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Challenges in identifying biomarkers for Smooth muscle tumors of uncertain malignant potential (STUMP)

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Abstract

Benign uterine leiomyoma (U.LMA) and malignant uterine leiomyosarcoma (U.LMS), which are both uterine mesenchymal tumors, are distinguished by the number of cells with mitotic activity. However, uterine mesenchymal tumors contain tumor cells with various cell morphologies; therefore, making a diagnosis, including differentiation between benign tumors and malignant tumors, is difficult. For example, uterine smooth muscle tumors of uncertain malignant potential (STUMPs) are a group of uterine mesenchymal tumors for which performing a differential diagnosis is challenging. A standardized classification system for uterine mesenchymal tumors has not yet been established. Furthermore, definitive preoperative imaging techniques or hematological examinations for the potential inclusion of STUMP in the differential diagnosis have not been defined. Several clinical studies showed that there is no correlation between biomarker expression and mitotic rate or tumor recurrence. The current immunohistochemical biomarkers cannot effectively help determine the malignant potential of STUMPs in patients who wish to become pregnant in the future. The establishment of gene expression profiles or detection of pathogenic variants by employing next-generation molecular techniques can aid in disease prediction, diagnosis, treatment, and prognosis. Here, we describe the problems in diagnosing uterine mesenchymal tumors along with the results of the latest clinical studies.

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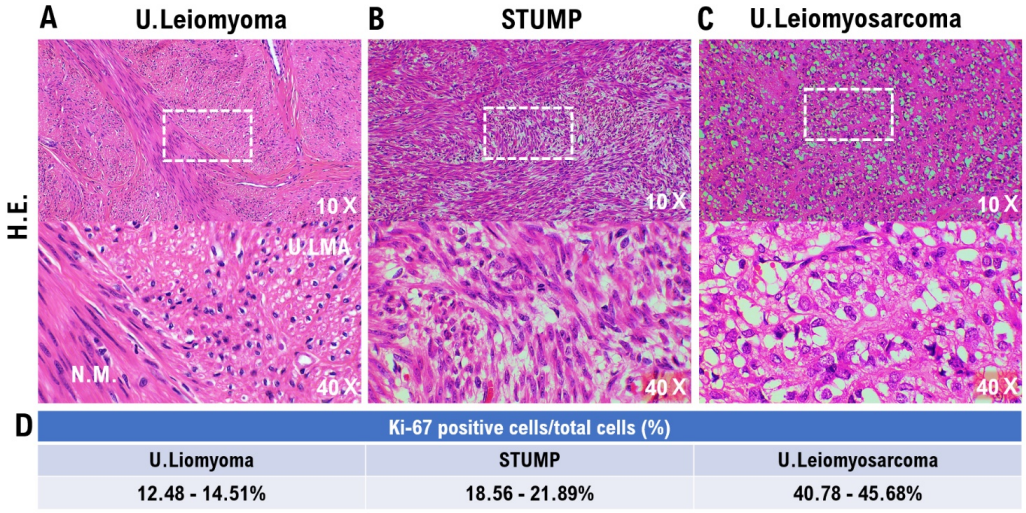
Short Review

A recent clinical study reported the analysis of immunohistochemical findings of smooth muscle tumors of uncertain malignant potential (STUMPs), which are considered difficult to pathologically diagnose based on prognosis [1]. Uterine smooth muscle tumors are the most common uterine mesenchymal tumors that have the properties of uterine smooth muscle cells. Uterine mesenchymal tumors are classified into three major types according to their malignant potential: benign leiomyoma (uterine fibroid), malignant uterine leiomyosarcoma, and STUMP, whose degree of malignancy cannot be clarified [2]. Surgery is the only treatment for uterine leiomyosarcoma, and the prognosis is poor. Therefore, determining the malignancy of uterine mesenchymal tumors is important. In clinical practice, this is carried out by histopathological analysis based on the observation of indicators such as nuclear atypia, mitotic count, and coagulative necrosis. Uterine smooth muscle cells are characterized by a proliferation of spindle-shaped cells consisting of obtuse, elongated nuclei at both ends and eosinophilic cytoplasm, which are oriented perpendicular to each other and multiply in bundles. In many cases, uterine leiomyomas and uterine leiomyosarcomas exhibit the same morphological characteristics as those of uterine smooth muscle cells [3]. Therefore, the diagnosis of mesenchymal tumors depends on the morphological features of the uterine smooth muscle cells [4]. However, uterine leiomyomas and uterine leiomyosarcomas have similar morphological characteristics; thus, differentiating between them is a key challenge. During surgical pathological examination, including malignancy determination, the cell morphology of STUMP and that of uterine leiomyosarcoma are very similar, which makes differential diagnosis difficult (Figure 1). A recent clinical research report revealed that the Ki-67/MIB1-positivity rates in uterine leiomyosarcoma and uterine leiomyoma tissues were approximately 41%–46% and approximately 12.5%–14.5%, respectively [4] (Figure 1). On the contrary, the Ki-67/MIB1-positivity rate in STUMP tissues was approximately 18.5%–22%. However, the relationship between Ki-67/MIB1-positivity rate and prognosis has not been clarified. In other words, among uterine mesenchymal tumors with more mitotic numbers than in uterine leiomyomas but fewer ones than in uterine leiomyosarcomas, those without clear tumor-induced coagulative necrosis are identified as STUMPs [5]. STUMPs typically occur in reproductive-aged or postmenopausal women with a mean age of approximately 43 years, which is a decade less than that of patients with leiomyosarcoma [6].



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Ki-67 positive cells/total cells (%)		
U.Liomyoma	STUMP	U.Leiomyosarcoma
12.48 - 14.51%	18.56 - 21.89%	40.78 - 45.68%

Figure 1. Cell morphology of uterine leiomyoma, STUMP, and uterine leiomyosarcoma. (A) Uterine leiomyoma (spindle cell leiomyoma). Low-power view (10×) shows a well-circumscribed tumor nodule in the myometrium comprising broad fascicles of spindle cells. High-power view (40×) shows spindle cells having bland cytological features, elongated nuclei, and fine nuclear chromatin. **(B)** Epithelioid smooth muscle tumor of uncertain malignant potential. Low-power view (10×) shows a tumor with multinodular growth at its periphery that might recur. The tumor has an irregular border with the surrounding myometrium. High-power view (40×) shows tumor recurrence in the peritoneum as multiple nodules. **(C)** Uterine leiomyosarcoma (spindle cell leiomyosarcoma). Low-power view (10×) shows a cellular tumor with fascicular growth and enlarged hyperchromatic nuclei. High-power view (40×) shows epithelioid leiomyosarcoma with round tumor cells having eosinophilic granular cytoplasm and irregularly shaped nuclei. **(D)** Ki-67/MIB1 positivity rate in uterine mesenchymal tumors. These values are approximately 41%–46%, 12.5%–14.5%, and 18.5%–22% in uterine leiomyosarcoma, uterine leiomyoma, and STUMP tissues, respectively. N.M.; normal myometrium, STUMP; smooth muscle tumors of uncertain malignant potential, U.LMA; uterine leiomyoma,

An increased mitotic rate in uterine leiomyoma-like uterine mesenchymal tumors is highly suggestive of a uterine leiomyosarcoma. However, uterine mesenchymal tumors with poor nuclear atypia and no tumor-induced coagulation necrosis are diagnosed as uterine leiomyomas with increased nuclear mitotic activity, and these tumors are benign [4]. In many of these cases, the mitotic rate is around 5–9/10 high-power field (HPF), although mitotic rates as high as 10–20/10 HPF also occurs. A uterine mesenchymal tumor with a mitotic rate of ≥20/10 HPF in the absence of nuclear atypia and tumor coagulation necrosis is diagnosed as STUMP. Uterine leiomyoma with nuclear atypia is referred to as uterine leiomyoma with bizarre nuclei that until recently was considered a benign tumor. However, in new clinical studies, foci of atypical cells with nuclear atypia have been found, and recurrence has been observed in uterine mesenchymal tumors with low mitotic numbers [7]. According to the latest World Health Organization classification, uterine leiomyoma with bizarre nuclei is categorized as STUMP [2][7].

A meta-analysis of the results of 11 clinical studies involving the follow-up of patients with STUMP revealed a 10% postoperative recurrence rate (15/150 cases) [8]. However, uterine STUMP is an exceedingly rare uterine mesenchymal tumor among gynecologic tumors. Therefore, there is no standardized pathologic classification or definitive preoperative

contrast-enhanced computed tomography (CT), magnetic resonance imaging or hematological examination for STUMP.

Recently, a Taiwanese clinical research group examined the medical history, etiology, risk factors, and prognosis of six patients with STUMP to establish a standardized pathologic classification [1]. Immunohistochemistry examination using appropriate monoclonal antibodies revealed marked expression of the cyclin-dependent kinase inhibitor 2A (CDKN2A), tumor protein p53 (TP53), and tumor antigen Ki-67/MIB1 in all six patients [1]. The expression rates of estrogen receptor (ER) and progesterone receptor (PgR) in this series were 50.0% (3/6) and 33.3% (2/6), respectively. Furthermore, no correlation was found between the expression of these immunohistochemical biomarkers and mitotic count or tumor recurrence, thus leading to the conclusion that the expression status of current immunohistochemical biomarkers is ineffective in determining the malignant potential in patients with STUMP who wish to conceive [1]. The identification of STUMP pathogenic variants by genome sequencing and gene expression profiling using next-generation molecular techniques may facilitate malignant potential prediction, surgical pathological diagnosis, clinical treatment, and prognostic assessment.

Previous clinical studies have demonstrated immunohistochemical positivity for CDKN2A and TP53 in STUMP cases with postoperative recurrence [9][10]. However, in recent years, cancer genome testing in clinical practice has also revealed pathogenic variants in cell cycle regulators, such as CDKN2A, TP53, CDKN1A, and CDKN1B, in gynecologic tumors, including uterine carcinosarcoma, and endometrial stromal sarcoma [11]. Therefore, the immunohistochemical findings related to CDKN2A, TP53, CDKN1A, CDKN1B, ER, and PgR have limited application in the differentiation between uterine leiomyomas and uterine leiomyosarcomas [12].

Owing to its high incidence, many patients present with the typical features of uterine leiomyoma. Therefore, it can be easily identified by surgical pathological examination. However, determining the malignancy of uterine mesenchymal tumors that exhibit atypical features is difficult. In cases of uterine leiomyoma, which has a high morbidity rate in actual clinical practice, a diagnostic exclusion method for uterine leiomyosarcoma (a malignant tumor) has not yet been established [13]. Therefore, an in-depth investigation of the relationship between cell morphology and prognosis of various uterine mesenchymal tumors, including uterine leiomyoma, is key to understanding the oncological characteristics of uterine mesenchymal tumors. In clinical practice, STUMP should be conclusively diagnosed. Furthermore, the detailed pathological findings and clinical information about uterine mesenchymal tumors must be documented to establish a more appropriate pathological concept of STUMP.

Conclusion

Considering a standardized classification for uterine mesenchymal tumors has not yet been established, the surgical pathological diagnosis of uterine mesenchymal tumors is often difficult. By using a next-generation sequencer to identify key biomarkers, i.e., pathogenic variants involved in the progression and tumorigenesis of various uterine mesenchymal tumors, the prediction of survival among patients with STUMP may be possible. In the future, the establishment of personalized treatment in clinical practice for uterine mesenchymal tumors, including STUMPs, is expected.

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Institutional Review Board Statement: This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo, Japan) on November 08, 2019 and Shinshu University (Nagano, Japan) on August 17, 2019, with approval codes NHO H31-02 and M192. The completion numbers for the authors are AP0000151756, AP0000151757, AP0000151769, and AP000351128. As this research was considered clinical research, consent to participate was required. After briefing regarding the clinical study and approval of the research contents, the participants signed an informed consent form.

Informed Consent Statement: The applicable for studies involving humans. We have obtained Informed Consent Statements from people participating in clinical studies.

Data Availability Statement: The study did not report any data.

Conflicts of Interest: The authors declare no conflict of interest.

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