Liposarcomas (LPSs) are the most frequent soft tissue sarcomas that occur in adults. LPSs are divided into four categories according to diagnostic criteria in histopathology: atypical lipomatous tumour/well differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma (MLPS) and pleomorphic liposarcoma (PLPS).\(^1\) WDLPS includes a variety of histologic subtypes: lipoma-like, sclerosing, inflammatory and spindle cell subtypes. DDLPS is found in up to 10% of WDLPS of any type and it has a more aggressive course than WDLPS or MLPS. MLPS can progress to the round cell liposarcoma. This feature can be used to make a differential diagnosis between lipomas and LPS, followed by the classification into subtypes, which is essential for providing patients with tailored medical services and predicting a prognosis of them. Unlike lipomas, a wide excision should be done for LPS to avoid its recurrence. MLPS is highly sensitive to the radioactivity and they show favourable responses to specific agents such as trabectedin.\(^1\) In some cases, however, LPS may not have notable findings on histopathology. This poses a diagnostic challenge to pathologists.

Molecular characteristics are useful to classify LPS into the subtypes. In cases of WDLPS, fluorescence in situ hybridization (FISH) studies have revealed the amplification of materials from 12q14-15, and these include the genes murine double minutes (MDM) 2 and cyclin-dependent kinase (CDK) 4.\(^2,3,5\) But the amplification of materials from 12q14-15 is not detected in lipomas. This feature can be used to make a differential diagnosis of WDLPS from benign lipomas.\(^6\) As shown in cases of WDLPS, the DDLPS is characterized by the amplification of materials from the 12q13-21 region. But the amplification of MDM2 gene is not consistently seen in cases of PLPS.\(^7\) In nearly all cases of MLPS, there is a mutation in a specific gene, i.e., a translocation mutation t(12;16)(q13;p11), leading to the fusion of the CHOP (DDIT3) gene located on 12q13 and the TLS (FUS) gene on 16p11, or t(12;22)(q13;q12), leading to the fusion of CHOP (DDIT3) and the EWSR1. These mutations...
are not detected in other cases of LPS.7

The aim of this study is to evaluate the added value of MDM2 amplification and DDIT3 rearrangement on the FISH in making a diagnosis and a classification of liposarcoma.

MATERIALS AND METHODS

A retrospective analysis of the pathology reports was performed for all the patients who were diagnosed with LPS and then treated at our medical institution during a period from 1995 to 2010. Among the 153 collected cases, 82 where paraffin-embedded blocks were available were enrolled in the current study. These 82 cases of LPS had been classified into 42 cases of WD-LPS, 14 cases of DDLPS, 20 cases of MLPS and six cases of PLPS. Medical data of these patients were collected. Sixty cases of lipoma of more than 10 cm in size were served as normal controls. All the pathologic specimens were independently reviewed by three pathologists (JC, SEL, and YLC).

According to the manufacturer’s instructions, the FISH was performed on interphase nuclei present on formalin-fixed, paraffin-embedded tissue sections. Unstained 4-μm sections were placed on electrostatically charged slides (SuperFrost, Fisher Scientific, Hampton, NH, USA) and then evaluated using MDM2 (12q15) dual-colour probe and DDIT3 (12q13) dual-colour, break-apart probe (Vysis, Downers Grove, IL, USA). The hybridized slides were reviewed on an Olympus IX-50 microscope (Olympus, Tokyo, Japan) at 100× magnification with oil immersion using a DAPI/Green/Red triple band pass filter set. The tissues were scored by evaluating a minimum of 100 tumour nuclei per sample. The amplification of the MDM2 was defined as an MDM2/CEP12 ratio of ≥2.2 in 100 tumour cells. The interpretation of intact and split signals of DDIT3 was done based on generally accepted guidelines recommended by the Vysis, for which the width of space between the two signals should be larger than that of one signal and this is essential for determining whether there is a split signal. Positive results for DDIT3 were defined when more than 10% of tumor nuclei had evidences demonstrating that rearrangement of the DDIT3 rearrangement. To avoid false-positive results originating from the nuclear truncation that occurs in a subset of cells in paraffin-embedded samples, we excluded overlapping cells indistinguishable as separate nuclei from the current analysis.

Our cases of LPS were diagnosed and classified into the subtypes based on histopathologic findings and molecular status. If necessary, we performed an immunohistochemical staining (IHC) for MDM2 (1:100, Invitrogen, Carlsbad, CA, USA), CD34 (1:400, Dako, Carpinteria, CA, USA), smooth muscle actin (1:100, Dako) and human melanoma black-45 (HMB-45; 1:50, Dako). In addition, we retrieved the clinical data through a retrospective analysis of the medical records.

A chi-square test was used to identify the correlations between the qualitative clinicopathological variables. Besides, a Mann-Whitney U-test was performed to identify the correlations between the variables including patient age, tumor size and the length of follow-up period. Both a disease-free survival (DFS) and an overall survival (OS) were estimated based on a Kaplan-Meier analysis, whose results were compared using the log rank test based on the original and revised diagnoses. Statistical analysis was done using SPSS ver. 18 (SPSS Inc., Chicago, IL, USA) and R 2.12.1. A p<0.05 was considered statistically significant.

RESULTS

After molecular analysis, the original diagnosis was revised in one case of lipoma and 16 cases of LPS (Table 1). In addition, the classification was revised to DDLPS in four cases of MLPS following a revision analysis of the slides and positive results for MDM2 on immunohistochemistry in non-lipogenic area. Based on the revised classification, the population was reduced to 36 cases of WDLPS, 23 cases of DDLPS, 15 cases of MLPS and one case of PLPS. In Table 2, the clinicopathologic data of these cases are summarized. The mean and median age of the patients was 53 and 56 years (range, 23 to 76 years), respectively. The mean follow-up period was 59.1±40.1 months (range, 2.0 to 175.3 months). There was an almost equal number of male and female patients with a male-to-female ratio of 1.22:1. The most frequent site of occurrence was the retroperitoneum (41 cases), which was followed by the thigh (16 cases) and mediastinum (six cases).

There were 43 cases of tumor recurrence during the follow-up period. The recurrence rates of WDLPS, DDLPS, and MLPS were 41.7% (15/36), 87.0% (20/23), and 53.3% (8/15), respectively. The median value of a ratio of MDM2/CEP12 was 13.4 (range, 3.0 to 25.5) in WDLPS, 24.2 (range 13.3 to 50.5) in DDLPS, 2.2 (range, 0.8 to 2.5) in MLPS and 0.6 in PLPS. In most amplified cases, there was a large homogeneously staining region. This indicates a high level of amplification in more than 20 copies. All the 15 cases of myxoid liposarcoma showed rearrangements involving the DDIT3 gene at a mean proportion of positive cells per case of 85% (range, 68 to 95%).
Table 1. Patients whose diagnosis was revised based on the FISH analysis of MDM2 and DDIT3

| No. | Sex/Age (yr) | Original diagnosis | Revised diagnosis | MDM2 FISH | DDIT3 FISH | Primary site | Size (cm) | Recurrence | DFS (mo) | Death | OS (mo) | F/U (mo) |
|-----|--------------|--------------------|------------------|-----------|------------|--------------|-----------|------------|---------|-------|---------|---------|
| 1   | M/76         | WDLP5              | Myxofibrosarcoma | 4-5G7-8R  | NR         | Chest wall   | 3.0       | O          | 4.2     | X     | 11      | -       |
| 2   | M/64         | WDLP5              | Spindle cell lipoma | 2G2R     | NR         | Neck         | 8.5       | ×          | -       | X     | 94.8    | 44.1    |
| 3   | F/52         | DLPLS              | Sclerosing mediastinitis | 2G2R     | NR         | Mediastinum  | 0.8       | ×          | -       | X     | 79.6    | 94.8    |
| 4   | M/40         | DLPLS              | LMS               | 4-5G4-5R  | NR         | Thigh        | 1.7       | O          | 43.6    | O     | 86.1    | 86.1    |
| 5   | F/56         | DLPLS              | LMS               | 2-3G6-7R  | NR         | Chest wall   | 6.0       | O          | 35.4    | X     | 56.9    | 56.9    |
| 6   | M/57         | DLPLS              | AML               | 2G2R     | NR         | Retroperitoneum | 20.0     | ×          | -       | X     | 15.6    | 15.6    |
| 7   | M/47         | MLPS               | Myxoid lipoma     | 2G2R     | NR         | Chest wall   | 1.5       | ×          | -       | X     | 29.4    | 29.4    |
| 8   | M/60         | MLPS               | DLPLS             | Amp      | NR         | Retroperitoneum | 15.0     | O          | 16.8    | O     | 39.2    | 39.2    |
| 9   | M/49         | MLPS               | DLPLS             | Amp      | NR         | Retroperitoneum | 40.0     | O          | 23.7    | O     | 23.7    | 23.7    |
| 10  | M/58         | MLPS               | DLPLS             | Amp      | NR         | Retroperitoneum | 12.0     | O          | 10.6    | O     | 83.5    | 83.5    |
| 11  | F/58         | MLPS               | DLPLS             | Amp      | NR         | Retroperitoneum | 40.0     | O          | 16.7    | O     | 33.0    | 33.0    |
| 12  | M/58         | PLPS               | DLPLS             | Amp      | NR         | Retroperitoneum | 30.0     | O          | 3.6     | O     | 35.2    | 35.2    |
| 13  | M/62         | PLPS               | DLPLS             | Amp      | NR         | Retroperitoneum | 17.0     | O          | 13.2    | X     | 7.0     | 7.0     |
| 14  | M/64         | PLPS               | DLPLS             | Amp      | NR         | Retroperitoneum | 18.0     | O          | 8.2     | O     | 21.9    | 21.9    |
| 15  | M/58         | PLPS               | DLPLS             | Amp      | NR         | Retroperitoneum | 12.0     | O          | 10.6    | O     | 83.5    | 83.5    |
| 16  | F/60         | PLPS               | DLPLS             | Amp      | NR         | Retroperitoneum | 40.0     | O          | 16.7    | O     | 33.0    | 33.0    |
| 17  | M/45         | Lipoma             | WDLP5             | Amp      | NR         | Neck         | 10.7      | ×          | -       | X     | 13.2    | -       |

FISH, fluorescence in situ hybridization; MDM2, murine double minutes; DFS, disease-free survival; OS, overall survival; F/U, follow-up period; M, male; WDLP5, well-differentiated liposarcoma; MLPS, myxoid liposarcoma; AML, angiomylipoma; PLPS, pleomorphic liposarcoma; LMS, leiomyosarcoma; AML, angiomylipoma; MLPS, myxoid liposarcoma; Amp, amplification; PLPS, pleomorphic liposarcomas.

Table 2. Clinical data of 75 patients with LPS after the classification was revised on the FISH analysis of MDM2 and DDIT3

|                  | Total | WDLP5 (n=36) | DDLP5 (n=23) | MLPS (n=15) | PLPS (n=1) | p-value* |
|------------------|-------|-------------|--------------|-------------|------------|----------|
| Age (yr)         | 52.9±12.4 (23-76) | 53.1±12.3 (30-76) | 56.4±12.0 (27-75) | 48.6±14.2 (23-69) | 55.0 | 0.160 |
| Male:Female      | 40:35 | 17:19       | 16:7         | 17.6        | M           | 0.442    |
| Size (cm)        | 16.4±10.5 (2-48)  | 16.7±9.8 (3-40)  | 20.6±11.9 (7-48) | 10.1±6.7 (2-23) | 8.0 | 0.012 |
| Recurrence (%)   | 43 (57.3) | 15 (41.7) | 20 (87.0) | 8 (53.3) | 1 (100) | 0.001 |
| Death (%)        | 22 (29.3) | 4 (11.1)   | 13 (56.5) | 5 (33.3) | 1 (100) | 0.001 |
| F/U (mo)         | 59.1±40.1 (2.0-175.3) | 69.7±43.1 (2.0-175.3) | 46.0±29.0 (3.2-117.6) | 55.5±43.1 (3.9-138.9) | 82.6 | 0.110 |

LPS, liposarcoma; FISH, fluorescence in situ hybridization; MDM2, murine double minutes; WDLP5, well-differentiated liposarcoma; DDLP5, dedifferentiated liposarcoma; MLPS, myxoid liposarcoma; PLPS, pleomorphic liposarcoma; F/U, follow-up.

*PLPS is not included in analysis; *Values are presented as mean±standard deviation (range).

Of the 42 cases which had been previously diagnosed as WDLP5, two had no amplification of MDM2. These two cases occurred in the neck (8.5 cm) and chest wall (4.0 cm), whose classification was revised to spindle cell lipoma and myxofibrosarcoma, respectively. In case of myxofibrosarcoma, there was an MDM2 polysomy on the FISH analysis. The spindle cell lipoma was strongly positive for CD34 on immunohistochemistry.

Of a total of 14 cases of DDLP5, four had no amplification of the MDM2 gene. These two cases occurred in the thigh (1.7 cm) or the chest wall (6.0 cm), whose classification was revised to WDLPS (Figs. 1J-O), some cases of high-grade MLPS showed its classification was revised to myxoid lipoma of the chest wall (4.0 cm), whose classification was revised to angiomylipoma. This was confirmed based on the positive staining results for HMB-45. The other case that occurred in the mediastinum (0.8 cm) turned out to be sclerosing mediastinitis on histologic re-examination.

Of the 20 cases which had originally been diagnosed as MLPS, four had an amplification of the MDM2 gene. All of these cases occurred in the retroperitoneum with relatively larger sizes, and their classification was revised to DDLP5 after histologic review (Fig. 1A-C). All the remaining cases but one had a break-apart rearrangement of CHOP (DDIT3) on the FISH analysis. In one case, the classification was revised to myxoid lipoma of the chest (Fig. 1D-F). Of the 60 cases of benign lipoma, one had an amplification of the MDM2 gene (MDM2/CEP12 ratio, 3.0) and its classification was revised to WDLP5 (Fig. 1G-I). In addition to the presence of a break-apart rearrangement of DDIT3 in typical MLPS (Figs. 1J-O), some cases of high-grade MLPS showed
a polysomy for DDIT3 (Fig. 1O). Five of six cases of PLPS had an amplification of the MDM2 gene, and the classification was revised to DDLPS.

A Kaplan-Meier survival analysis was performed to estimate the results of different cumulative DFS and OS in cases for which the original diagnosis and classification were revised. This show-
DISCUSSION

Most sarcomas are diagnosed based on their histologic features and immunohistochemical profiles. Recently, however, a molecular analysis of the specific alterations in some types of sarcoma has been stressed as helpful for diagnosis. Due to the histologic heterogeneity, LPS have a high frequency of discordant histopathological classification. \( MDM2 \) enhances the tumorigenic potential of cells by inactivating p53 in the cell cycle.\(^8\) Because \( MDM2 \) amplification is found in some cases of LPS, several testing modalities have been used to determine if there are underlying mutations in \( MDM2 \).

An IHC of \( MDM2 \) has been widely performed in adipocytic and non-adipocytic tumours. An IHC is a valuable diagnostic modality to make a differential diagnosis of WDLPS or DDLPS from benign lipomas and other mesenchymal tumors. In many non-adipocytic sarcomas, such as malignant peripheral nerve sheath tumours, myxofibrosarcomas and rhabdomyosarcomas, however, the \( MDM2 \) is expressed.\(^9,10\) In addition to the IHC, molecular methods such as quantitative polymerase chain reaction (Q-PCR) and FISH have also been used to determine the amplification of \( MDM2 \) in adipose tissue tumors. The Q-PCR and FISH showed highly concordant results, although their concordance with those of IHC was relatively lower.\(^11\)

The fusions between the genes, \( FUS-DDIT3 \) (TLS-CHOP) and \( EWSR1-DDIT3 \) (EWS-CHOP), are the characteristics of myxoid and round cell LPS but these characteristics are rarely seen in other neoplasms.\(^12\) Our results showed that a diagnosis of LPS could be confirmed based on the amplification of the \( MDM2 \) gene and a break-apart rearrangement of the \( DDIT3 \) gene on the FISH analysis. In particular, these diagnostic clues could also be applied to accurately making a differential diag-

Fig. 1. (Continued from the previous page) (J-L) Low-grade MLPS (MLPS-LG). (J, K) Loose myxoid tumour showing cystic changes with arborization of the capillary vessels. (L) A break-apart rearrangement of the \( DDIT3 \) gene is detected on the FISH analysis. (M-O) High-grade MLPS (MLPS-HG). (M, N) Tumor cells with a round-to-oval shape showing a nuclear pleomorphism in the myxoid stroma. (O) Multiple break-apart rearrangements of the \( DDIT3 \) gene are detected on the FISH analysis.
Fig. 2. The Kaplan-Meier survival curve of the disease-free survival (DFS) and overall survival (OS) based on the original (A, B) and revised (C, D) diagnosis. The DFS (A) and OS (B) for original diagnosis. The DFS (C) and OS (D) for revised diagnosis. WDLPS, well-differentiated liposarcoma; PLPS, pleomorphic liposarcoma; MLPS, myxoid liposarcoma; DDLPS, dedifferentiated liposarcoma.

nosis of WDLPS or DDLPS from benign lipomas and other sarcomas and of MLPS from other myxoid lesions. In the current study, we evaluated cases that had been diagnosed as LPS on conventional histologic examination.

Of a total of 42 cases which had been originally diagnosed as WDLPS, two had no \textit{MDM2} amplification on the FISH analysis. In cases whose diagnosis was revised to spindle cell lipoma, there were no recurrence or metastasis during a period of 94.8 months despite a lack of the adjuvant therapy. In other case whose diagnosis was revised to myxofibrosarcoma, however, the recurrence occurred at 42.2 months after the initial operation.

Of 36 cases of WDLPS, 22 occurred in the retroperitoneum. All these cases had a \textit{MDM2} amplification on the FISH analysis. According to a previous study, however, none of the 19 cases of retroperitoneal lipomatous tumor without cytologic atypia had an \textit{MDM2} amplification on the FISH analysis.\textsuperscript{13} We therefore recommend that a diagnosis of retroperitoneal lipomatous tumor be made only after a careful review of the morphologic and genetic results.

On the H&E slides of cases of WDLPS or DDLPS, whose diagnoses were revised to non-lipogenic lesions, the adipocytes were distributed between the spindle cells with variable nuclear atypia. It is probable that these adipocytes were mistaken for malignant neoplastic cells that are seen in LPS. In making a
differential diagnosis, it should be considered that there is a possibility of entrapped non-neoplastic adipose tissue or benign neoplasm containing adipose cellular components. We therefore do not recommend that a differential diagnosis of WDLPs/DDLPs be made from other lipomatous lesions solely based on histologic examination. The six non-lipomatous lesions occurred in the chest wall (three cases), neck (one case), mediastinum (one case) and thigh (one case), none of which were uncommon sites for LPS. In addition, they also reported that the original diagnosis of MLPS was largely correct with the exception of one case) and thigh (one case), none of which were uncommon sites for LPS. It would therefore mandatory to perform a molecular analysis including MDM2 FISH, as well as to evaluate the clinical data and histopathologic findings, in ruling out diverse lesions mimicking WDLPs or DDLPS.

Of the 20 cases which had originally been diagnosed as MLPS, four had an amplification of the MDM2 gene on the FISH analysis. Because there is a difference in the genetic mechanism of tumorigenesis between MLPS and WDLPs/DDLPs, the MDM2 amplification is not detected in cases of MLPS. Furthermore, de Vreeze et al. reported that the primary retroperitoneal MLPS is not a real disease entity based on immunohistochemical and molecular biological analyses. In these four cases, there were stromal myxoid features on histopathologic examination, in the surrounding area of necrosis in particular, which led to the misdiagnosis of myxoid liposarcoma as shown in cases 8 and 9 (Fig. 1A-F). The stromal myxoid change alone should not be considered a pathognomonic feature of the MLPS, and molecular tests for FUS-DDIT3 or EWSR1-DDIT3 gene fusions are essential for making an accurate diagnosis of myxoid lesion.

Of 60 cases of benign lipoma of more than 10 cm in diameter, occurring in the neck, one has been revised to WDLPs on the FISH analysis of MDM2. In this case, the ratio for MDM2/CEP12 was 3.0 and this corresponds to the lowest value of all of our collected cases. On histopathologic examination of the H&E slides, there were no notable nuclear atypia that might have been overlooked in the original diagnosis. A closer examination of the tumor showed, however, that there were both a marked proliferation of the lobules of mature adipocytes and a mild nuclear atypism. Lipomatous tumors of more than 5 cm in diameter may be of malignant nature. In any lipomatous lesions of more than 5 cm in size, where there is a marked proliferation, it would be mandatory to perform the MDM2 FISH in making a differential diagnosis from WDLPs. De Vreeze et al. reported that a molecular analysis was helpful for making a diagnosis of LPS based on their single-institution experience. These authors also noted that the classification of lipomas is frequently revised to WDLPs. In addition, they also reported that the original diagnosis of MLPS was largely correct with the exception of retroperitoneal tumors with morphological features mimicking those of MLPS. This is in agreement with our results.

PLPS is a high-grade sarcoma containing lipoblasts and it is mainly classified based on histology. Our results showed that there was an amplification of the MDM2 gene on the FISH analysis in five of six cases which had originally been diagnosed as PLPS. It has been argued that MDM2 gene amplification is not a consistent feature of PLPS. Recently, Mariño-Enríquez et al. showed that DDLPS can show a lipoblastic differentiation in the high-grade component and this is a clue for the differential diagnosis from PLPS. Thus, these authors proposed criteria for revising the diagnosis in cases of DDLPS. It is possible that the incidence of histologic diagnosis of PLPS will continue to decrease due to the ambiguity of this particular disease entity. In cases of PLPS with an amplification of the MDM2 gene, there were mixed histopathologic features of WDLPs. This indicates that these tumours could have originated from antecedent WDLPs or DDLPS. Our results showed that the classification was revised to DDLPS in five cases with an amplification of the MDM2 gene. There were no significant differences in the DFS or OS between the two diagnosis groups, although the P-value for the OS decreased from 0.010 to 0.005 in the group where the diagnosis was revised.

To summarize, our results indicate that the FISH analysis of MDM2 and DDIT3 FISH, as well as histopathological findings, is helpful for making a differential diagnosis of lipomatous tumors.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

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