยู่ที่ 2 และ 5 เท่าในผู้ป่วยที่มีค่า SS ratio 5.07 และ 1.55 โดยมีความจำเพาะร้อยละ 54.55 และ 90.91 ตามลำดับ*

สรุป: *DCE-MRI ด้วยเทคนิคที่ทำอยู่และการใช้ SS ratio มีข้อจำกัดในการวินิจฉัยแยกการกลับเป็นใหม่ของมะเร็งเนื้อเยื่ออ่อนกับการเปลี่ยนแปลงหลังการรักษา วิธีนี้จะเป็นประโยชน์เมื่อค่า SS ratio น้อยกว่า 1.05 (เป็นการกลับเป็นใหม่ของมะเร็งทั้งหมด) หรือมากกว่า 9.28 (เป็นการเปลี่ยนแปลงหลังการรักษาทั้งหมด) โอกาสที่จะเป็นการกลับเป็นใหม่ของมะเร็งเปรียบเทียบกับการเปลี่ยนแปลงหลังการรักษาอยู่ที่ 2 และ 5 เท่าในผู้ป่วยที่มีค่า SS ratio 5.07 และ 1.55 ตามลำดับ ค่า SS ratio ที่น้อยลงหมายถึงโอกาสที่จะเป็นการกลับเป็นใหม่ของมะเร็งมีมากขึ้น*