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Review Article

Candidate molecules as diagnostic biomarker for human uterine mesenchymal tumors

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Abstract

Unfortunately, uterine leiomyosarcoma still has a poor prognosis. The National Cancer Institute reported that the median overall survival (mOS) at stage I to stage IV of leiomyosarcoma was 31 months. Norwegian reports show that mOS of uterine leiomyosarcoma is as poor as eight years at stage I, four years at stage II, two years at stage III, and one year at stage IV. Preoperative diagnosis of uterine leiomyosarcoma is difficult in clinical practice. Treated as “uterine fibroids”, however, tumors are often differentially diagnosed from uterine leiomyosarcoma by pathological diagnosis with hysterectomy or myomectomy. Histopathological diagnosis may result in a diagnosis of “smooth muscle tumor of unremarkable potential (STUMP)” that cannot be declared as malignant or benign. In about half of stage I patients, uterine leiomyosarcoma recurs. Postoperative chemotherapy is attempted to prevent recurrence. However, at present, no anticancer drug that has been shown to be effective in preventing postoperative recurrence has not been established. It is almost clear that radiation therapy also does not help control recurrence. For this reason, we monitor patients without postoperative treatment, and start clinical treatment when recurrence is confirmed. Uterine leiomyomas, which occur in about 70% of women aged 40 and over in Japan and overseas, are benign tumors, but are extremely difficult to distinguish from uterine leiomyosarcoma. Although progress in diagnostic imaging such as MRI and PET-CT is remarkable, uterine leiomyosarcoma is difficult to distinguish from uterine leiomyoma. No differential marker has been identified for uterine leiomyoma and uterine leiomyosarcoma in surgical pathological diagnosis or clinical examination. This review describes the current diagnosis and treatment for uterine sarcoma, including new trends in the search for biomarkers for uterine leiomyosarcoma.



Uterine sarcoma is a particularly unfavorable gynecological tumor, and standard treatment has not been established. A major reason for the lack of established treatment is that it is difficult to conduct clinical trials due to its low frequency of occurrence. The majority of uterine sarcomas originate in the uterine corpus, and clinical studies of 2,677 uterine sarcomas in patients aged 35 years and older have shown to account for 8% of all uterine corpus malignancies [1]. About half of the sarcomas are carcinosarcomas, and most of the rest are leiomyosarcomas, endometrial stromal sarcomas, and adenosarcomas. In Japan, 43-46% of uterine corpus sarcomas were carcinosarcoma, 36-38% were leiomyosarcoma, and 13-19% were endometrial stromal sarcoma [2,3]. The peak age of onset is around 50 years for leiomyosarcoma and endometrial stromal sarcoma, whereas the peak age of onset for carcinosarcoma is 60 years of age and relatively older [2-4]. The 50% survival for endometrial stromal sarcoma is 76 months, while the 50% survival for carcinosarcoma or leiomyosarcoma is 28 and 31 months, respectively. Histopathological diagnosis of uterine sarcoma is often difficult because of the low frequency of uterine sarcoma and the various morphologies of the same histological type. However, it is important to determine the diagnosis of uterine sarcoma by sharing information between gynecologists, radiologists, and pathologists, because the treatment strategy and prognosis for uterine sarcoma depend on histological diagnosis.

Carcinosarcoma is a tumor that consists of a carcinoma component and a sarcoma component. Therefore, carcinosarcoma was called malignant müllerian (mesodermal) mixed tumor. If the sarcoma component does not show a differentiation tendency, it is called homologous, a sarcoma is called heterologous if it shows differentiation into mesenchymal tissue that does not naturally exist in the uterus, such as cartilage, striated muscle, and bone. In either case, a polyp-like ridge that protrudes into the intrauterine cavity is often formed macroscopically. Three theories have been proposed for the histogenesis of uterine sarcoma: combination tumor theory, collision tumor theory, and composition tumor theory. Chronality analysis showed that most of the carcinosarcomas were derived from single cells, and showed that during tumor development, they differentiated into epithelial-like and stromal-like morphologies [5]. Clinicopathologic findings indicate that carcinosarcoma is more like a carcinoma than a sarcoma, based on findings such as common risk factors and many lymphatic metastases. Therefore, surgery and postoperative treatment for carcinosarcoma are in accordance with high-grade endometrial cancer.

For histopathological diagnosis of uterine leiomyosarcoma, the diagnostic criteria proposed by the group of Hendrickson and Kempson are widely used [6]. In other words, in the diagnosis of uterine leiomyosarcoma, (1) cell atypia, (2) fission (index), and (3) coagulation necrosis are comprehensively evaluated. As the initial treatment for uterine leiomyosarcoma, simple abdominal total hysterectomy and bilateral adnexal excision may be the basic treatments in cases that can be removed. There is no clear evidence that extended surgery or additional lymph node dissection improves prognosis. Phase III clinical trials

have provided no clear evidence of the efficacy of radiation or chemotherapy as a postoperative treatment.

Endometrial stromal sarcomas were classified as low-grade and high-grade. However, according to the current WHO classification (2003), high-grade endometrial stromal sarcoma does not necessarily have similarity to endometrial stromal. Therefore, high-grade endometrial stromal sarcoma is called undifferentiated endometrial sarcoma [7]. Like leiomyosarcoma, treatment of endometrial stromal sarcoma is based on simple abdominal total hysterectomy and bilateral appendectomy. However, 9 to 33% of low-grade endometrial stromal sarcomas and 15 to 18% of undifferentiated endometrial sarcomas have metastases to the pelvic or para-aortic lymph nodes, lymph node dissection is required [8,9]. The efficacy of irradiation and chemotherapy, regardless of grade, is unclear, so phase II clinical trials will show the results of their therapeutic effects. Since hormone receptors are positive in low-grade endometrial stromal sarcoma, the efficacy of endocrine therapy is also an important issue to be studied [10].

Adenosarcoma is a mixed tumor consisting of benign glandular epithelium and sarcoma components, which form lobular polypoid prominent lesions. The frequency of adenosarcoma is only 1/9 that of carcinosarcoma [11]. The age of onset of adenosarcoma is younger than that of carcinosarcoma. In a study of 100 patients, the age distribution of patients was 14 to 89 years and the median was 58 years [12]. The onset tissues of glandular sarcoma are endometrium 76%, cervical endometrium 6%, and muscle layer 4%. Because the sarcoma component is not always clear, it is diagnosed as intimal or cervical polyp. Furthermore, careful follow-up is required to repeat the recurrence. Treatment of adenosarcoma, like other sarcomas, is based on abdominal total hysterectomy and bilateral appendectomy. The efficacy of lymph node dissection or postoperative treatment is unclear. Adenosarcoma has a better prognosis than other sarcomas, with a 5-year survival rate of 79% in patients considered stage I and 48% in patients considered stage II preoperatively [11]. Vascular invasion, differentiation into rhabdomyosarcoma, and (adenosarcoma with sarcomatous overgrowth) have been pointed out as poor histopathological prognostic factors for adenosarcoma [13]. Finally, FIGO 2008 advanced stage classification for fibroid sarcoma alone was adopted in the "Endometrial Carcinoma Handling Regulations 3rd Edition" [14,15]. This classification targets leiomyosarcoma, endometrial stromal sarcoma, and adenosarcoma, and the classification of carcinosarcoma follows that of endometrial cancer. In order to determine the stage of progression of primary uterine sarcoma, it is essential to determine the progress of the tumor and the histological type by laparotomy. It should be noted that T1 classification differs between leiomyosarcoma, endometrial stromal sarcoma and adenosarcoma.

In collaboration with Professor Susumu Tonegawa (Massachusetts Institute of Technology), Hayashi's group reported that uterine leiomyosarcoma spontaneously develops after 6 months of age in proteasome component proteasome beta subunit 9/β1i (PSMB9/β1i)-deficient female mice [16-18]. Hayashi, et al. also reported that the incidence of uterine



leiomyosarcoma up to 12 months of age is approximately 37% of in all PSMB9/ β 1i-deficient female mice [16-18]. Therefore, in a joint study with a collaborating medical institution, Hayashi, et al. examined the efficacy and reliability of PSMB9/ β 1i as a biomarker for uterine leiomyosarcoma. Hayashi, et al. examined the expression status of PSMB9/ β 1i in 40 cases of normal myometrium tissue, uterine leiomyoma tissue, and uterine leiomyosarcoma tissue obtained from the pathological file by immunohistochemical staining using an anti-PSMB9/ β 1i antibody [19,20]. As a result, PSMB9 expression was significantly reduced specifically in uterine leiomyosarcoma tissue. Even in cases where differential diagnosis was difficult with the current pathological diagnosis, it was easy to distinguish between uterine leiomyosarcoma and uterine leiomyoma based on the expression status of PSMB9/ β 1i [19]. Currently, Hayashi, et al. are collaborating with a comprehensive reagent and diagnostics manufacturer to examine a differential diagnosis method for uterine leiomyosarcoma by immunohistochemical staining using a combination of PSMB9/ β 1i with other candidate cellular factors. As a health and welfare activity of national and international governments, uterine cancer screening (including uterine leiomyoma with high incidence regardless of race) is recommended for women aged 20 and over. Although serum miRNAs with high diagnostic performance for preoperative uterine mesenchymal tumor screening have been investigated, there are still issues to be solved for the results of this research to be practically applied in the clinical practice.

In conclusion our investigation reviewed the current clinical evidence comparing different adjuvant strategies for the postoperative management of uterine-confined uterine leiomyosarcoma patients. On the light of these data, it seems that the administration of adjuvant chemotherapy does not improve progression free survival of early stage uterine leiomyosarcoma. Large prospective, randomized, multi-institutional studies are needed to better assess the value of different adjuvant strategies. Innovative target therapies need to be tested in order to improve patients' outcome that remains unsatisfactory. Defective expression of PSMB9/ β 1i is likely to be one of the risk factors for the development of human uterine leiomyosarcoma, as it is in the PSMB9/ β 1i deficient mouse. Thus, combination of PSMB9/ β 1i with other functional candidates is useful for a novel diagnostic biomarker for distinguishing human uterine leiomyosarcoma from other mesenchymal tumors. Additionally, gene therapy with PSMB9/ β 1i expression vectors may be a new treatment for human uterine leiomyosarcoma that exhibit a defect in PSMB9/ β 1i expression. Because there is no effective therapy for unresectable human uterine leiomyosarcoma, our results may bring us to specific molecular therapies to treat this malignant tumor.

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