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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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POTENTIAL DIAGNOSTIC BIOMARKERS FOR HUMAN MESENCHYMAL TUMORS, ESPECIALLY LMP2/B1I AND CYCLIN E1/MIB1 DIFFERENTIAL EXPRESSION: PRUM-IBIO STUDY

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Abstract.

Objectives: Most mesenchymal tumors found in the uterine corpus are benign tumors; however, uterine leiomyosarcoma is a malignant tumor with unknown risk factors that repeatedly recurs and metastasizes. In some cases, the histopathologic findings of uterine leiomyoma and uterine leiomyosarcoma are similar and surgical pathological diagnosis using excised tissue samples is difficult. It is necessary to analyze the risk factors for human uterine leiomyosarcoma and establish diagnostic biomarkers and treatments. Female mice deficient in the proteasome subunit low molecular mass peptide 2 (LMP2)/β1i develop uterine leiomyosarcoma spontaneously.

Methodology: Out of 334 patients with suspected uterine mesenchymal tumors, patients diagnosed with smooth muscle tumors of the uterus were selected from the pathological file. To investigate the expression status of biomarker candidate factors, immunohistochemical staining was performed with antibodies of biomarker candidate factors on thin-cut slides of human uterine leiomyosarcoma, uterine leiomyoma, and other uterine mesenchymal tumors.

Results: In human uterine leiomyosarcoma, there was a loss of LMP2/β1i expression and enhanced cyclin E1 and Ki-67/MIB1 expression. In human uterine leiomyomas and normal uterine smooth muscle layers, enhanced LMP2/β1i expression and the disappearance of the expression of E1 and Ki-67/MIB1 were noted. The pattern of expression of each factor in other uterine mesenchymal tumors was different from that of uterine leiomyosarcoma. **Conclusions:** LMP2/β1i, cyclin E1, and Ki-67/MIB1 may be candidate factors for biomarkers of human uterine leiomyosarcoma. Further large-cohort clinical trials should be conducted to establish treatments and diagnostics for uterine mesenchymal tumors.

Key words. LMP2/β1i, Cyclin B1, uterine leiomyosarcoma, diagnostic biomarkers.

Introduction.

The uterus, the organ that harbors embryos and fetuses, has the following three layers: the endometrium, which acts as a bed for the embryo, the uterine smooth muscle layer (myometrium) that protects the embryo, and the serous membrane (perimetrium) that envelops the uterus. In general, endometrial tumors represent epithelial malignancies of the endometrium and are broadly classified into tumors that develop in the cervix or inside the uterus. If smear screening for cervical cancer confirms the onset of cervical cancer early enough, the rate of cervical cancer-related mortality would decrease. Conversely, the incidence of endometrial cancer is increasing because simple methods of screening for endometrial cancer have not been established. Most cervical tumors are malignant tumors classified as squamous cell carcinoma and adenocarcinoma. Mesenchymal tumors that develop in the uterine smooth muscle layer are conventionally classified into benign uterine leiomyoma (uLMA) and malignant uterine leiomyosarcoma (Ut-LMS) based on cytological atypia, mitotic activity, and other criteria. Ut-LMS is relatively rare, with an estimated annual incidence of 0.64 per 100,000 women [1]. Ut-LMS occurs more frequently in the smooth muscle layer of the uterine body than in the cervix. Because Ut-LMS is resistant to chemotherapy and radiotherapy, surgery is virtually the only viable treatment option [2]. The prognosis of Ut-LMS is poor, with a 5-year overall survival rate of about 20% [3,4]. However, the development of efficient adjuvant therapies for Ut-LMS is expected to improve the prognosis of patients with Ut-LMS. The prevalence of uLMA in women aged up to 50 years is 70%~80% (FACT SHEET - Uterine Fibroids, 2010). The diagnosis of uterine mesenchymal tumors is assigned cases [5-7] using the diagnostic category and morphological criteria for uterine mesenchymal tumors (Note 1). However, due to the similarity in cell morphology of uLMA and Ut-LMS, it is hard to differentiate between uLMA and Ut-LMS in some cases. Therefore, the surgical pathological diagnosis is made by macroscopic and histopathological findings on excised tissue specimens [5]. Since nonstandard subtypes of uterine mesenchymal tumors such as endometrial stromal sarcoma and liposarcoma are classified based on the characteristics of these tumor cells, it is important to establish a diagnostic method for nonstandard smooth muscle cell differentiation in actual clinical practice.

Much remains unknown about the molecular mechanisms involved in the pathogenesis of uLMA and Ut-LMS. Tumors that develop in the myometrium for any reason are thought to gradually grow in size and form tumors due to the effects of somatic mutations by female hormones or mediator complex subunit 12 (MED12) [8]. However, to the best of our knowledge, the involvement of female hormones in the pathogenesis of Ut-LMS has not been observed and no obvious risk factors have been found. Cases of Ut-LMS with hypocalcemia or eosinophilia have been reported; however, neither clinical abnormality is an initial risk factor for Ut-LMS. The identification of risk factors

associated with the development of Ut-LMS contributes to the development of preventive measures and novel treatments.

Cellular proteins are predominantly degraded by a protease complex consisting of 28 subunits of 20–30 kDa, which is called the 20S proteasome [9]. The proteasome degradation pathway is essential for many cellular processes, including the cell cycle, gene expression regulation, and immune functions. Interferon-γ (IFN-γ) induces the combinational expression of the proteasome subunit's low-molecular-weight polypeptides (LMP)2/β1i, LMP7/β5i, and LMP10/β10i. Molecular approaches to studying the correlation between IFN-γ and tumor cell proliferation have attracted much attention [10]. LMP2/β1i expression may be associated with cell survival [11,12]. Homozygous mice deficient in LMP2/β1i show abnormalities in tissue-dependent or substrate-dependent proteasome biological functions. Ut-LMS occurred in female LMP2/β1i-deficient mice aged ≥6 months, with an incidence of uterine leiomyosarcoma of approximately 40% by 14 months of age [13,14]. The curve of the incidence showing the prevalence of Ut-LMS in mice by month is similar to the curve showing the morbidity of human Ut-LMS that occurs after menopause.

Advances in cell cycle research have demonstrated that interactions between cyclins, cyclin-dependent kinases (CDKs), and tumor suppressor gene products play an essential role in cell cycle progression [15]. Cyclins, which form complexes with CDKs, are a group of proteins that are periodically expressed during the cell cycle [16]. The expression of these cyclins, CDKs, or cell cycle regulators is regulated by proteasome activation. Thus, compared with normal uterine smooth muscle cells, different expression levels of these cell cycle-related factors are observed in uterine leiomyosarcoma cells that have lost LMP2/β1i expression [17]. Per previous experimental results, cyclin E1 is overexpressed in human mesenchymal tumors [18-21]. Therefore, an expression vector of LMP2/β1i can be inserted into uterine leiomyosarcoma cells (SK-LMS) that have lost LMP2/β1i expression, and LMP2/β1i stable transformant SK-LMS cells were created in which LMP2/β1i is constitutively expressed. To investigate the differences in gene expression between SK-LMS cells and stable transformant SK-LMS cells, gene profiling was created using these two cell types. We, the medical staff, used the factors specifically expressed in Ut-LMS cells obtained from the results of gene profiling as specific marker candidate factors for uterine leiomyosarcoma cells. In this clinical study, to develop targeted therapeutics and diagnostic methods for Ut-LMS, we investigated the expression levels of Ut-LMS cell-specific marker candidate factors in extracted tissues obtained from patients suspected of developing uterine mesenchymal tumors by the immunohistochemical (IHC) staining using the appropriate monoclonal antibodies and our results were examined. Based on the results of the clinical study, we verified the biomarker candidate factors for Ut-LMS. Five candidate factors were identified as pathological variants of Ut-LMS, including LMP2/β1i and cyclin E1. These biomarker candidate factors have the potential to be diagnostic biomarkers and target molecules for new therapeutic approaches.

Materials and Methods.

Tissue collection: A total of 334 patients aged 32–83 years with suspected development of uterine smooth muscle tumors were selected from the histopathological file [22,23]. Continuous sections were taken from at least two tissue blocks in each patient for hematoxylin and eosin staining and IHC. We performed an analysis of the removed tissue after obtaining each patient's written consent. This clinical study was approved by the ethics committees of Shinshu University, Kyoto Medical Center, and Kyoto University.

Immunohistochemistry (IHC) experiment: To examine the expression levels of the five candidate factors, IHC staining was performed on sequential sections of excised tissue from uterine mesenchymal tumors containing human Ut-LMS or uLMA. The anti-human cyclin E1 monoclonal antibody was purchased from Immunotech (Marseille, France). The anti-human LMP2/β1i antibody was produced in a joint research and development project of SIGMA-Aldrich Israel Ltd. (Rehovot, Israel) and our research team. Anti-human cyclin B monoclonal antibodies and anti-human caveolin monoclonal antibodies were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA). The IHC experiment was performed using the avidin-biotin complex method described above. Briefly, we prepared a 5-mm-thick slice of tissue sections from paraffin-embedded hysterectomy samples from each patient with a mesenchymal tumor. Tissue sections from the patients were deparaffinized and rehydrated in graded concentrations of ethyl alcohol. Tissue sections were incubated with normal mouse serum for 20 minutes and then incubated with primary antibodies for 4 hours at room temperature, after which they were incubated with a biotinylated secondary antibody (Dako, CA) and reacted with a streptavidin complex (Dako). Reacted tissue sections were stained with a solution of 3,3-diaminobenzidine (DAB; Dako, CA) and counterstained with hematoxylin. The normal myometrial portion of the tissue section as a specimen was used as a positive control. The negative control consisted of tissue sections incubated with normal rabbit IgG instead of the primary antibody. These experiments were conducted at Shinshu University, the National Hospital Organization Kyoto Medical Center, and Kyoto University Hospital per local guidelines (Approval No. M192).

Results.

Mice deficient in the Lmp2/β1i gene have been reported to develop Ut-LMS spontaneously [24]. Compared with normal uterine smooth muscle and uterine smooth muscle type tissues, LMP2/β1i expression is significantly lower or negative in Ut-LMS tissues. Therefore, defective LMP2/β1i expression is considered one of the risk factors for Ut-LMS [25,18]. The antitumor response mediated by MHC class I molecules is a process influenced by the function of the proteasome induced by stimulation with interferon γ (IFN-γ) [26,27]. These findings support the fact that IFN-γ prevents the development of primary tumors and exhibits tumor suppression effects through immune responses [26,28]. LMP2/β1i expression is significantly induced by IFN-γ, and the activation of signal transducer and activator of transcription (STAT) 1 by stimulation with IFN-γ induces upregulation of tumor suppressors, including interferon regulatory factor 1 (IRF1). IRF1 functions as a transcriptional regulator that plays an important role in the regulation of LMP2/β1i expression [29,30]. Reduced IRF1 levels caused by

LMP2/β1i deficiency could constitute a risk factor for Ut-LMS [25]. In 85% of tissues removed from patients with Ut-LMS, a marked decrease in LMP2/β1i protein expression is noted. The results of LMP2/β1i immunostaining are useful for the differential diagnosis of Ut-LMS and ULMA [31]. LMP2/β1i is a promising diagnostic marker candidate factor for Ut-LMS, and it has the potential to become a target molecule for new therapies. One Ut-LMS case was stained with LMP2/β1i. In our clinical studies, expression of LMP2/β1i was negative in most human uterine leiomyosarcoma tissues. However, expression of LMP2/β1i was observed in only one case of human uterine leiomyosarcoma. In this one case, an amino acid mutation was found in the activation region of LMP2/β1i. It is likely that this amino acid mutation causes the loss of biological activation of LMP2/β1i.

Since the expression of cyclin E1 in Ut-LMS was observed to be higher than that of uLMA and normal uterine smooth muscle layers, this clinical study aimed to verify the expression of cyclin E1 in the extracted tissue obtained from each case. The results of IHC experiments showed that staining with cyclin E1 was observed in all tissue samples obtained from patients with Ut-LMS. Pathological examinations of excised tissue samples revealed the presence of a mass with a diameter of up to 3 cm in the lumbar quadriceps muscle without a fibrous capsule. All lymph node tissues tested negative for Ut-LMS metastases. The results of the IHC experiments showed the positive expression of cyclin E1 and Ki-67 and the negative expression of LMP2/β1i. The histopathologic findings of metastatic Ut-LMS of skeletal muscle and rectal lesions were consistent with the primary histopathologic findings of Ut-LMS.

Our medical staff has previously demonstrated an association between the abnormal expression of the female hormone estrogen receptor and tumor protein 53 (TP53) and the proliferation marker Ki-67/MIB1 (Ki-67/MIB1) and the mutation of TP53 and the pathogenesis of Ut-LMS. LMP2/β1i expression deficiency is associated with these factors [32,33]. Compared with these factors, LMP2/β1i expression deficiency is highly useful as a feature of Ut-LMS (Table). In subsequent experiments, both estrogen receptor and progesterone receptor were stained in almost all uLMAs, regardless of the phase of the menstrual cycle, and the number of Ki-67/MIB1 positive cells in the uLMA was significantly lower than in the Ut-LMS (Table). The IHC experiment performed using candidate biomarkers of uterine mesenchymal tumors (i.e., cyclin E, Ki-67, LMP2/β1i) may facilitate the differentiation of smooth muscle tumor uncertain malignancy potential (STUMP), which is difficult to diagnose via histopathological examinations of excised tissue samples, and uterine leiomyomas and leiomyosarcoma.

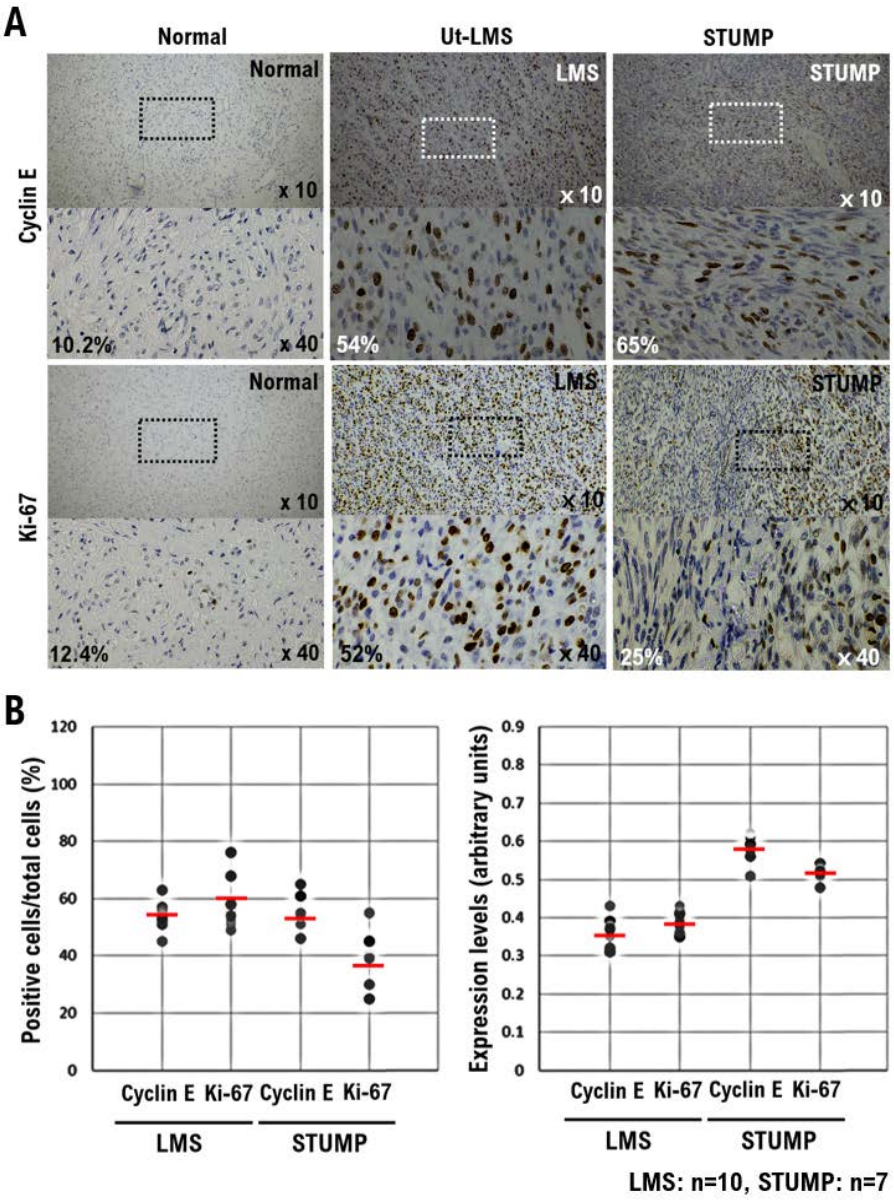
STUMP is a general term for uterine mesenchymal tumors whose malignancy is difficult to determine through pathological examination based on the malignancy category and findings such as cytoskeleton. In a clinical study conducted by our research group, IHC testing was performed using anti-human cyclin E monoclonal antibody and anti-human Ki-67/MIB1 monoclonal antibody on tumor tissues removed by surgical treatment from patients who were diagnosed with Ut-LMS or STUMP and died within 5 years after surgical treatment (Ut-LMS = 10 cases, STUMP = 7 cases). Compared to Ut-LMS tumor tissue, the percentage of Ki-67/MIB1 positive cells in STUMP tumor tissue is lower (Figure 1). However, the expression level of Ki-67/

Table 1. *Differential expressions of SMA, Caveolin1, Cyclin B, Cyclin E, LMP2, NT5DC2, CD133, and Ki-67 in human uterine mesenchymal tumors and uterine LANT-like tumor.*

Mesenchymal tumor types	**Age years**	**n**	**Protein expression***							
			SMA	**CAV1**	**CCNB**	**CCNE**	**LMP2**	**NT5DC2**	**CD133**	**Ki-67**
Normal	30s-80s	**84**	+++	-	-	-	+++	-	-	-
Leiomyoma (LMA)	30s-80s	**102**	+++	++	-/+	-/(+)	+++	-/+	-	+/-
(Ordinally leiomyoma)		(57)	+++	++	-/+	-	+++	-/+		+/-
(Cellular leiomyoma)		(45)	++	++	-/+	-/(+)	++	-/+		+/-
Cotyledonoid dissecting leiomyoma (CDL)	50s	**2**	+++	++	+	+	++	-/+	-	++
STUMP	40s-60s	**34**	++	++	+	-/+	-/+	-/+	NA	+/++
Lipoleiomyoma	40-50s	**4**	NA	++	-/+	+	+++	NA	NA	++
Bizarre Leiomyoma	40s-50s	**12**	++	++	-/+	+	Focal+	+	NA	+
Intravenous LMA	50s	**5**	++	++	+	+	-	NA	++	+
Benign metastasizing	50s	**1**	++	++	+	++	-	NA	NA	++
Leiomyosarcoma	30s-80s	**127**	-/+	+	++	+++	-/+	++	++	++/+++
Rhabdomyosarcoma	10s,50s	**3**	NA	++	-/+	+++	+++	NA	NA	NA
U.LANT[#]-like tumour	40s	**1**	++	+	NA	++	-	NA	NA	-

**Staining score of expression of SMA, CAV1 (Caveorin 1), CCNB (Cyclin B), CCNE (Cyclin E), LMP2 (low molecular protein 2), NT5DC2 (5'-Nucleotidase Domain Containing 2) and Ki-67 from results of IHC experiments. Protein expression*; estimated-protein expressions by immunoblot analysis, immunohistochemistry (IHC) and/or RT-PCR (quantitative-PCR),-/+; partially positive (5% to 10% of cells stained and ≤0.2), Focal+; Focal-positive (focal or sporadic staining with less than 5% of cells stained and <0.3), ++; staining with 5% or more, less than 80% of cells stained and ≥0.3, +++; diffuse-positive (homogenecus distribution with more than 80% of cells stained and ≥0.4), -; negative (no stained cells). U.LANT-like tumour; uterine leiomyomatoid angiomatous neuroendocrine tumour-like tumour, LMP2, cyclin E, caveolin1, NT5DC2, CD133, Ki-67. STUMP (Smooth muscle tumor of uncertain malignant potential). Cyclin E, LMP2, Caveolin1 are potential biomarker for human uterine mesenchymal tumors. LANT[#], leiomyomatoid angiomatous neuroendocrin tumour (LANT) is described as a dimorphic neurosecretory tumor with a leiomyomatous vascular component. NA; no answer.*

MIB1 in STUMP tumor tissues was higher than that in Ut-LMS tumor tissues (Figure 1). Compared to Ut-LMS tumor tissue, the percentage of cyclin E-positive cells in STUMP tumor tissue is slightly lower (Figure 1). However, the expression level of cyclin E in STUMP tumor tissues was higher than that in Ut-LMS tumor tissues (Figure 1). Therefore, the over survival was compared between a group of uterine leiomyosarcoma and STUMP with high expression of Cyclin E and Ki-67/MIB1 and a group of uterine leiomyosarcoma and STUMP with low expression of Cyclin E and Ki-67/MIB1. Survival curves indicated that the expression levels of Cyclin E and Ki-67/MIB1 in uterine leiomyosarcoma or STUMP tissues may indicate the prognosis of patients with uterine leiomyosarcoma or STUMP (Figure 2).These results suggest that cases of gynecological mesenchymal tumors whose malignancy was not determined by surgical pathology and who were differentiated as STUMP and whose IHC tests showed high expression levels of cyclin E and ki-67/MIB1 may have a poor prognosis. The expression levels of cyclin E and Ki-67/MIB1 in uterine mesenchymal tumors are considered to be candidate factors for predictive markers of life prognosis.



A. *High expression of Cyclin E and Ki-67/MIB1 was observed in Ut-LMP tissues and STUMP tissues removed by surgical treatment from Ut-LMS or STUMP patients who died within 5 years of surgical treatment. However, in Ut-LMP tissues and STUMP tissues removed by surgical treatment, no correlation was found between the Cyclin E or Ki-67/MIB1 positivity rate % (number of cells positive for each factor/total number of cells x 100) and the life prognosis of Ut-LMS or STUMP patients.*

B. *The positive rate of cells expressing Cyclin E or Ki-67/MIB1 is the number of cells expressing Cyclin E or Ki-67/MIB1 divided by the total number of cells. The positive rate of cells expressing Cyclin E or Ki-67/MIB1 are plotted in the graphs. The expression levels of Cyclin E or Ki-67/MIB1 were quantified by an image analysis device, Mantra 2™ Quantitative Pathology Workstation (Akoya Biosciences, Inc. Marlborough, MA, USA). The expression levels of Cyclin E or Ki-67/MIB1 are plotted in the graphs.*

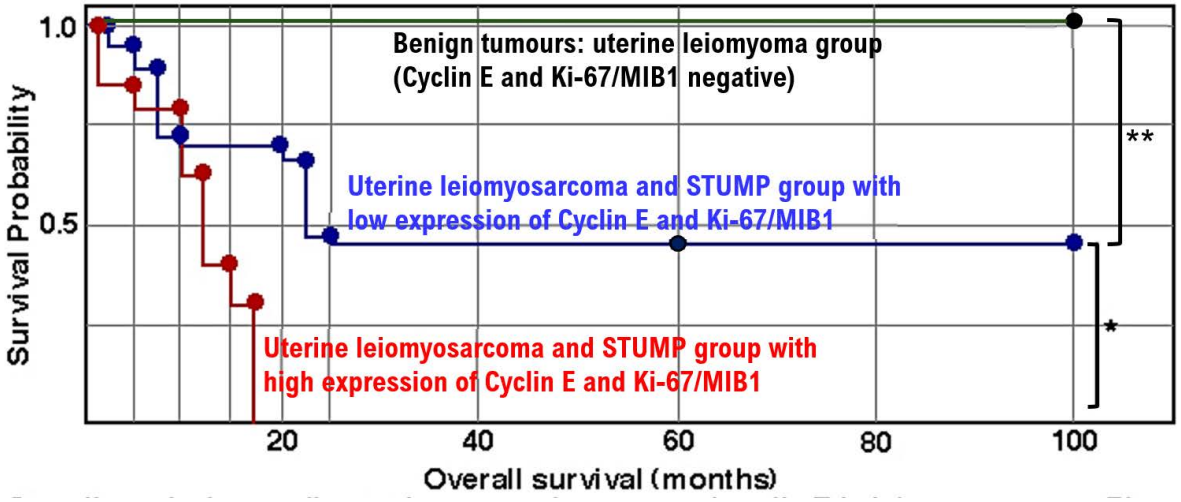


Figure 2. *Correlation between expression levels of Cyclin E and Ki-67/MIB1 and prognosis of uterine leiomyosarcoma and STUMP. The over survival was compared between a group of uterine leiomyosarcoma and STUMP with high expression of Cyclin E and Ki-67/MIB1 and a group of uterine leiomyosarcoma and STUMP with low expression of Cyclin E and Ki-67/MIB1. Survival of patients with benign mesenchymal tumors is consistently 100%. A correlation was observed between the expression levels of Cyclin E and Ki-67/MIB1 and the prognosis of uterine leiomyosarcoma and STUMP.*

Discussion.

Recent clinical reports have shown the expression of Lmp2/β1i mRNA and proteins in luminal and glandular epithelium, chorionic placenta, chorionic pancreatic cells, and arterial endothelial cells [34]. These results suggest that LMP2/β1i is involved in placental villus infiltration, extracellular matrix degradation, immune tolerance, glandular secretion, and angiogenesis [34]. This study is expected to help elucidate the regulatory role of LMP2/β1i in embryo implantation. Cyclin E1 immunoreactivity was observed in the nucleus and cytoplasm of cells in all Ut-LMS cases studied, while most cases of uLMA and normal myometrium tested negative for cyclin E1. Cyclin E1 is a regulatory protein involved in mitosis, and CDK and the gene product complex combine to form a maturation-promoting factor (MPF) [35]. Cyclin E1/CDK2 is involved in early mitotic events such as chromosomal condensation, nuclear membrane disruption, and spindle pole assembly. When cyclin E1 levels are depleted, the cyclin E1/CDK1 complex cannot be formed, and cells cannot enter the M phase, which slows down cell division. Some anticancer therapies are designed to prevent the formation of cyclin E1/CDK2 complexes in cancer cells and slow down or prevent cell division [36]. While most of these methods target the CDK2 subunit, there is growing interest in targeting cyclin E1 as well in the field of oncology. In other words, cyclin E1 regulation may provide clues to the development of new treatment options for uterine leiomyosarcoma. However, clinical risk factors for its development have not been identified due to the absence of suitable experimental animals. LMP2/β1i-deficient mice were the first spontaneous animal models of Ut-LMS. Therefore, poor LMP2/β1i expression might be one of the causes of Ut-LMS.

To date, several candidate factors as biomarkers have been reported for uterine leiomyosarcoma. For example, 5'-Nucleotidase Domain Containing 2 (NT5DC2) and tyrosine kinase-like orphan receptor 1 (ROR1) have been identified as possible factors that induce Ut-LMS proliferation. It was not detected as a biomarker candidate for Ut-LMS [37,38]. In actual clinical practice, cancer genomic medicine is used to select new antitumor agents for patients with advanced recurrent cancer by cancer gene panel testing. To date, new antitumor agents have been selected for several patients with advanced recurrent Ut-LMS by oncology gene panel testing; however, pathological variants of NT5DC2 and ROR1 molecules have not been detected.

Nevertheless, this clinical study has a few limitations, the main one being the fact that it was conducted in a cohort with a small number of cases. Therefore, to adequately demonstrate whether LMP2/β1i and cyclin E1 and Ki-67/MIB1 are potential biomarkers to differentiate between Ut-LMSs and uLMAs, the reliability and properties of LMP2/β1i and cyclin E1 as diagnostic indicators are being investigated at several clinical research sites. Clinical research is not over yet, and large-scale clinical trials need to be conducted to verify the findings obtained this time.

Conclusion.

The correlation between candidate biomarkers for uterine mesenchymal tumors (LMP2/β1i, cyclin E1, Ki-67) and the development of Ut-LMS has been revealed, and the identification of specific risk factors may lead to the development of new treatments for this disease. Ut-LMS is resistant to chemotherapy and has a poor prognosis. Molecular biological and cytological information derived from further research experiments with human tissues and LMP2/β1i-deficient mice will contribute significantly to the development of prophylaxis, potential diagnostic biomarkers, and new therapies for Ut-LMS.

(Note 1) The typical macroscopic appearance is a large (>10 cm), poorly bounded mass with a soft, fleshy consistency and a gray yellow to pink variegated cut surface with foci of hemorrhage and necrosis [6,7]. The histological classification of uterine sarcoma is based on homology with normal cell types

and includes human Ut-LMS (similar to the myometrium), stromal sarcoma (similar to the endometrial stroma), and other heterogeneous cell types (i.e., osteosarcoma and liposarcoma). Microscopically, most human Ut-LMS are clearly malignant, with hypercellularity, coagulative tumor cell necrosis, and abundant mitoses [>10–20 mitotis per 10 high-power fields] mf)], atypical mitosis, and cytological atypia. The mitotic rate is the most important determinant of malignant tumors; however, it is corrected by the presence of necrosis and cytological atypia. The diagnosis of human Ut-LMS can be made in the presence of tumor necrosis and mitosis. In the absence of tumor necrosis, the diagnosis can be made in the case of moderate-to-severe cytological atypia and a mitotic index greater than 10 mf/10 hpf. In the absence of necrosis and significant atypia, a high mitotic index is compatible with a benign clinical course; however, supporting data are limited [6,7].

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Competing Interest statement: The authors state No competing interest.

Data Availability: The authors declare that data supporting the findings of this study are available within the article.

Ethics approval and consent to participate: 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 Kyoto University School of Medicine (Kyoto, Japan) on August 25, 2023, 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.

Clinical Research: A multi-center retrospective observational clinical study of subjects who underwent cancer genomic medicine at a cancer medical facility in Kyoto, Japan. This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo, Japan) on November 18, 2020, and Kyoto University School of Medicine (Kyoto, Japan) on August 24, 2022, with approval codes NHO R4-04 and M237. All participants agreed to take part in the present study. We have obtained Informed Consent Statements from people participating in clinical studies.

Author Contributions: All authors had full access to the data in the study and took responsibility for the integrity of the data and accuracy of the data analysis. Y.T., T.H., M.O. and H.A.; Research Conduction, T.H., K.A.; Writing-Original Draft, S.T.; Discussion on Biochemical Function, T.H., K.A. and I.K.; Writing-Review & Editing, I.K.; Visualization, T.H. and I.K.; Supervision, T.H. and I.K.; Funding Acquisition.

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