Review

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Review

Clinicopathological Predictors of Recurrence in Uterine Sarcomas—A Narrative Review

Emmanuel N Kontomanolis [1] , Ioakeim Sapantzoglou [2]*, Konstantinos Nikolettos [3] , Evangelia Kontogeorgi [2], Vasiliki Lampraki [2], Dimitrios Papageorgiou [4], Paraskevas Perros [2], Zacharias Fasoulakis [2] , Aristotelis – Marios Koulakmanidis [2], Maria- Anastasia Daskalaki [2], Vasileios Pergialiotis [2], Panagiotis Antsaklis [2], Marianna Theodora [2] and George Daskalakis [2]

[1] Department of Obstetrics and Gynecology, Democritus University, Alexandroupolis, Greece
[2] 1st Department of Obstetrics and Gynecology, Alexandra Hospital, National and Kapodistrian University of Athens, Vasilissis Sofias 80 Aven., 11528 Athens, Greece
[3] Department of Gynecological Oncology, Maidstone and Turnbridge Wells, NHS Trust, Maidstone, UK
[4] Department of Gynecology, Athens Naval and Veterans Hospital, 115 21 Athens, Greece
* Correspondence: kimsap1990@hotmail.com

Abstract: Background: Sarcomas are a rare and biologically diverse group of malignant tumors that originate from mesenchymal tissues. They are characterized by a broad range of histopathological subtypes, varying clinical courses, and differing responses to treatment. This study seeks to clarify the clinicopathological and molecular predictors of recurrence in leiomyosarcomas, carcinosarcomas, and endometrial stromal sarcomas to enhance our understanding, thereby improving clinical knowledge, consultation practices, and the overall patient benefit. **Methods**: A literature search was conducted utilizing PubMed/MEDLINE, Embase, Cochrane Library, and Scopus to execute a comprehensive structured narrative review of articles published until 31 March 2025 **Results**: We summarized the current evidence on clinical, histological and molecular predictors of recurrence and poor prognosis of leiomyosarcomas, carcinosarcomas and endometrial stromal sarcomas. The stage, the grade and the tumour size, as well as, novel molecular biomarkers constitute crucial high risk parameters that have been associated with recurrence but data, so far, demonstrate contradictory results with the need of further research deemed necessary. **Conclusions**: Recent advancements in next-generation sequencing have facilitated the identification of women at increased risk of recurrence, poor disease-free survival, and overall adverse prognosis. The stratification of this risk requires a comprehensive understanding of the clinical, histological, and molecular risk factors involved. An understanding of those underlying factors is essential for effectively addressing the initial consultation, guiding management, and, considering the novel treatment modalities, individualizing the care for affected women.

Keywords: uterine sarcomas; recurrence; leiomyosarcoma; carcinosarcoma; endometrial stromal sarcoma; predictors

1. Introduction

Sarcomas represent a rare and biologically heterogeneous group of malignant neoplasms originating from mesenchymal tissues, distinguished by a wide spectrum of histopathological subtypes, variable clinical trajectories, and diverse therapeutic responses. Sarcomas account for approximately 1% of all malignancies of the female genital tract and represent about 3–7% of uterine cancers. [1,2]

Uterine sarcomas are subclassified into homologous and heterologous types. Homologous sarcomas arise from mesenchymal elements normally present in the uterus, such as uterine leiomyosarcoma (u-LMS, representing 30% of uterine sarcomas) and endometrial stromal sarcoma

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(ESS) (representing 15% of uterine sarcomas). Heterologous sarcomas originate from cell types not typically found in the uterus, including rhabdomyosarcoma, liposarcoma, and carcinosarcoma. Carcinosarcomas (also referred as "Malignant Mixed Müllerian Tumor") account for 50% of uterine sarcomas and although previously categorized as a subtype of uterine sarcoma due to their biphasic histology, they have been recently reclassified by the World Health Organization as high-grade endometrial carcinoma with sarcomatoid differentiation. [3,4]

Uterine sarcomas are associated with a significantly poorer prognosis and exhibit more aggressive clinical behaviour compared to the endometrial carcinomas. Five-year survival rates range from 30% to 48%, and relapse rates approach 60%, with 42% of the relapses occurring outside the pelvis. [5] This is attributed not only to their intrinsic biological aggressiveness, but also to the absence of specific early symptoms, limitations in diagnostic modalities, and the lack of well-established, standardized treatment protocols. Prognosis is closely influenced by histopathological subtype and the extent to which optimal multimodal therapy can be achieved. [6]

The present study aims to elucidate the underlying clinicopathological and molecular predictors of recurrence of leiomyosarcoma, carcinosarcoma and endometrial stromal sarcomas that have been investigated in the existing literature in an effort to enrich our understanding of their nature aiming as such to improve the clinical knowledge, our consultation and the overall survival of affected patients.

2. Materials and Methods

A literature search was conducted utilizing PubMed/MEDLINE, Embase, Cochrane Library, and Scopus to execute a comprehensive structured narrative review of articles published until 31 March 2025, employing the following search terms: "uterine sarcomas" AND "recurrence", OR "leiomyosarcoma", "recurrence" OR "carcinosarcoma", "recurrence" OR "endometrial stromal sarcoma", "recurrence". Chosen articles were mandated to be original works composed in English. Included studies contained systematic reviews, original studies, and case reports/series. Commentaries and news pieces were omitted. The studies underwent independent assessment by author I.S. The references of the papers were examined for any potentially overlooked studies. All publications found in prior systematic reviews were incorporated.

3. Results

3.1. Uterine Leiomyosarcomas(u-LMS)

3.1.1. Demographic Characteristics

The age at initial diagnosis of u-LMS has been repeatedly reported as a prognostic factor of the overall survival (OS) and recurrence free survival (RFS). Denschlag et al. in their retrospective analysis of 94 patients with different histologic types of uterine sarcoma demonstrated that in both univariate and multivariate analysis, OS was significantly associated with patient's age. [7] Similar to the above, D'Angelo et al. in their cohort of 52 patients with mesenchymal uterine tumours which included 20 cases of u-LMS patient's age was a significant contributor to the prognosis according to the univariate analysis, correlation that was not confirmed, however, after the multivariate analysis. [8] Those findings were, further, confirmed by larger study groups such as the studies by Kapp et al. and Tirumani et al., which investigated prognostic factors and survival in cohorts including 1396 and 113 patients with uterine sarcomas, respectively, a fact that was mostly attributed to the presentation of higher grade u-LMS in older patients. [9,10]

In accordance to the above, menopausal status has been, also, implicated to the poor prognosis and increase recurrence rates of u-LMS by several studies. A 1986 study which investigated prognostic factors and a number of treatment modalities in 209 patients, of which 81 with confirmed LMS and a 2-year recurrence rate of 23%, revealed that in their cohort the strongest prognostic marker of OS was the menopausal status of the women. [11] Similar results were demonstrated by a more recent study by Wang et al. in which univariate analysis associated both menopausal status and age

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above 50 years old with poor outcome but after multivariate analysis performed only menopause retained its statistical significance. [12]

3.1.2. Stage, Grade and Tumour Size

The tumour stage is the paramount prognostic determinant. Historically, uterine sarcomas were classified according to a staging method introduced in 1988 for endometrial cancer. However, this has not demonstrated adequacy and as such, in 2009, a novel FIGO staging method was established for uterine sarcomas. This updated staging system comprises two divisions: one for leiomyosarcoma and endometrial stromal sarcoma (ESS), and another for adenosarcoma. Carcinosarcoma is currently staged according to the endometrial carcinoma staging system. [13] Various studies have shown inconsistency in the correlation between survival and factors such as clinical stage, grade and tumour size with those factors being the most investigated parameters in terms of recurrence and OS. [14] Several older studies have demonstrated that FIGO tumour stage appear to be a significant contributor to the OS and recurrence rates. [8, 15,16] To be more specific, D'Angelo et al. revealed that stage was the only parameter that remained statistically significant after the multivariate analysis. [8] However, parameters such as the tumour size and the mitotic count did not demonstrate any significant correlation with survival, findings that were inconsistent with the results of a previous study by Abeler et al. involving 245 leiomyosarcomas confined to the uterus that identified tumour size and mitotic index as significant prognostic factors, eventually facilitating the stratification of the patients into three distinct risk groups, demonstrating notable differences in prognosis. [17] In their next study, though, which included a larger study group, the same authors demonstrated that tumour size greater than 10 cm (with all stages being included) demonstrated prognostic significance in both univariate and multivariate analyses. [18] More recent studies have produced contradicting results in relation to the association of tumor stage with OS and recurrence but most of them agree on the fact that tumor size constitutes an independent risk factor both for OS and progression-free survival (PFS).[6,10,12,19,20] To be more specific, Dermawan et al. [20] and Wang et al.[6] reviewed the data from 177 and 63 patients with u-LMS of any stage demonstrating that tumor size above 10 cm and 7.5cm ,respectively, is correlated with an unfavourable outcome in terms of OS and recurrence and its prognostic significance seems to remain even in uterine confined disease(FIGO Stage 1).[19] The grade of the u- LMS has been also investigated by some studies but only 2 of the retrieved studies have revealed an association between the documentation of high grade tumour and poor prognosis with the authors ,however, acknowledging a number of limitations for their studies and the generalizability of their results. [9,16]

3.1.3. Mitotic Index/Count

The mitotic index quantifies the proportion of cells undergoing division observed in a high-power field under a microscope and the combination of typically 15 mitotic figures per 10 high-power fields (MF/10HPF), along with hypercellularity and severe nuclear atypia characterizes malignant smooth muscle tumours of the uterus. [2] A number of published studies have associated the detection of high mitotic count, using different cut-offs, with worse prognosis. [17,18,19]. D'Angelo et al. stratified patients into two categories demonstrating different prognosis with a mitotic index of ≥ 20 MF/10 HPF being a predictor of adverse prognosis while Chen et al signified a cut off of >10/10HPF as an independent prognostic factor. Another study that included 349 patients with either intra-abdominal or distant metastatic disease revealed that mitotic count >10M/10HPF was the only parameter that carried a statistically significant risk for poor prognosis. [21] The significance of mitotic index is further highlighted by its implementation, along with other 6 clinicopathologic features, in a u – LMS specific nomogram that was created in an effort to stratify patient groups regarding their post-surgery prognosis more precisely. [22] This model was both internally and externally validated [23] demonstrating a prediction accuracy which was very close to the actual outcomes in terms of overall survival.

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3.1.4. Molecular Biomarkers

Several molecular markers have been investigated to assess their contribution to the prediction of recurrence and OS in patients with u- LMS. [8, 15,18-21] ki67 and p53 have been thoroughly explored with Zhai et al. [24] reporting statistically increased number of ki67 positive cells and abnormally higher expression of the tumour suppressor gene oncogene p53 in cases of u-LMS compared to cellular and usual leiomyoma , as well as, tumours of uncertain malignant potential, with ki67 being useful in differentiating those entities among each other. More recent studies have demonstrated that that strong expression of ki-67 and p53 is associated with recurrence and poor OS on long term follow up [8,19] To be more precise, D'Angelo et al. on their 2009 study revealed that u-LMS that were negative or expressing low levels of Ki-67, p53, p16, and Twist were associated with a more favourable outcome with the same authors on a study that followed 2 years later concluding that tumours measuring 10 cm or more in diameter, exhibiting 20 or more mitotic figures per 10 high-power fields, demonstrating 10% or greater immunoreactive nuclei for Ki67 and testing negative for Bcl-2, were associated with a poorer prognosis. [8,18]. Contrary to the above, the investigation of bcl-2 (a biomarker correlated with cellular apoptosis) has produced contradictory results with Lusby et al. concluding that increased levels of bcl-2 may predict longer disease-specific survival while other authors have associated its presence and expression with an adverse outcome. [8,18,21] b-catenin (a contributing factor to the Wnt signalling pathway) has, also, been investigated with the overexpression of its nuclear subtype being associated with both extension of the malignancy outside the uterus at initial diagnosis and intraperitoneal recurrence. [21,25] Wilms tumour gene 1 (WT1) has been, also, identified by a study as an independent prognostic marker for OS [15] while a recent study has demonstrated that u – LMS negative for the expression with dystrophin demonstrate a worse overall survival compared to the u – LMS positive malignancies. [26] Finally, recently, Dermawan presented a genomic model of stratification patients with u – LMS which demonstrated a significantly increased risk of poor progression-free survival and disease-specific survival when TP53 mutation and chr20q amplification/ATRX mutations were present at the same time, concluding that such a stratification seems to outperforms traditional clinicopathologic models in predicting clinical outcomes. [20]

3.2. Uterine Carcinosarcomas (UCS)

Uterine carcinosarcoma, also known as malignant mixed Müllerian tumor, is a high-grade endometrial-originated neoplasm that comprises about 5% of endometrial cancers, characterized by poor prognosis. [28]

Although uterine carcinosarcoma was historically categorized as a type of sarcoma, advances in molecular and genetic research have highlighted that the sarcomatous element of carcinosarcomas arises through trans-differentiation from the epithelial (carcinomatous) component. Consequently, UCS is now widely regarded as a form of metaplastic endometrial carcinoma. [29,30,31,32]

3.2.1. Demographic Characteristics

Uterine carcinosarcoma is typically considered an elderly disease, with peak incidence reported in the 70–79-year age group. However, Matsuzaki S. et al reported a significant increase in the age-adjusted incidence rate of UCS, rising from 1.0 to 1.4 per 100,000 between 2000 and 2016 .[33] During the same period, the incidence rate increased by 1.7% annually (95% CI, 1.2–2.2). [33,34] Notably, women aged 60–69 years exhibited the largest interval increase in incidence, with an annual percent change (APC) of 2.7% (95% CI, 1.9–3.4, $P < 0.001$), followed by those aged 70–79 years (APC 2.0%, 95% CI, 1.2–2.9, $P = 0.001$) and those aged 50–59 years (APC 1.2%, 95% CI, 0.5–2.0, $P = 0.002$). This trend reflects a decrease in the average age of diagnosis, which has shifted from 71.7 years to 67.0 years between 1989 and 2013. [33]

An elevated risk of uterine carcinosarcoma has been reported among black women and those with obesity, aligning with known risk factors for endometrial malignancies. [35,36,37] According to

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the findings of Matsuzaki et al., black women exhibited a disproportionately higher incidence of uterine carcinosarcoma compared to other racial and ethnic groups, with an age-adjusted rate of 2.9 per 100,000, in contrast to 0.8–1.2 per 100,000 among other populations. Of note, the greatest interval increase in UCS incidence from 2000 to 2016 was observed among Hispanic women (annual percent change [APC] 2.7; 95% CI, 1.7–3.6; P < 0.001), followed by black (APC 2.3; 95% CI, 1.4–3.3; P < 0.001) and white women (APC 1.1; 95% CI, 0.5–1.7; P = 0.002).[33]

3.2.2. Stage, Grade and Tumour Size

Uterine carcinosarcoma is associated with a notably poor prognosis across all stages of disease. According to SEER, while approximately 43.9% of uterine carcinosarcoma cases are diagnosed at stage I, a substantial proportion present with advanced-stage disease, with 8.7% at stage II, 22.9% at stage III, and 24.4% at stage IV.[38]

As reported in recent reviews, even patients with stage I disease experience limited survival, with a 5-year overall survival rate of 54.8%. Survival decreases significantly with disease progression, with corresponding 5-year OS rates of 36.9% for stage II, 24.9% for stage III, and only 9.2% for stage IV (P < 0.001). Median OS similarly declines from 78 months in stage I to 30, 19, and 8 months in stages II, III, and IV, respectively. These data underscore the strong prognostic value of disease stage in determining survival outcomes in patients with uterine carcinosarcoma. [3,33]

Several additional clinicopathological parameters have been shown to negatively influence 3-year overall survival in uterine carcinosarcoma. These include a primary tumor diameter ≥5 cm (hazard ratio [HR] 2.23; 95% confidence interval [CI] 1.32–3.77; p = 0.003), deep myometrial invasion (HR 2.82; 95% CI 1.77–4.48; p = 0.001), lymphovascular space invasion (LVSI) (HR 2.11; 95% CI 1.26–3.52; p = 0.005), rhabdomyoblastic differentiation of the sarcomatous component (HR 2.58; 95% CI 1.30–7.35; p = 0.046), and the presence of residual tumor >1 cm after surgery (HR 1.75; 95% CI 1.07–2.84; p = 0.0245). [39,40] Furthermore, a rising trend in lymph node metastasis has been noted over time, with nodal involvement observed in nearly 25% of UCS cases as of 2016. [38,39]

The carcinomatous component of uterine carcinosarcomas, particularly when high-grade, has been identified in multiple studies as an adverse prognostic factor. This may be attributed to the intrinsically aggressive behavior of the epithelial element, which is more frequently associated with metastatic dissemination and lympho-vascular invasion compared to the mesenchymal component. [41,42,43] Nordal et al. demonstrated that the presence of serous and clear cell histologic subtypes within the carcinomatous component is associated with an adverse prognosis. In contrast, the histologic grade of differentiation of the carcinomatous component did not appear to influence clinical outcomes. [34] Kim et al. investigated the prognostic impact of the heterologous element in gynecologic carcinosarcomas. In their meta-analysis, including uterine and ovarian carcinosarcomas, the presence of heterologous components was significantly associated with decreased overall survival, while no significant correlation was found with pooled RFS or disease-free survival (DFS), further supported by subgroup analysis. [44]

3.2.3. Molecular Biomarkers

Multiple molecular classifications have been explored for their potential prognostic relevance in UCS. The Cancer Genome Atlas (TCGA) has proposed four molecular subgroups: the POLE-ultra mutated (POLEmut) subtype, associated with favorable prognosis; the microsatellite instability/mismatch repair-deficient (MSI/MMRd) group and the no specific molecular profile (NSMP) group, both associated with intermediate prognosis; and the TP53-mutant/p53-abnormal (TP53mut/p53abn) subtype, which is linked to poor clinical outcomes. [29,45-50] According to Tavaglino et al., patients with NSMP and TP53mut/p53abn UCS demonstrated inferior progression-free survival (PFS) compared to those with MSI/MMRd tumors (HR of 0.19 (95% confidence interval [CI] 0.08– 0.46; P < 0.001). However, overall survival was comparable between MSI/MMRd, NSMP, and TP53mut/p53abn subgroups (HR of 0.91 (95% CI 0.44– 1.87; P = 0.788) and 1.51 (95% CI 0.76–2.99; P = 0.240). Among patients with POLE-mutated tumors, no cases of disease progression or death

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were observed during the follow-up period, indicating an excellent prognosis in terms of both progression-free and overall survival. [51]

Epithelial–mesenchymal transition (EMT) is a biological process in which epithelial cells lose apical–basal polarity and intercellular adhesion, acquiring mesenchymal properties such as enhanced motility, invasiveness, and resistance to apoptosis. [52,53] EMT is critically involved in the sarcomatous dedifferentiation observed in uterine carcinosarcomas. [54] Among the commonly altered genes in these tumors, such as TP53, PIK3CA, FBXW7, PTEN, and ARID1A, the tumor suppressor FBXW7 appears to have a significant impact in promoting EMT. In vivo evidence has demonstrated that co-inactivation of Fbxw7 and Pten in murine models leads to a stepwise progression from endometrioid intraepithelial neoplasia to invasive adenocarcinoma and ultimately to carcinosarcoma. [30,55] Notably, all resulting carcinosarcomas exhibited heterologous sarcomatous elements, suggesting that FBXW7 may also contribute to the development of heterologous components. [56]

WT1 has been recognized as an independent negative prognostic marker for overall survival, highlighting its biological and clinical significance in uterine sarcomas. [15]

Han et al demonstrated that aurora kinase expression may serve as a novel adverse prognostic biomarker in uterine carcinosarcoma, given its apparent association with lymphatic metastasis, vascular invasion, and omental dissemination. High expression levels of both phospho-aurora kinase A and aurora kinase B have been identified as predictors of reduced progression-free survival ($P = 0.049$). Furthermore, aurora kinase activity appears to promote bidirectional tumor dissemination through both lymphatic and hematogenous pathways. These findings highlight the biological relevance of aurora kinases in UCS pathogenesis and suggest that aurora kinase inhibitors may represent a promising therapeutic strategy. [57]

HER2 oncogene expression in uterine carcinosarcoma has been reported with considerable variability in the literature, ranging from 6% to 56%. [58,59] The presence of HER2 is a well-established adverse prognostic marker in various malignancies, such as uterine serous carcinoma. [60,61] Further research is warranted to elucidate the potential therapeutic benefit of HER2-targeted treatments in uterine carcinosarcoma and their impact on improving the disease prognosis. [62,63]

3.3. Endometrial Stromal Sarcoma (ESS)

Endometrial stromal sarcoma is a rare subtype of uterine mesenchymal neoplasm representing approximately 1% of all uterine malignancies and less than 10% of uterine sarcomas [64].

3.3.1. Stage, Grade and Surgical Approach

The ESS classification has changed over the years, being historically divided into two types: the low grade endometrial stromal sarcoma (LGESS) and undifferentiated endometrial sarcoma (UES) [65]. However, in 2014, WHO classified the endometrial stromal tumors (ESTs) based on their immunohistochemistry and molecular findings into 4 subtypes- endometrial stromal nodule (ESN), low grade ESS (LGESS), high grade ESS (HGESS) and undifferentiated uterine sarcoma (UUS) [66]. This categorization stems from findings indicating that LGESS and HGESS display relatively simple karyotypes at the molecular level, in contrast to UUS, in which specific chromosomal rearrangements are absent [66]. Several studies [67-75] have identified tumor size, mitotic count, tumor stage, histologic grade, margin involvement, menopausal status, and age as factors of prognostic importance.

Despite observed differences in clinical outcomes, there remains considerable controversy regarding the factors that determine prognosis with studies reporting that early-stage disease, low mitotic count, and absence of deep myometrial invasion are associated with improved overall survival, whereas patient's age and adjuvant therapy had no significant impact. [76,77] Contrary to the above, other studies such as Nordal et al., in their cohort study, identified free surgical margins at primary resection as the strongest prognostic factor, followed by tumor grade, tumor size, and menopausal status .[67] Furthermore, Bodner et al. identified early tumor stage, limited myometrial

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invasion, and low mitotic count as prognostic factors associated with prolonged overall survival in patients with ESS while age, histologic grade, and the use of adjuvant therapy did not appear to impact overall survival [77] Ongoing uncertainty about the natural history and prognostic indicators of this disease continues to hinder the development of a standardized management approach.

Surgery, typically involving hysterectomy and bilateral salpingo-oophorectomy (BSO), has consistently been regarded as the most effective treatment for uterine sarcomas . [78,79,80], In line with previous studies, the findings of a study of Nordal et al., indicate that early tumor stage (FIGO stage I) is the most significant prognostic factor in ESS [67, 24, 25]. A low FIGO stage seems to facilitate complete primary surgical resection, thereby improving the likelihood of long-term survival in patients with ESS. . However, the prognostic value of lymph node metastasis and the therapeutic role of lymphadenectomy remains controversial [81,82,83].

As such, the prognosis of patients diagnosed at an early stage is generally excellent [75, 84]. Nevertheless, late recurrences have been reported [75,85]. In view of the above along with the younger age at diagnosis and the favorable early-stage prognosis has led the authors of a recent systematic review to advocate that ovarian preservation may be considered to avoid the adverse effects of surgical menopause [86].

However, data regarding the impact of ovarian preservation on the recurrence of endometrial stromal sarcoma are conflicting. While patients who undergo BSO tend to have improved DFS [84,86], BSO does not appear to significantly influence time to recurrence or overall survival (OS) [85]. However, the study included heterogeneous patient populations encompassing all disease stages and was limited by a relatively short follow-up period. The Gynecologic Cancer InterGroup (GCIG) consensus review indicated that ovarian preservation does not adversely affect survival. As a result, it recommended that ovarian preservation be considered, particularly in younger women, to avoid menopausal symptoms and maintain quality of life [85].

Contrary to the above, a recent retrospective analysis suggested that oophorectomy in patients with retained ovaries was associated with an improved DFS compared to patients without oophorectomy [87].

The prognostic relevance of lymph node metastasis and the role of complete lymphadenectomy in endometrial stromal sarcoma remains a subject of ongoing debate [81, 82, 83, 88]. Reported rates of nodal metastasis vary widely, with incidence ranging from 6.6% to 7% and prevalence from 0% to 37% [84, 89-91]. A retrospective analysis of factors affecting recurrence on endometrial stromal sarcomas, in European Journal of Obstetrics an d Gynecology was unable to confirm a clear prognostic impact of lymphadenectomy. Nevertheless, the surgical removal of metastatic lymph nodes, along with resection of visible extra-uterine disease, was associated with improved DFS [87].

Cytoreductive surgery has become a well-established component of treatment for advanced endometrial cancer [92,93]. Evidence from a multicenter retrospective study indicates that reducing tumor burden to less than 2 cm is significantly linked to better survival outcomes in patients with HGESS [94]. The findings of this study of Leath et al. also demonstrate that thorough staging and cytoreductive surgery lead to improved disease-free survival in both high-grade (HGESS) and low-grade (LGESS) variants. However, the most effective adjuvant treatment approach remains uncertain [80].

In line with published literature, the study of Leath et al also confirms that HGESS carry a worse prognosis than LGESS, underscoring the necessity of combining cytoreductive surgery with adjuvant treatment in these high-grade cases [94]. It is worth noting that most existing studies on adjuvant therapy for HGESS are retrospective and often include cases of UUS, based on earlier WHO classifications [95].

3.3.2. Immunohistochemical/Molecular Markers

Recent advancements have demonstrated that immunohistochemistry is valuable not only for distinguishing between different malignant types but also for assessing the prognosis of tumors in the female reproductive system. However, there are still no immunohistochemical markers that are

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uniquely specific for diagnosing ESS. Studies have demonstrated that ESS may be positive for several markers, including CD10, vimentin, HHF35, desmin, CD34, cytokeratin (CK), CD99, smooth muscle actin, as well as estrogen and progesterone receptors [88]. CD10, also referred to as the acute lymphoblastic leukemia antigen, is a neutral endopeptidase located on the cell surface that inactivates biologically active peptides and may represent a molecular marker that correlates with prognosis of ESS patients [88]. Recent findings by Oliva et al. [96] showed that only 10% of endometrial stromal tumors were tested positive for CD10 but studies by Agoff et al. [97] and McCluggage et al. [98] reported the absence of CD10 in 4 out of 4 and 4 out of 6 high-grade ESS cases, respectively. The authors suggested that reduced CD10 expression in high-grade ESS may be associated with the level of tumor differentiation.

In addition, there was an attempt by Youn Jin Choy et al. to demonstrate potential genetic features of UUSs, tumors that by definition do not harbor any of the ESS-specific fusions [42].In their analysis, the ESS cases included demonstrated between 6 and 36 non-silent somatic mutations per genome. However, these did not involve commonly known mutations such as TP53, KRAS, or PIK3CA. Regarding copy number alterations (CNAs), the study revealed that ESSs contain not only gene fusions specific to ESS but also somatic mutations and copy number alterations involving driver genes suggesting that gene fusions by themselves may not be sufficient for the full development of ESS, similar to what has been observed in other types of tumors.

In accordance to the above, several studies identified a number of genes in undifferentiated uterine sarcomas that showed both copy number alterations and corresponding changes in gene expression. Specifically, PRKAR1A, CDH1, RB1, and TP53 were downregulated alongside CNA losses, while EZR was upregulated with a CNA gain. It was demonstrated that the loss of CDH1, which is a tumor suppressor gene encoding E-cadherin, has been linked to the development of various cancers [100,101] and increased invasiveness and tumor progression.

As is commonly known, in 2003, the World Health Organization revised the classification of endometrial stromal sarcomas by removing mitotic count as a criterion and emphasizing nuclear atypia and necrosis as key diagnostic features for distinguishing between low-grade endometrial stromal sarcoma, which has a favourable prognosis (over 90% recurrence-free survival), and undifferentiated endometrial sarcoma, which is associated with poor outcomes. In the study of Weiwei Feng et al, the authors investigated whether proliferation biomarkers could predict recurrence in WHO 2003-defined ESS-LG cases. A survival analysis was conducted to assess the prognostic value of traditional mitotic counts (Mitotic Activity Index) from H&E-stained sections, along with immunohistochemical markers of proliferation such as Ki-67 and Phosphohistone H3 (PPH3) in a cohort of 24 invasive ESS cases. Recurrence occurred in 3 out of 24 patients (12.5%). All three biomarkers—MAI, PPH3, and Ki-67—showed significant prognostic value, with p-values of 0.001, 0.002, and 0.03, respectively [102]. With standardized protocols now available for assessing the Mitotic Activity Index and the immunohistochemical proliferation markers Ki-67 and PPH3, a diagnostic model that incorporates these three indicators may provide enhanced diagnostic utility [102]. Ki-67 is expressed in nearly all phases of the cell cycle—G1, S, and G2—making it a broad marker of cell proliferation while, in contrast, the PPH3 antigen is expressed almost exclusively in cells during the late G2 phase and throughout the M phase, where mitotic figures are visible. The prognostic significance of those three proliferation markers is particularly noteworthy, as they reflect distinct phases of the cell cycle and exhibit only partial overlap in their expression patterns. These finding highlight that the elevated levels of these markers in recurrent ESS-LG cases truly represent a biologically increased growth rate [102].

The cell proliferation index, evaluated using the MIB-1 antibody targeting the Ki-67 antigen, is widely utilized and accepted due to its clear, high-contrast staining pattern and its compatibility with standard laboratory procedures. Numerous studies have demonstrated its diagnostic and prognostic utility. In a small series of 11 low-grade ESS cases, it accurately identified the 2 patients who went on to develop recurrent disease [103]. In summary, the combined evaluation of MAI, Ki-67, and PPH3

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may be valuable in cases of low-grade ESS in identifying approximately 10% of patients who are at an elevated risk of recurrence.

Other studies have also demonstrated a link between high recurrence risk and increased cellular proliferation in LGESS [92]. Additionally, ESSs have been shown to express the MIB-1 proliferation marker significantly more frequently than endometrial stromal nodules (ESNs) [104]. The role of EGFR (epidermal growth factor receptor) in ESS remains unclear. While up to 70% of low-grade ESS cases have shown positive EGFR expression [104], suggesting the potential for targeted therapy using monoclonal antibodies against EGFR, other studies have reported much lower expression rates (as low as 11%), with no evidence of EGFR gene amplification. Therefore, findings of EGFR overexpression in the absence of gene amplification should be interpreted with caution [102].

3.4. Future Directions

Despite recent advancements in the comprehension of their genetic and molecular characteristics, high-grade variants such as HG-ESS and UUS presents considerable challenges in both diagnosis and treatment, given the fact that they present significant clinical challenges due to their molecular heterogeneity, aggressive characteristics, and restricted therapeutic alternatives. The necessity for innovative pharmacological approaches, as such, is critical, given that traditional treatments, such as chemotherapy and radiation, frequently demonstrate restricted effectiveness. Immunotherapy seems to demonstrate promising outcomes but additional research is necessary to identify potential responders and the underlying factors that are associated with increased risk of recurrence or overall poor prognosis. Furthermore, future research should focus on identifying pertinent mutations in diagnostically challenging cases, further improving the accuracy of conventional diagnostics and while surgery is to date the primary treatment modality for uterine sarcomas, studies seem to highlight that the incorporation of molecular typing and molecular-specific individualized therapies may enhance patient outcomes.

4. Conclusions

Over the past years, advancements in the field of next-generation sequencing has enabled the identification of multiple genetic anomalies, particularly fusions, in various uterine mesenchymal tumors leading not only to the distinction of histological patterns that further enhance the existing categorization and treatment options for sarcomas but also to the identification of the women who display increased risk of recurrence, poor disease free survival and an overall adverse prognosis. The stratification of this risk necessitates a deep knowledge of the underlying clinical, histological and molecular risk factors. Such an understanding is a crucial component in an effort to address in the most appropriate way the initial consultation, to guide the management and ,in view of the novel treatment modalities, to individualize the care of those women based on the histological and molecular characteristics of their disease.

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Abbreviations

The following abbreviations are used in this manuscript:
u-LMS - uterine leiomyosarcoma
CS - carcinosarcoma
ESS - endometrial stromal sarcoma
OS – Overall Survival
DFS – Disease Free Survival
MF - mitotic figures
HPF - high-power fields
WT1 - Wilms tumour gene 1
APC - annual percent change
PFS - progression-free survival
LVSI - lymphovascular space invasion
TCGA - The Cancer Genome Atlas
POLEmut - POLE-ultra mutated
MSI/MMRd - microsatellite instability/mismatch repair-deficient
NSMP - no specific molecular profile
TP53mut/p53abn - TP53-mutant/p53-abnormal
EMT - Epithelial–mesenchymal transition
LGESS - low grade endometrial stromal sarcoma
UES - undifferentiated endometrial sarcoma
BSO - bilateral salpingo-oophorectomy
GCIG - Gynecologic Cancer InterGroup
CNA - copy number alterations
PPH3 - Phosphohistone H3
EGFR - epidermal growth factor receptor

References

1. Major FJ et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. *Cancer*.**1993**;71:1702–1709
2. Roy M, Musa F, Taylor SE, Huang M. Uterine Sarcomas: How to Navigate an Ever-Growing List of Subtypes. *Am Soc Clin Oncol Educ Book*. 2022 Apr;42:1-10. doi: 10.1200/EDBK_350955. PMID: 35471831.
3. Mbatani N et al. Uterine sarcomas. *Int J Gynaecol Obstet*. **2018** Oct:143 Suppl 2:51-58.
4. Croce S et al. Uterine sarcomas and rare uterine mesenchymal tumors with malignant potential. Diagnostic guidelines of the French Sarcoma Group and the Rare Gynecological Tumors Group. *Gynecol Oncol*. **2022** Nov;167(2):373-389.
5. Sharmilee B. Korets et al. Surgical options for recurrent uterine sarcomas. *Am Soc Clin Oncol Educ Book*. 2012:362-6.
6. Wang F et al. Clinical characteristics and prognosis analysis of uterine sarcoma. *BMC Cancer*. **2022** Oct 7;22(1):1050.
7. Denschlag D, Masoud I, Stanimir G, Gilbert L. Prognostic factors and outcome in women with uterine sarcoma. *Eur J Surg Oncol*. **2007** Feb;33(1):91-5. doi: 10.1016/j.ejso.2006.11.012.
8. D'Angelo E, Spagnoli LG, Prat J. Comparative clinicopathologic and immunohistochemical analysis of uterine sarcomas diagnosed using the World Health Organization classification system. *Hum Pathol*. **2009** Nov;40(11):1571-85. doi: 10.1016/j.humpath.2009.03.018
9. Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. *Cancer*. **2008** Feb 15;112(4):820-30. doi: 10.1002/cncr.23245. PMID: 18189292.

 doi:10.20944/preprints202506.0846.v1

11. Tirumani SH, Deaver P, Shinagare AB, Tirumani H, Hornick JL, George S, Ramaiya NH. Metastatic pattern of uterine leiomyosarcoma: retrospective analysis of the predictors and outcome in 113 patients. *J Gynecol Oncol*. **2014** Oct;25(4):306-12. doi: 10.3802/jgo.2014.25.4.306.
12. George M, Pejovic MH, Kramar A. Uterine sarcomas: prognostic factors and treatment modalities--study on 209 patients. *Gynecol Oncol*. **1986** May;24(1):58-67. doi: 10.1016/0090-8258(86)90008-9. PMID: 3699577.
12. Wang JF, Li C, Yang JY, Wang YL, Ji J. Clinicopathological characteristics and prognosis of uterine sarcoma: a 10-year retrospective single-center study in China. *Diagn Pathol*. **2024** Jul 5;19(1):94. doi: 10.1186/s13000-024-01517-x. PMID: 38970112; PMCID: PMC11225383.
13. Prat J. FIGO staging for uterine sarcomas. *Int J Gynaecol Obstet*. **2009** Mar;104(3):177-8. doi: 10.1016/j.ijgo.2008.12.008.
14. Oliva E. Cellular mesenchymal tumors of the uterus: a review emphasizing recent observations. *Int J Gynecol Pathol*. **2014** Jul;33(4):374-84. doi: 10.1097/PGP.0000000000000141. PMID: 24901397.
15. Coosemans A, Van Calster B, Verbist G, Moerman P, Vergote I, Van Gool SW, Amant F. Wilms tumor gene 1 (WT1) is a prognostic marker in high-grade uterine sarcoma. *Int J Gynecol Cancer*. **2011** Feb;21(2):302-8. doi: 10.1097/IGC.0b013e318207cab5. PMID: 21734473.
16. Giuntoli RL 2nd, Metzinger DS, DiMarco CS, Cha SS, Sloan JA, Keeney GL, Gostout BS. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. *Gynecol Oncol*. **2003** Jun;89(3):460-9. doi: 10.1016/s0090-8258(03)00137-9. PMID: 12798712.
17. Abeler VM, Røyne O, Thoresen S, Danielsen HE, Nesland JM, Kristensen GB. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. *Histopathology*. **2009** Feb;54(3):355-64. doi: 10.1111/j.1365-2559.2009.03231.x. PMID: 19236512.
18. D'Angelo E, Espinosa I, Ali R, Gilks CB, Rijn Mv, Lee CH, Prat J. Uterine leiomyosarcomas: tumor size, mitotic index, and biomarkers Ki67, and Bcl-2 identify two groups with different prognosis. *Gynecol Oncol*. **2011** May 1;121(2):328-33. doi: 10.1016/j.ygyno.2011.01.022.
19. Chen S, Deng Y, Zhai Y, Zhan Y, Li X, Wang J, Bai H. Clinical Analysis and Prognostic Prediction Model for Patients with Uterine Leiomyosarcoma at FIGO Stage I. *Int J Womens Health*. **2023** Apr 11;15:545-557. doi: 10.2147/IJWH.S406381. PMID: 37069963; PMCID: PMC10105571.
20. Dermawan JK, Chiang S, Singer S, Jadeja B, Hensley ML, Tap WD, Movva S, Maki RG, Antonescu CR. Developing Novel Genomic Risk Stratification Models in Soft Tissue and Uterine Leiomyosarcoma. *Clin Cancer Res*. **2024** May 15;30(10):2260-2271. doi: 10.1158/1078-0432.CCR-24-0148. PMID: 38488807; PMCID: PMC11096044.
22. Lusby K, Savannah KB, Demicco EG, Zhang Y, Ghadimi MP, Young ED, Colombo C, Lam R, Dogan TE, Hornick JL, Lazar AJ, Hunt KK, Anderson ML, Creighton CJ, Lev D, Pollock RE. Uterine leiomyosarcoma management, outcome, and associated molecular biomarkers: a single institution's experience. *Ann Surg Oncol*. **2013** Jul;20(7):2364-72. doi: 10.1245/s10434-012-2834-0.
23. Zivanovic O, Jacks LM, Iasonos A, Leitao MM Jr, Soslow RA, Veras E, Chi DS, Abu-Rustum NR, Barakat RR, Brennan MF, Hensley ML. A nomogram to predict postresection 5-year overall survival for patients with uterine leiomyosarcoma. *Cancer*. **2012** Feb 1;118(3):660-9. doi: 10.1002/cncr.26333.
24. Iasonos A, Keung EZ, Zivanovic O, Mancari R, Peiretti M, Nucci M, George S, Colombo N, Carinelli S, Hensley ML, Raut CP. External validation of a prognostic nomogram for overall survival in women with uterine leiomyosarcoma. *Cancer*. **2013** May 15;119(10):1816-22. doi: 10.1002/cncr.27971.
25. Zhai YL, Kobayashi Y, Mori A, Orii A, Nikaido T, Konishi I, Fujii S. Expression of steroid receptors, Ki-67, and p53 in uterine leiomyosarcomas. *Int J Gynecol Pathol*. **1999** Jan;18(1):20-8. doi: 10.1097/00004347-199901000-00004. PMID: 9891238.
26. Kildal W, Pradhan M, Abeler VM, Kristensen GB, Danielsen HE. Beta-catenin expression in uterine sarcomas and its relation to clinicopathological parameters. *Eur J Cancer*. **2009** Sep;45(13):2412-7. doi: 10.1016/j.ejca.2009.06.017.
27. Vadasz B, Felicelli C, Feng Y, Yin P, Zhang Q, Bulun S, Wei JJ. Loss of dystrophin is common in uterine leiomyosarcoma: a potential biomarker for clinical application. *Hum Pathol*. **2023** Apr;134:85-91. doi: 10.1016/j.humpath.2022.12.011.

 doi:10.20944/preprints202506.0846.v1

28. Yang Q, Falahati A, Khosh A, Lastra RR, Boyer TG, Al-Hendy A. Unraveling the Role of Bromodomain and Extra-Terminal Proteins in Human Uterine Leiomyosarcoma. *Cells*. **2024** Aug 28;13(17):1443. doi: 10.3390/cells13171443. PMID: 39273015; PMCID: PMC11394028.
28. Cantrell L.A., Blank S.V., Duska L.R. Uterine carcinosarcoma: a review of the literature, *Gynecol. Oncol*. **2015**; 137, 581–588
29. Gotoh O., Sugiyama Y., Takazawa Y., Kato K., Tanaka K., Omatsu K., Takeshima N., Nomura H., Hasegawa K., Fujiwara K., Taki M., Matsumura N., Noda T., Mori S. Clinically relevant molecular subtypes and genomic alteration-independent differentiation in gynecologic carcinosarcoma, *Nat. Commun*. **2019**; 10, 4965.
30. Cherniack A.D., Shen H., Walter V., Stewart C., Murray B.A., Bowlby R., Hu X., Ling S., Soslow R.A., Broaddus R.R., Zuna R.E., Robertson G., Laird P.W., Kucherlapati R., Mills G.B., Weinstein J.N., Zhang J., Akbani R., Levine D.A. Integrated molecular characterization of uterine carcinosarcoma, *Cancer Cell*. **2017**; 411–423.
31. Zhao S. et al. Mutational landscape of uterine and ovarian carcinosarcomas implicates histone genes in epithelial-mesenchymal transition, *Proceedings of the National Academy of Sciences of the United States of America*. **2016**; 113 , 12238–12243.
32. Berton-Rigaud D., Devouassoux-Shisheboran M., Ledermann J.A., Leitao M.M, Powell M.A., Poveda A., Beale P., Glasspool R.M., Creutzberg C.L., Harter P., Kim J.W., Reed N.S., Ray-Coquard I. Gynecologic Cancer Inter Group (GCIG) consensus review for uterine and ovarian carcinosarcoma. *International journal of gynecological cancer*.**2014**; 24 , S55–S60.
33. Matsuzaki S., Klar M., Matsuzaki S., Roman L.D., Sood A.K., Matsuo K. Uterine carcinosarcoma: Contemporary clinical summary, molecular updates, and future research opportunity. *Gynecol Oncol*. **2021** Feb;160(2):586-601.
34. Nordal R.R., Kristensen G.B., Stenwig A.E., Nesland J.M., Pettersen E.O., Trope C.G. An evaluation of prognostic factors in uterine carcinosarcoma. *Gynecol. Oncol*. **1997** Dec;67(3):316-21.
35. Matsuo K., Ross M.S., Machida H., Blake E.A., Roman L.D. Trends of uterine carcinosarcoma in the United States, *J. Gynecol. Oncol*. **2018**; 29, e22
36. Sherman M.E., Devesa S.S. Analysis of racial differences in incidence, survival, and mortality for malignant tumors of the uterine corpus, *Cancer*.**2003**; 98 , 176–186.
37. Zelmanowicz A., Hildesheim A., Sherman M.E., Sturgeon S.R., Kurman R.J., Barrett R.J., Berman M.L., Mortel R., Twiggs L.B., Wilbanks G.D., Brinton L.A. Evidence for a common etiology for endometrial carcinomas and malignant mixed mullerian tumors, *Gynecol. Oncol*. **1998**;69, 253–257.
38. National Cancer Institute's The Surveillance, Epidemiology, and End Results (SEER) Program, http://seer.cancer.gov/
39. Abdulfatah, E., Lordello, L., Khurram, M., Van de Vijver, K., Alosh, B., Bandyopadhyay, S., Oliva, E., Ali-Fehmi, R. Predictive histologic factors in Carcinosarcomas of the uterus: a multi-institutional study. *Int. J. gynecological Patho. Off. J. Int. Soc. Gynecological Pathol*. **2019**; 38, 205–215.
40. Pezzicolig G., Moscaritolo F., Silvestris E., Silvestris F., Cormio G., Porta C., D'Oronzo S. Uterine carcinosarcoma: An overview. *Crit Rev Oncol Hematol*. **2021** Jul:163:103369.
41. Matsuo K, Takazawa Y, Ross MS, Elishaev E, Podzielinski I, Yunokawa M, et al. Significance of histologic pattern of carcinoma and sarcoma components on survival outcomes of uterine carcinosarcoma. *Ann Oncol* **2016**;27:1257-66.
42. Harano K, Hirakawa A, Yunokawa M, Nakamura T, Satoh T, Nishikawa T, et al. Prognostic factors in patients with uterine carcinosarcoma: a multi-institutional retrospective study from the Japanese Gynecologic Oncology Group. *Int J Clin Oncol* **2016**;21:168-76.
43. de Jong RA, Nijman HW, Wijbrandi TF, Reyners AK, Boezen HM, Hollema H. Molecular markers and clinical behavior of uterine carcinosarcomas: focus on the epithelial tumor component. *Mod Pathol.* **2011** Oct;24(10):1368-79.
44. Kim Y., Kang G.H., Kim H. Prognostic significance of heterologous component in carcinosarcoma of the gynecologic organs: a systematic review and meta-analysis. *J Gynecol Oncol*. **2023** Nov;34(6):e73.

 doi:10.20944/preprints202506.0846.v1

45. Network CGAR, et al. Integrated genomic characterization of endometrial carcinoma. *Nature*. **2013**;497(7447):67- 73.
46. Talhouk A, McConechy MK, Leung S, et al. A clinically applicable molecular- based classification for endometrial cancers. *Br J Cancer*. **2015**;113(2):299- 310.
47. Talhouk A, McConechy MK, Leung S, et al. Confirmation of ProMisE: a simple, genomics- based clinical classifier for endometrial cancer. *Cancer*. **2017**;123(5):802- 813.
48. Kommoss S, McConechy MK, Kommoss F, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population- based case series. *Ann Oncol*. **2018**;29(5):1180- 1188.
49. Raffone A, Travaglino A, Mascolo M, et al. TCGA molecular groups of endometrial cancer: pooled data about prognosis. *Gynecol Oncol*. **2019**;155(2):374- 383.
50. Britton H, Huang L, Lum A, et al. Molecular classification defines outcomes and opportunities in young women with endometrial car cinoma. *Gynecol Oncol*. **2019**;153(3):487- 495.
51. Tavaglino A.et al. Prognostic value of the TCGA molecular classification in uterine carcinosarcoma. *Int J Gynaecol. Obstet*. **2022** Jul;158(1):13-20.
52. Dongre A., Weinberg R.A. New insights into the mechanisms of epithelial mesenchymal transition and implications for cancer. *Nat Rev Mol Cell Biol* .**2019**;20 ,69–84.
53. Gopinatha Pillai M.S., Shaw P., Bhowmik A.D., Bhattacharya R., Rao G., Dhar Dwivedi S.K. Uterine carcinosarcoma: Unraveling the role of epithelial-to-mesenchymal transition in progression and therapeutic potential. *FASEB J*. **2024** Nov 15;38(21):e70132.
54. King B., et al. The ubiquitin ligase FBXW7 modulates leukemia-initiating cell activity by regulating MYC stability. *Cell*. **2013**; 153, 1552–1566.
55. Kandoth C., et al. Cancer Genome Atlas Research Network, Integrated genomic characterization of endometrial carcinoma. *Nature*. **2013** ; 497, 67–73.
56. Cuevas IC, Sahoo SS, Kumar A, Zhang H, Westcott J, Aguilar M, et al. Fbxw7 is a driver of uterine carcinosarcoma by promoting epithelial-mesenchymal transition. *Proc Natl Acad Sci U S A* **2019**;116:25880-90.
57. Han, K.H., Kim, M.A., Park, N.H. Expression of aurora kinases: predictor of tumor dissemination in uterine carcinosarcoma. *Histol. Histopathol*. **2017**; 32, 717–724.
58. Rahib L., Wehner M.R., Matrisian L.M., Nead K.T. Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Netw. Open* **2021**, 4, e214708.
59. El-Sahwi K.S., Schwartz P.E., Santin A.D. Development of Targeted Therapy in Uterine Serous Carcinoma, a Biologically Aggressive Variant of Endometrial Cancer. *Expert Rev. Anticancer. Ther*. **2012**, 12, 41–49.
60. Santin A.D., Bellone S., Van Stedum S., Bushen W., Palmieri M., Siegel E.R., De Las Casas L.E., Roman J.J., Burnett A., Pecorelli S. Amplification of C-ErbB2 Oncogene: A Major Prognostic Indicator in Uterine Serous Papillary Carcinoma. *Cancer* **2005**, 104, 1391–1397.
61. Erickson B.K., Najjar O., Damast, S., Blakaj, A., Tymon-Rosario J., Shahi M., Santin A., Klein M., Dolan M., Cimino-Mathews A. et al. Human Epidermal Growth Factor 2 (HER2) in Earl- Stage Uterine Serous Carcinoma: A Multi Institutional Cohort Study. *Gynecol. Oncol*. **2020**, 159, 17–22.
62. McNamara B., Mutlu L., Greenman M., Harold J., Santin A. HER2Oncogeneas Molecular Target in Uterine Serous Carcinoma and Uterine Carcinosarcoma. *Cancers (Basel).* **2023** Aug 14;15(16):4085.
63. Talia K., Banet N., BuzaN. The role of HER2 as a therapeutic biomarker in gynaecological malignancy: potential for use beyond uterine serous carcinoma. *Pathology*. **2023** Feb;55(1):8-18.
64. Chan JK, Kawar NM, Shin JY, Osann K, Chen LM, Powell CB, Kapp DS. Endometrial stromal sarcoma: a population-based analysis. *Br J Cancer*. **2008** Oct 21;99(8):1210-5. doi: 10.1038/sj.bjc.6604527.
65. Hanby, A.M., walker, C. Tavassoli FA, Devilee P: Pathology and Genetics: Tumours of the Breast and Female Genital Organs. WHO Classification of Tumours series - volume IV. Lyon, France: IARC Press. *Breast Cancer Res* , **2004** ; 6, 133. https://doi.org/10.1186/bcr788
66. Ali RH, Rouzbahman M. Endometrial stromal tumours revisited: an update based on the 2014 WHO classification. *J Clin Pathol*. **2015** May;68(5):325-32. doi: 10.1136/jclinpath-2014-202829.

 doi:10.20944/preprints202506.0846.v1

67. Nordal RR, Kristensen GB, Kaern J, Stenwig AE, Pettersen EO, Tropé CG. The prognostic significance of surgery, tumor size, malignancy grade, menopausal status, and DNA ploidy in endometrial stromal sarcoma. *Gynecol Oncol*. **1996** Aug;62(2):254-9. doi: 10.1006/gyno.1996.0224. PMID: 8751558.
68. Berchuck A, Rubin SC, Hoskins WJ, Saigo PE, Pierce VK, Lewis JL Jr. Treatment of endometrial stromal tumors. *Gynecol Oncol*. **1990** Jan;36(1):60-5. doi: 10.1016/0090-8258(90)90109-x. PMID: 2295453..
69. Mansi JL, Ramachandra S, Wiltshaw E, Fisher C. Endometrial stromal sarcomas. *Gynecol Oncol*. **1990** Jan;36(1):113-8. doi: 10.1016/0090-8258(90)90120-a. PMID: 2295442
70. Katz L, Merino MJ, Sakamoto H, Schwartz PE. Endometrial stromal sarcoma: a clinicopathologic study of 11 cases with determination of estrogen and progestin receptor levels in three tumors. *Gynecol Oncol*. **1987** Jan;26(1):87-97. doi: 10.1016/0090-8258(87)90074-6. PMID: 3792939.
71. Sutton GP, Stehman FB, Michael H, Young PC, Ehrlich CE. Estrogen and progesterone receptors in uterine sarcomas. *Obstet Gynecol*. **1986** Nov;68(5):709-14. PMID:
72. Scribner DR Jr, Walker JL. Low-grade endometrial stromal sarcoma preoperative treatment with Depo-Lupron and Megace. *Gynecol Oncol*. **1998** Dec;71(3):458-60. doi: 10.1006/gyno.1998.5174. PMID: 9887250..
73. Liokumovich P, Goldberg I, Davidson B, Gotlieb WH, Zahavi T, Ben-Baruch G, Reder I, Kopolovic J. Expression of metalloproteinases endometrial stromal sarcoma: immunohistochemical study using image analysis. *J Clin Pathol*. **1999** Mar;52(3):198-202. doi: 10.1136/jcp.52.3.198. PMID: 10450179; PMCID: PMC501079.
74. Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR. Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases. *Am J Surg Pathol*. **1990** May;14(5):415-38. doi: 10.1097/00000478-199005000-00002. PMID: 2327549.
75. Bodner K, Bodner-Adler B, Obermair A, Windbichler G, Petru E, Mayerhofer S, Czerwenka K, Leodolter S, Kainz C, Mayerhofer K. Prognostic parameters in endometrial stromal sarcoma: a clinicopathologic study in 31 patients. *Gynecol Oncol*. **2001** May;81(2):160-5. doi: 10.1006/gyno.2001.6152. PMID: 11330943..
76. Bodner K, Bodner-Adler B, Kimberger O, Czerwenka K, Leodolter S, Mayerhofer K. Evaluating prognostic parameters in women with uterine leiomyosarcoma. A clinicopathologic study. *J Reprod Med*. **2003** Feb;48(2):95-100. PMID: 12621792.
77. Thangappah RBP. Uterine Sarcoma: A Clinico-Pathological Study. *J Obstet Gynaecol India*. **2019** Oct;69(Suppl 2):147-152. doi: 10.1007/s13224-018-1141-5.
78. Ashraf-Ganjoei T, Behtash N, Shariat M, Mosavi A. Low grade endometrial stromal sarcoma of uterine corpus, a clinico-pathological and survey study in 14 cases. *World J Surg Oncol*. **2006** Aug 9;4:50. doi: 10.1186/1477-7819-4-50. PMID: 16895611; PMCID: PMC1560376.
79. D'Angelo E, Prat J. Uterine sarcomas: a review. *Gynecol Oncol*. **2010** Jan;116(1):131-9. doi: 10.1016/j.ygyno.2009.09.023. Epub 2009 Oct 23. PMID: 19853898
80. Reichardt P. The treatment of uterine sarcomas. *Ann Oncol*. **2012** Sep;23 Suppl 10:x151-7. doi: 10.1093/annonc/mds359. PMID: 22987952.
81. Gadducci A, Cosio S, Romanini A, Genazzani AR. The management of patients with uterine sarcoma: a debated clinical challenge. *Crit Rev Oncol Hematol*. **2008** Feb;65(2):129-42. doi: 10.1016/j.critrevonc.2007.06.011.
82. Li AJ, Giuntoli RL 2nd, Drake R, Byun SY, Rojas F, Barbuto D, Klipfel N, Edmonds P, Miller DS, Karlan BY. Ovarian preservation in stage I low-grade endometrial stromal sarcomas. *Obstet Gynecol*. **2005** Dec;106(6):1304-8. doi: 10.1097/01.AOG.0000185511.91694.1e. PMID: 16319256.
83. Chu MC, Mor G, Lim C, Zheng W, Parkash V, Schwartz PE. Low-grade endometrial stromal sarcoma: hormonal aspects. *Gynecol Oncol*. **2003** Jul;90(1):170-6. doi: 10.1016/s0090-8258(03)00258-0. PMID: 12821359.
84. Yoon A, Park JY, Park JY, Lee YY, Kim TJ, Choi CH, Bae DS, Kim BG, Lee JW, Nam JH. Prognostic factors and outcomes in endometrial stromal sarcoma with the 2009 FIGO staging system: a multicenter review of 114 cases. *Gynecol Oncol*. **2014** Jan;132(1):70-5. doi: 10.1016/j.ygyno.2013.10.029.
85. Amant F, Floquet A, Friedlander M, Kristensen G, Mahner S, Nam EJ, Powell MA, Ray-Coquard I, Siddiqui N, Sykes P, Westermann AM, Seddon B. Gynecologic Cancer InterGroup (GCIG) consensus review for endometrial stromal sarcoma. *Int J Gynecol Cancer*. **2014** Nov;24(9 Suppl 3):S67-72. doi: 10.1097/IGC.0000000000000205. PMID: 25033257.

 doi:10.20944/preprints202506.0846.v1

86. Nasioudis D, Ko EM, Kolovos G, Vagios S, Kalliouris D, Giuntoli RL. Ovarian preservation for low-grade endometrial stromal sarcoma: a systematic review of the literature and meta-analysis. *Int J Gynecol Cancer*. **2019** Jan;29(1):126-132. doi: 10.1136/ijgc-2018-000063. PMID: 30640694.
87. Agarwal R, Rajanbabu A, Nair IR, Satish C, Jose G, Unikrishnan UG. Endometrial stromal sarcoma-A retropsective analysis of factors affecting recurrence. *Eur J Obstet Gynecol Reprod Biol.* **2017** Sep;216:92-97. doi: 10.1016/j.ejogrb.2017.07.011.
88. He L, Li JD, Xiong Y, Huang X, Huang L, Lin JX, Zhou Y, Zheng M. Clinicopathological and molecular markers associated with prognosis and treatment effectiveness of endometrial stromal sarcoma: a retrospective study in China. *Arch Gynecol Obstet.* **2014** Feb;289(2):383-91. doi: 10.1007/s00404-013-2987-5. PMID: 23959089; PMCID: PMC3894427.
89. Shah JP, Bryant CS, Kumar S, Ali-Fehmi R, Malone JM Jr, Morris RT. Lymphadenectomy and ovarian preservation in low-grade endometrial stromal sarcoma. *Obstet Gynecol.* **2008** Nov;112(5):1102-8. doi: 10.1097/AOG.0b013e31818aa89a. PMID: 18978112.
90. Bai H, Yang J, Cao D, Huang H, Xiang Y, Wu M, Cui Q, Chen J, Lang J, Shen K. Ovary and uterus-sparing procedures for low-grade endometrial stromal sarcoma: a retrospective study of 153 cases. *Gynecol Oncol*. **2014** Mar;132(3):654-60. doi: 10.1016/j.ygyno.2013.12.032
91. Signorelli M, Fruscio R, Dell'Anna T, Buda A, Giuliani D, Ceppi L, Milani R. Lymphadenectomy in uterine low-grade endometrial stromal sarcoma: an analysis of 19 cases and a literature review. *Int J Gynecol Cancer*. **2010** Nov;20(8):1363-6. doi: 10.1111/IGC.0b013e3181efd861. PMID: 21051978.
92. Alagkiozidis I, Grossman A, Tang NZ, Weedon J, Mize B, Salame G, Lee YC, Abulafia O. Survival impact of cytoreduction to microscopic disease for advanced stage cancer of the uterine corpus: a retrospective cohort study. *Int J Surg*. **2015** Feb;14:61-6. doi: 10.1016/j.ijsu.2015.01.001.
93. Solmaz U, Mat E, Dereli ML, Turan V, Ekin A, Tosun G, Dogan A, Ozdemir IA, Oztekin O, Sanci M. Stage-III and -IV endometrial cancer: A single oncology centre review of 104 cases. *J Obstet Gynaecol*. **2016**;36(1):81-6. doi: 10.3109/01443615.2015.1041890. Epub 2015 Oct 14. PMID: 26467294.
94. Leath CA 3rd, Huh WK, Hyde J Jr, Cohn DE, Resnick KE, Taylor NP, Powell MA, Mutch DG, Bradley WH, Geller MA, Argenta PA, Gold MA. A multi-institutional review of outcomes of endometrial stromal sarcoma. *Gynecol Oncol*. **2007** Jun;105(3):630-4. doi: 10.1016/j.ygyno.2007.01.031.
95. Dahhan T, Fons G, Buist MR, Ten Kate FJ, van der Velden J. The efficacy of hormonal treatment for residual or recurrent low-grade endometrial stromal sarcoma. A retrospective study. *Eur J Obstet Gynecol Reprod Biol*. **2009** May;144(1):80-4. doi: 10.1016/j.ejogrb.2009.02.005.
96. Oliva E, Young RH, Amin MB, Clement PB. An immunohistochemical analysis of endometrial stromal and smooth muscle tumors of the uterus: a study of 54 cases emphasizing the importance of using a panel because of overlap in immunoreactivity for individual antibodies. *Am J Surg Pathol*. **2002** Apr;26(4):403-12. doi: 10.1097/00000478-200204000-00001. PMID: 11914617.
97. Agoff SN, Grieco VS, Garcia R, Gown AM. Immunohistochemical distinction of endometrial stromal sarcoma and cellular leiomyoma. *Appl Immunohistochem Mol Morphol.* **2001** Jun;9(2):164-9. doi: 10.1097/00129039-200106000-00009. PMID: 11396634.
98. McCluggage WG, Sumathi VP, Maxwell P. CD10 is a sensitive and diagnostically useful immunohistochemical marker of normal endometrial stroma and of endometrial stromal neoplasms. *Histopathology*. **2001** Sep;39(3):273-8. doi: 10.1046/j.1365-2559.2001.01215.x. PMID: 11532038.
99. Choi YJ, Jung SH, Kim MS, Baek IP, Rhee JK, Lee SH, Hur SY, Kim TM, Chung YJ, Lee SH. Genomic landscape of endometrial stromal sarcoma of uterus. *Oncotarget.* **2015** Oct 20;6(32):33319-28. doi: 10.18632/oncotarget.5384. PMID: 26429873; PMCID: PMC4741768.
100. van Roy F. Beyond E-cadherin: roles of other cadherin superfamily members in cancer. *Nat Rev Cancer*. **2014** Feb;14(2):121-34. doi: 10.1038/nrc3647.
101. Herzig M, Savarese F, Novatchkova M, Semb H, Christofori G. Tumor progression induced by the loss of E-cadherin independent of beta-catenin/Tcf-mediated Wnt signaling. *Oncogene.* **2007** Apr 5;26(16):2290-8. doi: 10.1038/sj.onc.1210029.

 doi:10.20944/preprints202506.0846.v1

102. Feng W, Malpica A, Skaland I, Gudlaugsson E, Robboy SJ, et al.. Can Proliferation Biomarkers Reliably Predict Recurrence in World Health Organization 2003 Defined Endometrial Stromal Sarcoma, Low Grade? *PLoS ONE*. **2013**; 8(10): e75899. doi:10.1371/journal.pone.0075899

103. Popiolek D, Yee H, Levine P, Vamvakas E, Demopoulos RI. MIB1 as a possible predictor of recurrence in low-grade endometrial stromal sarcoma of the uterus. *Gynecol Oncol*. **2003** Aug;90(2):353-7. doi: 10.1016/s0090-8258(03)00281-6. PMID: 12893199..

104. Amant F, Woestenborghs H, Vandenbroucke V, Berteloot P, Neven P, Moerman P, Vergote I. Transition of endometrial stromal sarcoma into high-grade sarcoma. *Gynecol Oncol*. **2006** Dec;103(3):1137-40. doi: 10.1016/j.ygyno.2006.07.013.