The importance of diffusion apparent diffusion coefficient values in the evaluation of soft tissue sarcomas after treatment

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Abstract

\textbf{Purpose}: In our study, we aimed to show the efficiency of diffusion-weighted images at different $b$-values and apparent diffusion coefficient (ADC) values in the differentiation of recurrent tumours from post-treatment tissue changes.

\textbf{Material and methods}: The conventional and diffusion magnetic resonance images (MRIs) of 42 patients operated for soft tissue sarcomas between June 2012 and March 2015 followed up with MRIs that were evaluated by 2 radiologists retrospectively: Diffusion MRIs were acquired at 4 different $b$-values ($50$, $400$, $800$, $1000$ $\text{s/mm}^2$). The lesions were classified according to conventional MRI findings as post-treatment changes and recurrent tumours.

\textbf{Results}: When the patient group with recurrent tumours was compared with the patient group with postoperative changes the ADC calculations were statistically significantly lower for the recurrent tumours at all $b$-levels ($p < 0.001$ for all $b$-levels). The sensitivity of $b$-50 values lower than $3.01 \times 10^3$ $\text{mm}^2/\text{s}$ in showing recurrent tumours was 100% and the specificity was 77.78%. The sensitivity of $b$-400 values lower than $2.1 \times 10^3$ $\text{mm}^2/\text{s}$ in showing recurrent tumours was 80% and the specificity was 96.3%. The sensitivity of $b$-800 values lower than $2.26 \times 10^3$ $\text{mm}^2/\text{s}$ in showing recurrent tumours was 100% and the specificity was 88.89%. The sensitivity of $b$-1000 values lower than $2 \times 10^3$ $\text{mm}^2/\text{s}$ in showing recurrent tumours was 93.3% and the specificity was 92.5%.

\textbf{Conclusions}: The ADC values obtained from diffusion-weighted images have high sensitivity and specificity in differentiating recurring soft tissue sarcomas during monitoring after treatment from postoperative changes.

\textbf{Key words}: MR imaging, diffusion-weighted magnetic resonance imaging, soft tissue tumours, recurrent sarcomas, posttreatment changes.

Introduction

Soft tissue sarcomas account for less than 1% of all adult malignancies [1,2]. Despite combined and aggressive treatment methods, including radiotherapy, chemotherapy, and surgical treatment, local relapse rates of soft tissue sarcomas are between 5 and 35% [2]. Most relapses develop within the first 2 years after surgery [3]. For this reason, postoperative follow-up must be done every 36 months with imaging. The lesion size, location, histological grade, surgical resection efficiency, and response to adjuvant treatments are important risk factors for the
development of local recurrence [2]. Benign changes like haematoma, seroma, fibrosis, and granulation tissue that develop in the operation lodge after surgical treatment and radiotherapy may confuse local recurrence on magnetic resonance image (MRI) scans. In cases where a definite differentiation is not possible, the clinical approach is MRI follow-up or evaluation with positron emission tomography [4-6]. Diffusion MRI is currently routinely used in radiology clinics to identify fibrosis and tumours; it is a non-invasive method that generates contrasted images of the molecular movement of water. The diffusion sensitivity may vary at different $b$-values of diffusion. Images with low $b$-values are less diffusion weighted and use lower gradients. The diffusion sensitivity is also affected by perfusion at low $b$-values. Higher $b$-value images are more diffusion weighted and have low signal-to-noise ratios. For a meaningful evaluation of diffusion MRIs, they must be obtained with at least 2 separate $b$-values. Mistakes in apparent diffusion coefficient (ADC) calculations can be prevented by obtaining more than one $b$-value [7,8]. There is no common consensus about the $b$-value and the number of different $b$-values required to be used in the MRI evaluations of the muscular-skeletal system.

In our study, we aimed to show the efficacy of diffusion-weighted images at different $b$-levels and ADC values in the differentiation of recurrent and residual tumours.

**Material and methods**

**Patient selection**

Fifty-six patients who had undergone surgery with the diagnosis of soft tissue sarcomas between June 2012 and March 2015 that were followed-up with MRIs were evaluated. After the surgery, 5 patients with positive surgical margins and residual disease, 5 patients with detected lung metastases, and 2 patients with a history of a second primary cancer (one was colon cancer, the other was papillary thyroid cancer) were excluded from the trial. In addition, 2 patients with a groin localized tumour and a hip prosthesis were excluded from the trial to avoid artifacts. Forty-two patients who underwent extensive resection and had clean surgical margins, who attended their MRI follow-ups at month 6 and later were included in the trial. The study was approved by our institutional review board, and all patients gave their informed consent. The patient MRI findings were re-evaluated by radiologists with 8 years of experience (BS) and 10 years of experience (EA) in musculoskeletal MRI, respectively. The signal characteristics, contrast enhancement patterns, locoregional distribution of the postoperative tissue areas, and suspicious lesions were evaluated. The haematoma, seroma, and areas of postsurgical or postradiotherapy soft tissue changes and the masses that may relapse were identified based on the study by Garner et al. according to the T1, T2, and contrasting patterns observed in the patients [6].Lesions hyperintense in T1-weighted and T2-weighted images that did not demonstrate significant contrast enhancement following IV contrast administration were classified as haematoma (Figure 1A-D); lesions with hypointense signal characteristics in T1-weighted images and hyperintense in T2-weighted images that did not enhance with contrast after IV contrast administration or contrasted peripherally were classified as seroma (Figure 1E-H); areas with hypointense signal characteristics in T1-weighted images and hyperintense in T2-weighted images that were mildly enhanced with contrast after IV contrast administration were classified as changes after operation and radiotherapy (Figure 1I-L); and lesions that were T1 hypointense, T2 hyperintense, and enhanced with contrast after IV contrast administration were classified as potential recurrent masses (Figure 1M-P, Figure 2, Table 1).

**Magnetic resonance imaging analysis and data collection**

All images were transferred to a workstation (Advantage Windows version 4.2_07, GE Healthcare) and the DWI sequence was post-processed with commercial software (FuncTool, GE Healthcare) to obtain ADC maps (black/white and colour, the latter with a Puh-thallium colour scheme, ranging from black, diffusion restriction, to red, no diffusion restriction). The ADC maps of each lesion were calculated using four $b$-values (50, 400, 800, and 1000 s/mm²). The scanner software provided the mean value within the ROI, which equaled the ADC value (multiplied by $10^{-3}$).

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In diffusion-weighted images, 1 cm² ROIs were placed in postoperative tissue areas with hyperintense areas in T2-weighted images and 3 different areas with an appearance suspicious of recurrent masses, and the mean ADC values were calculated. ADC calculation was not done in the hypointense areas in T1-T2-weighted images and were considered as fibrosis. After MRI examinations, biopsies were obtained from the suspicious lesions with wire localization biopsies in 2 patients, and 13 patients underwent total excision. The mean diameter of the lesions excised was measured as 4.3 ± 1.5 cm (range 2-8 cm). Patients regarded as post-treatment tissue changes according to the T1, T2, and contrasting characteristics were followed up for a mean period of 17.8 ± 6.7 months (range, 8-32 months).
Figure 2. In month 12 magnetic resonance imaging (MRI) follow-up of a 67-year-old patient operated for a liposarcoma located in the proximal of the groin the lesions (A) hypointense in T1-weighted images, (B) hyperintense in T2-weighted images and (C) that enhanced with contrast after IV contrast administration were primarily regarded as recurrent masses and (D) were hyperintense in diffusion weighted images and the ADC value was calculated as $1.3 \times 10^{-3}$ mm$^2$/s in the apparent diffusion coefficient (ADC) map.

Table 1. Magnetic resonance imaging findings after treatment of soft-tissue sarcomas

|                      | T1 WI         | T2 WI         | CE                              | DWI            |
|----------------------|---------------|---------------|---------------------------------|----------------|
| Haematoma            | Hypo-hyperintense$^1$ | Hypo-hyperintense$^1$ | No contrast                      | Hyper-hyperintense$^1$ |
| Seroma               | Hypointense   | Hyperintense  | No contrast or contrasted peripherally | Hyperintense   |
| Post-treatment fibrous changes | Hypointense | Hyperintense | Mildly enhanced                  | Hyperintense   |
| Recurrent mass       | Hypointense   | Hyperintense  | Enhanced                        | Hyperintense   |

$^1$Age dependent

No relapse or change in the tissue areas was identified during follow-up.

Pathology

One patient underwent surgery for an alveolar rhabdomyosarcoma, 1 for embryonal rhabdomyosarcoma, 8 for fibrosarcomas, 6 for leiomyosarcomas, 8 for pleomorphic liposarcomas, 6 for myxoid liposarcomas, 2 for angiosarcomas, 1 for a malign schwannoma, 4 for pleomorphic sarcomas, 1 for a myxofibrosarcoma, 3 for synovial sarcomas, and 1 for soft tissue osteosarcoma. Among the tumours that relapsed, 1 was an alveolar rhabdomyosarcoma, 3 were fibrosarcomas, 2 were leiomyosarcomas, 3 were pleomorphic liposarcomas, 1 was a myxoid liposarcoma, 2 were angiosarcomas, 1 was a malignant schwannoma, 1 was a synovial sarcoma, and 1 was soft tissue osteosarcoma. Five (11.9%) of the sarcomas were grade 1, 21 (50%) were grade 2, and 16 (38.1%) were grade 3.

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation for continuous variables, and count and percentage for categorical variables. A $\chi^2$ test was used to compare differences between groups for categorical variables.
Recurrent tumours were identified in 15 of the 42 patients included in the study. Out of these patients, 6 (40%) were female and 9 (60%) were male. Out of the 27 patients classified as postoperative tissue changes, 14 (51.8%) were female and 12 (48.1%) were male. There was no statistical difference with respect to gender between the 2 groups ($p = 0.183$). The mean age of patients with recurrent tumours identified was 51.6 ± 19.5 years, and the mean age of patients with postoperative tissue changes was 51.07 ± 13.7 years. No significant difference was identified between the groups with respect to age ($p = 0.909$) (Table 2).

Table 2. Comparison of demographic characteristics and apparent diffusion coefficients values between groups

|                  | Recurrent tumour, $n = 15$ | Postoperative inflammation, $n = 25$ | $p$  |
|------------------|----------------------------|------------------------------------|------|
| Age (year)       | 51.66 ± 19.5              | 51.07 ± 14.1                       | 0.909|
| Gender, n (%)    |                            |                                    |      |
| Female           | 6 (40)                    | 14 (52)                            | 0.342|
| Male             | 9 (60)                    | 13 (48)                            |      |
| b-50 (× 10⁻³ mm²/s) | 2.10 ± 0.57              | 3.28 ± 0.49                        | < 0.001|
| b-400 (× 10⁻³ mm²/s) | 1.73 ± 0.52              | 3.02 ± 0.55                        | < 0.001|
| b-800 (× 10⁻³ mm²/s) | 1.49 ± 0.54              | 2.90 ± 0.55                        | < 0.001|
| b-1000 (× 10⁻³ mm²/s) | 1.44 ± 0.59              | 2.72 ± 0.57                        | < 0.001|
| Mean ADC value of adjacent tissue (× 10⁻³ mm²/s) | 2.66 ± 0.57              | 2.86 ± 0.72                        | < 0.350|

$P < 0.05$ was statistically significant

No statistical difference was present between the tumour types with respect to the ADC calculations at all $b$-values. There was no meaningful correlation between the histopathological grade and ADC values. Twenty-two of the tumours were located in the thigh. Of the other tumours, 5 were in the leg, 3 in the popliteal fossa, 3 in the forearm, 2 neighbouring the knee, 2 in the shoulder, 2 in the arm, 1 in the antecubital fossa, 1 neighbouring the hip, and 1 in the elbow. Among the lesions considered as post-treatment tissue changes, 4 were fluid collections; 3 were postoperative haematoma. The other 18 lesions were T1 hypointense and T2 hyperintense and enhanced minimally following IV contrast administration.

When the group of recurrent tumour patients was compared to the postoperative changes group, the ADC calculations were statistically significantly lower at all $b$-levels ($p < 0.001$) (Table 2). The ADC values of recurrent tumours, areas of postoperative tissue change, and adjacent healthy muscular tissues measured at different $b$-values are summarized in Table 2. The sensitivity of $b$-50 values lower than 3.01 × 10⁻³ mm²/s in showing recurrent tumours was 100% and the specificity was 77.78%. The sensitivity of $b$-400 values lower than 2.1 × 10⁻³ mm²/s in showing recurrent tumours was 80% and the specificity was 96.3%. The sensitivity of $b$-800 values lower than 2.26 × 10⁻³ mm²/s in showing recurrent tumours was 100% and the specificity was 88.89%. The sensitivity of $b$-1000 values lower than 2.05 × 10⁻³ mm²/s in showing recurrent tumours was 93.3% and the specificity was 92.5% (Table 3, Figure 3). No significant difference was identified among the $b$-50, $b$-400, $b$-800, and $b$-1000 $b$-levels.

Table 3. Area under the receiver operating characteristics curve (AUC) and criteria (apparent diffusion coefficient – ADC) observed to maximize sensitivity and specificity for predicting recurrent tumour ($n = 42$)

| $b$-value | AUC | Prediction of recurrent tumour |
|-----------|-----|-----------------------------|
| ADC criteria (mm²/s) | Sensitivity (%) | Specificity (%) |
| 50        | 0.951 | ≤ 3.01                     | 100 | 77.78 |
| 400       | 0.947 | ≤ 2.10                     | 80  | 96.30 |
| 800       | 0.981 | ≤ 2.26                     | 100 | 88.89 |
| 1000      | 0.937 | ≤ 2.00                     | 93.33 | 92.59 |

Discussion

Our study identified that the ADC calculations obtained from diffusion-weighted images at different $b$-levels are highly sensitive and specific in the differentiation of soft tissue sarcoma recurrence and postoperative benign changes.
tions are delivered radiotherapy and chemotherapy after sur-
erative evaluation of soft tissue sarcomas. However, once pa-
currence can be differentiated from post-treatment tissue
postoperative haematomas. Therefore, the tumour re-
Tumours with haemorrhagic components may be confused
components may be confused with postoperative scar tissue [2].

tumours can be confused with postoperative seroma because
[14]. The sensitivity of dynamic evaluation has been reported
as 87% and the positive predictive value as 70% [15]. Myxoid
hers following radiotherapy are hyperintense in T2-weighted
quences, and most tumour recurrences also appear hyper-
tensity in T2-weighted sequences [9-12]. Vanel et al. showed
hypointense signal changes in T2-weighted images have
consistency of 96% in ruling out tumour recurrence and resi-
dues [11]. In addition, the preservation of the muscle texture
sign finding in T1-weighted images can also be used to
rule out tumours [13]. In dynamic evaluations, the areas of
post-treatment tissue changes enhance with contrast in the
later stage, and tumour recurrence enhances in earlier stages
[14]. The sensitivity of dynamic evaluation has been reported
as 87% and the positive predictive value as 70% [15]. Myxoid
hums can be confused with postoperative seroma because
of their high signal intensities in T2-weighted images [16,17].
Tumours that contain high mineralization and fibrous com-
ponents may be confused with postoperative scar tissue [2].
Tumours with haemorrhagic components may be confused
with postoperative haematomas. Therefore, the tumour re-
currence can be differentiated from post-treatment tissue
changes to a limited extent in some tumours [10]. In cases
where conventional methods fall short, and if contrast is
not administered to the patient, new imaging methods are
needed to differentiate recurrent tumours from postoperative
tissue changes and to guide the surgery.

ADC mapping in diffusion MRI evaluations is used to
prove the levels of cellularity in different areas
of the body. Diffusion-weighted images can be used to
differentiate tumour recurrence from posttreatment soft
tissue changes. Low ADC values are obtained in malign
tumours with high cellularity, fibromuscular tissue, and
fat tissue; high ADC levels are obtained from tumours
with low cellularity, lesions with fluid content, necrot-
ic regions, and acellular regions [7,9]. Most of our pa-
tients included in the study had high-grade sarcomas
that demonstrated high cellularity. However, we could
not identify a meaningful correlation between the histo-
pathological grades and the ADC values. The ADC values
of relapsed massive lesions were lower when compared
to the areas of benign changes. When the ADC values
of benign changes like haematoma, seroma, edema, and
inflammatory changes that develop after treatment were
compared with recurrent tumours, they were higher, and
these results are consistent with the literature. Low ADC
values are obtained in the development of fibrous tissue
change [18]. In the study conducted by Del Grande et al.
it was shown that lower ADC values were obtained from
fibrous tissue areas than the tumour tissues. This is why
we did not perform calculations in the areas we regarded
as fibrous tissue that had hypointense signal characteristics
in T1-T2 weighted images and did not enhance with
contrast after IV contrast administration in our study.
Baur et al. reported that ADC mapping can be used to
identify sarcoma recurrence and that diffusion ADC
mapping is effective in differentiating muscular edema
and postoperative seroma from recurrent tumours [19].
In the study conducted by Grande et al., with a small
number of patients, using a 3 tesla MRI, they found that
the ADC values obtained from diffusion-weighted MRIs
were statistically significantly different for recurrence,
postoperative scar tissue, and haematoma. They identified
that the mean ADC for recurrence was 1.08 × 10⁻³ mm²/s,
0.9 × 10⁻³ mm²/s for postoperative scar tissue, and 0.9 × 10⁻³
mm²/s for haematoma [18]. We calculated the mean ADC
value of relapsed masses as 1.69 × 10⁻³ mm²/s and as 2.98 × 10⁻³
mm²/s for areas of post-treatment tissue changes. Because
we did not measure the ADC values of fibrous tissues in
our study, we may have calculated a higher ADC value
for post-treatment changes than the ADC value calculated
by Grande et al. for postoperative scar tissue. When the
hums in our study were evaluated according to the hist-
ological subtypes, it was seen that 2 angiosarcomas had
higher ADC values than the other soft tissue sarcoma re-
currences (mean 2.7 × 10⁻³ mm²/s). The ADCs obtained
might be higher because of the different histological con-
tent of angiosarcomas like haemorrhages.

The role of different b-values in showing soft tissue sarcomas and sarcoma recurrences has not been inves-
tigated before [18,20]. Different b-values can change the
sensitivity of the diffusion. At lower b-values, a signal de-
crease may occur in water molecules that have high levels
of motion similar to intravascular space. This is why ADC
is significantly affected by vascular perfusion. At high
b-values, the signal-to-noise ratio decreases, which also
affects ADC calculations [19-24]. Due to this, to obtain
accurate ADC values, calculations must be done with at
least 3 different b-values [20]. We performed 4 different

![Figure 3. ROC (receiver operating characteristic) curves of different b-values are shown](image_url)
ADC calculations in our study. The mean ADC calculations at $b$-values of 50 ($2.10 \times 10^{-7} \pm 0.57, p < 0.01$) were higher when compared to other $b$-values, but we found meaningful results in showing recurrence just as in other $b$-values. We found that all $b$-values had high sensitivity and specificity and identified that the sensitivity and specificity were highest at $b$-1000 values. To avoid artifacts, it may be sufficient to shorten the duration and carry out evaluations at 2 different $b$-values.

Because the signal-to-noise ratio is lower in diffusion-weighted images, more artifacts may be present, especially in the postoperative period, compared to conventional sequences [19,20]. We did not include patients who had prostheses or operation material that cause artifacts in the study.

Our study had some limitations. Our study was retrospective, and we worked with a heterogeneous patient group. Because the tumours were located in different areas of the body, the imaging protocols differed accordingly. Because we used 4 different $b$-values, the imaging duration was prolonged, and movement artifacts were more common.

Another limitation was the number of patients. Both the overall number of patients and the number of relapse patients were low (15/40). Further research, with more patients, directed to the ADC evaluation of specific sarcoma diagnoses and research that evaluates the ADC calculations of benign neoplasias like low-grade tumours and fibromatosis that have high recurrence rates are necessary.

**Conclusions**

The ADC values obtained from diffusion-weighted images have high sensitivity and specificity in differentiating recurring soft tissue sarcomas during monitoring after treatment from postoperative changes. The highest sensitivity and specificity were obtained at the $b$-1000 level.

**Conflict of interest**

The authors report no conflict of interest.

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