Differentiating and Categorizing of Liposarcoma and Synovial Sarcoma Neoplasms by Fluorescence in Situ Hybridization

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KEYWORDS

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ABSTRACT

Background & Objective: Soft tissue sarcomas (STS) constitute an uncommon and heterogeneous group of tumors of mesenchymal origin and various cytogenetic abnormalities ranging from distinct genomic rearrangements, such as chromosomal translocations and amplifications, to more intricate rearrangements involving multiple chromosomes. Fluorescence in situ hybridization (FISH) can be used to identify these chromosomal translocations and amplifications, and sub classify STS precisely. The current study aimed at investigating the usefulness of FISH, as a diagnostic ancillary aid, to detect cytogenetic abnormalities such as MDM2 (murine double minute 2) amplification and CHOP (C/EBP homologous protein) rearrangement in liposarcoma, as well as SYT (synaptotagmin) rearrangement in synovial sarcoma.

Methods: The FISH technique was used to analyze 17 specimens of liposarcoma for MDM2 amplification and CHOP rearrangement, and 10 specimens of synovial sarcomas for SYT rearrangement. The subtypes of liposarcoma and synovial sarcomas were reclassified according to the FISH results and compared with those of the respective histological findings.

Results: According to the FISH results in 17 liposarcoma cases, well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), and myxoid liposarcoma (MLPS) subtypes were 41%, 53%, and 6%, respectively. In different subtypes of liposarcoma, a total of 30% mismatches were observed between pathologic and cytogenetic results. According to the histological findings from FISH analysis, SYT rearrangement was found only in three out of 10 (30%) synovial sarcomas.

Conclusion: The detection of cytogenetic abnormalities in patients with liposarcoma and synovial sarcoma by FISH technique provides an important objective tool to confirm sarcoma diagnosis and sub classification of specific sarcoma subtypes in such patients.

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Introduction

Soft tissue sarcomas (STS) are a biologically complex and remarkably heterogeneous group of uncommon tumors of mesenchymal origin that represent only 1% of all human malignancies (1). These tumors have distinctive histology and a wide spectrum of clinicopathological features. More than 100 different malignant and benign soft tissue neoplasms are classified by the World Health Organization (WHO). This vastness and variety of soft tissue neoplasms makes their diagnosis and classification difficult, and undoubtedly one of the most complex areas in clinical pathology, resulting in a high rate of misdiagnosis and misclassification (2, 3). Although assessment of pathologic subtypes or grades of an individual sarcoma is a means of predicting its clinical behavior and is important to determine therapeutic strategies, it is a frequent diagnostic dilemma; therefore, a disagreement rate of 40% exists between expert pathologists (4). Due to difficulties to diagnose and classify soft tissue sarcomas, molecular methods such as FISH and polymerase chain reaction (PCR)-based techniques are routinely used to diagnose and classify some types of STS as alternative methods (5). The two most important and prevalent soft tissue sarcomas in adults are liposarcomas (LPS) and synovial sarcomas (SS), representing about 17% to 25% and 10% of total cases, respectively (6, 7).

According to histopathological diagnostic criteria, liposarcomas and synovial sarcomas can be subdivided into four and three main subtypes, respectively; each with its own specific and unique clinicopathological characteristics and behavior. Well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma (MLPS), and pleomorphic liposarcoma (PLPS) are the main subtypes of liposarcoma; mono phasic, biphasic, and poorly differentiated synovial sarcomas are the main subtypes of synovial sarcomas (8, 9).

The morphological diversity of liposarcomas and synovial sarcomas reflects the variation in their clinicopathological behavior ranging from tumors with low risk for metastasis, such as WDLPS, to tumors with high risk for metastasis, such as the round cell (RC) variant of MLPS or PLPS, and poorly differentiated synovial sarcoma (10, 11). Differential diagnosis is of the critical importance to diagnose and treat liposarcomas and synovial sarcomas. Differentiating liposarcomas from lipomas, synovial sarcomas from fibrosarcomas or leiomyosarcomas, and classification of these types of sarcomas are crucial to provide patients with therapeutic strategies and predict their prognosis, although LPS and SS may not have notable findings on histopathology; the result is a high rate of their misdiagnosis and misclassification.

Several studies showed the potential utility of genetic approaches to detect liposarcoma and synovial sarcoma and their classification (12-15). Liposarcomas and synovial sarcomas, similar to many types of soft tissue sarcomas, are associated with specific genetic alterations such as translocations and amplifications, which are helpful to diagnose individual cases (16).

Regarding liposarcomas, MDM2 gene amplification and CHOP gene rearrangement are useful to sub classify liposarcomas, and can be utilized to differentiate certain subtypes of liposarcomas from benign lipomas (17). Primary amplification of MDM2 is predominantly observed in WDLPS and DDLPS, but not in benign lipomas and PLP cases, making this feature a useful tool to differentiate WDLPS and DDLPS from benign lipomas and PLP (18). MDM2 amplification is not observed in PLP cases (19).

CHOP (DDIT3) gene rearrangement is the main feature of myxoid liposarcomas (MLPS) and is observed in nearly all cases of MLPS. A t(12;16), or t(12;22) translocation, leading to fusion of CHOP (DDIT3) located on 12q13 with TLS (FUS) on 16p11 or EWSR1 on 22q12, can be found in nearly all cases of MLPS.

Regarding synovial sarcomas, a t(X;18) translocation is used to directly assist differentiating synovial sarcoma from other STS (20). The translocation fuses SYT gene from chromosome 18 to either of the two highly homologous genes at Xp11, SSX1 or SSX2, or in less than 1% of SSX4 cases (21).
These genomic alterations can be detected in patients’ specimens with high accuracy by FISH. Fluorescence in situ hybridization (FISH) is one of the most powerful cytogenetic techniques used by biomedical researchers, and is a routine ancillary tool for pathological diagnosis of different subtypes of STS.

Regarding liposarcomas and synovial sarcomas, FISH is commonly used to detect MDM2 amplification and CHOP rearrangement in liposarcomas and SYT rearrangement in synovial sarcomas (18, 22).

The current study used the FISH technique as an ancillary tool to detect MDM2 amplification and CHOP rearrangement in liposarcomas and SYT rearrangement in synovial sarcomas, aiming at differentiating liposarcoma and synovial sarcoma subtypes from other morphologically similar sarcomas and benign conditions. Also, the study investigated the rate of discordance between pathologic and cytogenetic results, and reclassified sarcomas according to cytogenetic results.

### Materials and Methods

#### Specimens

A total of 17 liposarcomas and 10 synovial sarcomas archival formalin-fixed, paraffin-embedded (FFPE) tissue blocks were retrieved from the Pathology Department of Cancer Institute, Imam Khomeini Hospital Complex and Kamalian Pathology Lab, from October 2014 to December 2015.

Hematoxylin-Eosin (H&E)-stained slides were prepared, their histopathological features were reviewed by an expert pathologist, and the specimens were classified according to the criteria of the WHO classification system (7).

The specimens consisted of four atypical well-differentiated liposarcomas (WDLS) (14.8%), six myxoid liposarcomas (22.2%), two pleomorphic liposarcomas (7.4%), five unclassified liposarcomas (18.5%), four synovial sarcomas (14.8%), one small round cell synovial sarcoma (3.7%), and five spindle cell tumors in favor of synovial sarcoma (18.5%) (Table 1).

### Table 1. Characteristics of Patients and Tumors

| No | Gender | Age (years) | Original Diagnosis | Primary Site | Tumor Size (cm) |
|----|--------|-------------|--------------------|--------------|-----------------|
| 1  | Male   | 60          | PLPS               | Right leg    | 8               |
| 2  | Female | 50          | Liposarcoma        | Kidney       | 10              |
| 3  | Female | 74          | MLPS               | Abdominal    | 38              |
| 4  | Male   | 57          | MLPS               | Abdominal    | 30              |
| 5  | Male   | 63          | MLPS               | Right tight  | 15              |
| 6  | Male   | 38          | MLPS               | Elbow        | 1.7             |
| 7  | Female | 48          | MLPS               | Abdominal    | 19              |
| 8  | Male   | 74          | PLPS               | Intraabdominal | 7.5          |
| 9  | Male   | 54          | WDLPs              | Retropertoneal | 30            |
| 10 | Male   | 76          | MLPS               | Retropertoneal | 30            |
| 11 | Male   | 45          | Liposarcoma        | Left leg     | 8               |
| 12 | Male   | 20          | Liposarcoma        | Proximal tibia | 5.5          |
| 13 | Male   | 72          | Liposarcoma        | Retropertoneal | 8            |
| 14 | Male   | 69          | WDLPS              | Retropertoneal | 15            |
| 15 | Female | 65          | MLPS               | Left shoulder | 17              |
| 16 | Male   | 82          | MLPS               | Abdominal    | 7               |
| 17 | Female | 22          | WDLPS              | Abdominal    | 40              |
| 18 | Female | 50          | Synovial sarcoma   | Right chest  | 13.5            |
| 19 | Female | 28          | Small round cell synovial sarcoma | Right forearm | 9             |
| 20 | Female | 39          | Mono phasic spindle cell sarcoma | Right foot, below knee | 17            |
| 21 | Female | 58          | Spindle cell tumor in favor of synovial sarcoma | Pelvic | 16            |
| 22 | Male   | 32          | Spindle cell tumor in favor of synovial sarcoma | Left foot | 7             |
| 23 | Male   | 25          | Spindle cell tumor in favor of synovial sarcoma | Right leg | 4             |
| 24 | Female | 41          | Synovial sarcoma   | Right axillary and shoulder | 19           |
| 25 | Female | 32          | Synovial sarcoma   | Abdominal wall | 22          |
| 26 | Male   | 49          | Synovial sarcoma   | Chest wall   | 16              |
| 27 | Female | 34          | Spindle cell tumor in favor of synovial sarcoma | Left leg | 12            |

PLPS, Pleomorphic Liposarcoma; MLPS, Myxoidliposarcoma; WDLPS, Well-differentiated Liposarcoma
FISH was performed on interphase nuclei present on FFPE tissue sections, according to the manufacturer’s instructions. Unstained 3-μm parallel sections were placed on electro-statically positively charged slides (Menzel-Gläster, Braunschweig, Germany). One slide of each patient was stained by H&E and the malignant cell areas were marked by an expert pathologist. The **MDM2** (12q15) dual-color probe, **CHOP** (12q13) dual-color, break-apart probe, and **SYT** (18q11) dual-color, break-apart probe (Cytocell Aquarius, England) were applied on the marked areas of parallel sections where the malignant cells were present. The hybridized slides were reviewed on an Olympus, BX51 microscope (Olympus, Tokyo, Japan) at x100 magnification with immersion oil using a DAPI/Green/Red triple band pass filter set.

The tissue segments were scored through evaluating a minimum of 100 tumor nuclei per sample. The amplification of **MDM2** was defined as an **MDM2/CEP12** ratio of ≥2 in 100 tumor cells. The results were considered positive for **CHOP** and **SYT** when more than 5% of tumor nuclei had evidence of **CHOP** or **SYT** rearrangement.

Regardless of histological classification of samples, they were reclassified according to FISH results and compared with each other.

**Results**

A total of 27 sarcoma tumor specimens, already diagnosed according to histopathological criteria, were analyzed in the current study. They included 17 liposarcomas (63%) and 10 synovial sarcomas (37%). The specimens belonged to 15 males (55.6%) and 12 females (44.4%) with a mean age of 50 years; ranged from 20 to 82.

Table 1 summarizes the tumors histological subtypes, size, and site at the time of diagnosis. The mean and median of tumor size were 16.75 cm and 15 cm (1.7 to 40 cm) in liposarcomas and 13.55 cm and 14.75 cm (4 to 22 cm) in synovial sarcomas cases, respectively. Abdomen and retro peritoneum were the commonest sites of liposarcomas (58.8%), while 70% of synovial sarcomas were located around the limbs. After the initial diagnosis and initiation of treatment, the patients with sarcoma were followed-up. The mean of follow-up period of the patients was 32.3 months (2 to 45 months).

FISH was carried out by commercially available probes for **MDM2** gene amplification and **CHOP** rearrangement in liposarcomas, and for **SYT** rearrangement in synovial sarcomas. The results of FISH were used to reclassify the tumors (Figure 1).

![Figure 1](image_url)

**Figure 1.** A) CHOP rearrangement in a case with myxoidliposarcoma, ISCN Result: nucish12q13 (CHOPx2) (5′CHOP sep3′CHOPx1) [65/100]

FISH analysis on a paraffin-embedded tumor with the CHOP probe showed evidence of a 12q13 rearrangement in 65% of interphase nuclei scored. CHOP rearrangements are recurrent, non-random abnormalities associated with myxoidliposarcomas, and are observed in approximately 95% of cases.

B) MDM2 amplification in a case with liposarcoma

ISCN Result: nucish12q15 (MDM2x3-10), 12cen (D12Z1x2) [60/100]

FISH analysis on a paraffin-embedded tumor with the MDM2 probe showed evidence of amplification of the MDM2 gene in 60% of interphase nuclei scored. CHOP rearrangements are recurrent, non-random abnormalities associated with myxoidliposarcomas, and are observed in approximately 95% of cases.

C) SYT rearrangement in a case with synovial sarcoma

ISCN Result: nucish18q11.2 (SYTx2) (5′SYT sep3′SYTtx1) [53/100]

FISH analysis on a paraffin-embedded tumor with the SYT probe showed evidence of an SYT gene rearrangement in 53% of interphase nuclei scored. The most common SYT rearrangement is the translocation (X; 18) (p11.2; q11.2), which is a recurrent, non-random abnormality associated with synovial sarcomas and is observed in up to 90% of tumor specimens.

The pathological and FISH results of the patients with liposarcomawere listed in details in Table 2.
Table 2. Revised Diagnosis of Liposarcoma Cases According to FISH Results

| DDIT3 FISH | MDM2 FISH | Original Diagnosis | Revised Diagnosis |
|------------|-----------|--------------------|-------------------|
| NR         | AMP       | PLPS               | WDLPS             |
| TR         | NR        | Liposarcoma        | MLS               |
| NR         | AMP       | MLPS               | WDLPS             |
| NR         | AMP       | WDLPS              | WDLPS             |
| NR         | NR        | MLPS               | DLPS              |
| NR         | NR        | Liposarcoma        | DLPS              |
| NR         | AMP       | MLP with necrosis  | WDLPS             |
| NR         | AMP       | PLPS               | WDLPS             |
| NR         | AMP       | WDLPS              | WDLPS             |
| NR         | NR        | Liposarcoma        | DLPS              |
| NR         | NR        | WDLPS              | DLPS              |
| NR         | AMP       | MLPS               | WDLPS             |
| NR         | NR        | MLPS               | DLPS              |
| NR         | NR        | WDLPS              | DLPS              |

AMP, Amplification; NR, Normal, PLPS, pleomorphic liposarcoma; MLPS, myxoid liposarcoma; WDLPS, well-differentiated liposarcoma; FISH, fluorescence in situ hybridization.

**MDM2** amplification was observed in seven cases (41.2%) and **CHOP** rearrangement in two cases (11.8%). According to the results of FISH, the original pathology-based diagnoses were revised in nine cases (52.9%) and all unclassified liposarcomas were successfully classified, including two PLPS reclassified as WDLPS, five Myxoid Liposarcomas (MLS) reclassified as three WDLS and two DDLPS, two WDLPS reclassified as DDLPS, and five unclassified liposarcomas classified as four DDLPS and one MLP. The pathological and FISH results of the patients with synovial sarcoma are shown in Table 3.

Table 3. Revised Diagnosis of Synovial Sarcoma Cases According to FISH Results

| Original Diagnosis(OD)                  | Revised Diagnosis(RD) | SYT FISH |
|----------------------------------------|-----------------------|----------|
| Synovial sarcoma                       | Normal                | NR       |
| Small round cell synovial sarcoma      | Synovial sarcoma      | TR       |
| Monophasic spindle cell sarcoma        | Synovial sarcoma      | TR       |
| Spindlecell tumor in favor of synovial sarcoma | Normal             | NR       |
| Spindlecell tumor in favor of synovial sarcoma | Normal             | NR       |
| Spindlecell tumor in favor of synovial sarcoma | Normal             | NR       |
| Synovial sarcoma                       | Synovial sarcoma      | TR       |
| Malignant synovial                     | Normal                | NR       |
| Synovial sarcoma                       | Normal                | NR       |
| Spindle cell tumor in favor of synovial sarcoma | Normal             | NR       |

FISH, fluorescence in situ hybridization; NR, Normal

In the cases of synovial sarcomas, **SYT** rearrangement was observed in three cases (30%) based on the results of FISH; therefore, the diagnosis of synovial sarcoma was revised in seven cases (70%) and changed to other types of sarcoma.

During the follow-up, the rate of recurrence was 82% in liposarcomas and 60% of the patients with synovial sarcoma.

Regarding liposarcomas, the recurrence rate of WDLPS and DDLPS subtypes were 70% and 85%, respectively.

**Discussion**

An accurate diagnosis of different types of STS is important not only to differentiate benign from malignant tumors, but also to predict the
behavior of tumors and determine suitable therapeutic strategies.

Although the analysis of histomorphological and immunohistological features is the main procedure for pathological diagnosis of most types of STS, rarity and wide diversity of these malignancies provide specific diagnostic dilemma. Given the tumor-specific genetic alterations elucidated in recent years, molecular analysis has modified the routine diagnostic workup of different types of STS.

Currently, it is estimated that about 30% of sarcomas harbor specific chromosomal abnormalities such as chromosomal translocations and amplifications result in fusion genes; this provides a useful tool for diagnosis and offers novel and potential targets for future therapeutic approaches (23).

Various molecular genetic abnormalities are detected in 12q in different subtypes of liposarcoma including t(12;16)(q13;p11), or t(12;22)(q13;q12) translocations, which lead to fusion of transcription factor gene CHOP (DDIT3) (a negative regulator of adipocyte differentiation) with TLS (FUS) or EWS genes in at least 95% of MLS cases, as well as amplification of 12q13-15 encompassing MDM2 and CDK4 genes in well-differentiated and dedifferentiated liposarcomas(24).

A specific t(X;18)(p11.2;q11.2) translocation resulting in fusion of genes between SYT, on chromosome 18, and SSX1, SSX2, or rarely SSX4 on chromosome X is detectable in 90% of synovial sarcomas (25, 26). The translocation is found both in the spindle and epithelial components of synovial sarcomas, but not in other spindle cell sarcomas.

FISH and histopathological findings were matched in 48.8% for WDLPS, 12% for MLPS, and poorly matched for DDLPS. According to the histopathological findings, the tumors in the synovial sarcoma group were classified as follows: four synovial sarcomas (40%), one small round cell synovial sarcoma (10%), and five spindle cell tumors in favor of synovial sarcoma (50%); SYT rearrangements were observed in only three specimens (30%) with no SYT rearrangements in seven specimens (70%).

These results showed that histopathological findings could not provide conclusive results in 70% of synovial sarcomas and in agreement with
previous studies, FISH analysis should be mandatory to accurately diagnose synovial sarcoma and apply appropriate clinical management(29).

Based on the obtained results of FISH performed to detect **MDM2** gene amplification and **CHOP** gene rearrangement in liposarcomas, and **SYT** gene rearrangement in synovial sarcomas, this technique confirmed the diagnosis of such tumors. In particular, detection of such genetic abnormalities with FISH provides means to accurately differentiate the subtypes of liposarcoma from synovial sarcoma.

The current study assessed the specimens already diagnosed as liposarcomas or synovial sarcomas, based on conventional histopathologic examination. After the initial diagnosis and initiation of treatment, the patients with sarcoma were followed-up. The current study results showed that patients with liposarcoma and amplification of **MDM2** had a high rate of recurrence (47%), and patients with **CHOP** rearrangement had no recurrence after treatment. In patients with synovial sarcoma, recurrence occurred after initial operation in two out of three cases with **SYT** rearrangement. In agreement with previous studies, the current study results showed that the detection of these abnormalities by FISH, as an alternative diagnostic approach, is important to predict clinical behavior in patients with liposarcoma and synovial sarcoma (18, 30).

An interesting facet of the current study was that in cases with unclassified liposarcomas without a definitive histological diagnosis, FISH analysis can be used as an ancillary method to accurately diagnose and classify such cases.

In addition to being a diagnostic utility, detection of **MDM2** amplification and **CHOP** rearrangement impact liposarcoma treatments that use selective **MDM2** inhibitors and blockers of trans-activating ability of FUS-CHOP fusion protein(31).

In brief, the current study results indicated that FISH analysis of **MDM2** amplification and **CHOP** rearrangement in liposarcomas and **SYT** rearrangement in synovial sarcomas, as well as histopathological findings, were helpful to differentiate such sarcoma subtypes.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

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