RYBIN, A. I., KUZNETSOVA, O. V., ZAMYSHLYAK, V. I. Historical aspects of endometrial cancer staging: the transition to molecular classification (a literature review). Pedagogy and Psychology of Sport. 2026;29:70270. elSSN 2450-6605.
https://doi.org/10.12775/PPS.2026.29.70270
https://apcz.umk.pl/PPS/article/view/70270

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 30.12.2025. Revised: 30.12.2025. Accepted: 11.01.2026. Published: 29.01.2026.

UDC 618.14-006

Historical aspects of endometrial cancer staging: the transition to molecular classification (a literature review)

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Abstract

Determining the stage of a tumour is a crucial step in the management of patients with malignant diseases; it is directly linked to prognosis and the choice of specialised treatment, whilst facilitating the exchange of information between healthcare professionals. A staging system must possess three key characteristics: it must be effective, reliable and practical. The current staging (classification) system for endometrial cancer, developed in 2009, is highly reproducible and does not require excessive diagnostic investigations. However, the classification contains numerous ‘grey areas’ that hinder the evidence-based selection of appropriate treatment for patients falling within them. The most striking example is the need for lymph node dissection in clinical stage I endometrial cancer, where, in cases of intermediate risk, the decision to proceed is left to the discretion of the treating physician. To address this issue, and in an effort to individualise treatment and stratify the risk of recurrence, molecular classification has become widely adopted in recent years. Furthermore, in 2023, the International Federation of Gynaecologists proposed a new staging system for

endometrial cancer. This review focuses on the historical aspects of the evolution of the concept of systematic assessment of endometrial cancer and provides a better understanding of recent advances in the biology of endometrial tumours.

Keywords: endometrial cancer; staging system; molecular classification

Introduction. Endometrial cancer (EC) ranks first among tumours of the reproductive organs and accounts for 8.1% of all malignant neoplasms in women. In the incidence of malignant neoplasms among women in Ukraine, EC ranks third; in 70.8% of cases, it is detected at stage I of the disease [1,2]. The stage of the disease correlates directly with the prognosis; thus, at stage I, the five-year overall survival rate is 94.2%, whilst in cases of spread beyond the primary site (regional spread) it drops to 68.3%, and at stage IV the rate does not exceed 19% [3, 4]. Whilst the prognosis remains good for those diagnosed with early-stage RE, for patients with recurrent or metastatic disease it deteriorates significantly, and the median overall survival is reduced [3, 4].

The primary treatment option for primary endometrial cancer is surgery involving total hysterectomy with bilateral salpingo-oophorectomy and assessment of the lymph node status [5]. First and foremost, surgery allows for local control of the tumour, particularly in patients with heavy uterine bleeding.

The second important aspect of surgical treatment at the initial stage is surgical staging, which allows the extent of the tumour to be assessed, specifically whether the ovaries, fallopian tubes, and lymphatic collectors are involved. Thirdly, it provides sufficient material for in-depth morphological and molecular-genetic analysis of the tumour.

All of this enables patients to be classified into risk categories to determine the necessity and type of adjuvant treatment based on the clinical, morphological, and molecular-genetic characteristics of the tumour in a specific patient.

A significant achievement in the diagnosis and treatment of ER over the last decade has been the development of molecular classification [4, 7]. Four molecular subtypes have been identified: POLE-ultramutated; MMR-deficient; p53-mutant; and a non-specific molecular subtype [8, 9, 10]. All subtypes are associated with different prognoses. In 2023, the International Federation of Gynaecologists (FIGO) proposed a new staging system for endometrial cancer, which incorporates various insights into tumour biology and their role in disease prognosis [11, 12]. This classification should enable better identification of prognostic groups and sub-stages, which will improve patient selection for surgical, radiotherapy and systemic treatment. This review presents an analysis of key studies that define the current

understanding of endometrial cancer classification. It examines studies that have justified the transition from clinical staging to surgical staging, and subsequently to molecular classification. The aim of this review is to improve gynaecological oncologists' understanding of the historical aspects of endometrial cancer staging, to identify patterns and outline the main directions for future research, thereby facilitating effective collaboration between clinicians during this transitional period.

Clinical classification of endometrial cancer.

The first staging system for endometrial cancer was proposed by the International Federation of Gynaecologists in 1950 and was based on data obtained from clinical and laboratory examinations. The 1950 FIGO classification comprised three stages of the disease: stage 0 included cases suspected of being cancerous, stage I of the tumour process was confined to the body of the uterus, and stage II was diagnosed when the tumour had spread beyond the body of the uterus [13]. The decisive criterion in the staging of uterine body cancer in those years was the feasibility of surgery. According to the classification, stage I of the tumour process was confined to the uterine body and was subdivided into two groups: group 1 — operable cancer; group 2 — surgery associated with high risk. The reasons for this division of Stage I were linked to the high prevalence of obesity, hypertension and diabetes mellitus among patients, which limited surgical options. This classification is also associated with the quality of anaesthesia, the availability of blood products and the presence of qualified gynaecological surgeons with experience in performing more extensive operations on high-risk patients [13].

As clinical data accumulated, the staging system for endometrial cancer underwent numerous revisions. In 1962, it was expanded to a four-stage system, with cervical involvement being designated as a separate stage (Stage II). Tumour spread beyond the uterus but confined to the pelvic cavity defined stage III of the disease. Stage IV included cases of involvement of the bladder or rectal mucosa, or tumour spread beyond the pelvic cavity [13]. The primary treatment option was total hysterectomy with bilateral salpingo-oophorectomy, combined with preoperative radium administration or postoperative radiotherapy. However, combined treatment did not improve 5-year overall survival (OS) rates. Thus, in the 14th FIGO report (1967), out of 3,985 cases of stage I tumours, the 5-year OS rate was 73.8% with preoperative intrauterine administration of radium, whereas in 4,668 stage I patients, the 5-year OS rate was 76.2%, although they did not undergo preoperative radiotherapy.

An analysis of the literature from those years indicates that the frequency of metastasis to lymph nodes (LN) is approximately 10% for stage I and 35% for stage II cases [14, 15, 16,

17, 18]. At the same time, the 5-year OS remained high, reaching 40% [14, 15]. These observations indicate that there is a risk of lymphogenous metastasis in early-stage endometrial cancer. Thus, patients may derive clear benefit from extending the scope of surgery to include lymph node dissection. It was also found that the frequency of metastasis is directly correlated with loss of tumour differentiation and increased depth of invasion into the myometrium. In 1970, a study was published in which all patients with endometrial cancer underwent radical hysterectomy and pelvic lymphadenectomy [14]. Preoperative intrauterine administration of radium was also used, and only patients with metastases to the lymph nodes underwent postoperative radiotherapy. This study showed that the risk of metastasis to the lymph nodes is 11.2% in stage I and rises to 13.2% when the cervix is involved. Thus, metastases to the cervical lymph nodes are detected in only 1 in 10 patients with early-stage endometrial cancer; therefore, lymph node dissection is unjustified for the majority of patients. This is particularly relevant for patients with endometrial cancer who, due to advanced age and the presence of significant comorbidities, are at high surgical risk. The routine use of preoperative radium administration into the uterus does not improve survival rates; however, in cases of lymph node involvement, the use of postoperative radiotherapy helps to increase the 5-year overall survival rate to 36%. This study allowed for a synthesis of the accumulated experience and raised the question of selecting patients who would derive the maximum benefit from extended surgery and combined treatment methods.

The accumulated clinical experience enabled the FIGO committee in 1971 to revise the classification of endometrial cancer and identify three high-risk factors for progression of endometrial cancer: the degree of tumour differentiation, tumour spread to the cervix, and the length of the uterine cavity. In the new classification, stage I, as in 1962, was confined to the uterine body and subdivided into Ia and Ib depending on the length of the uterine cavity. In stage Ia, the length of the uterine cavity from the external os of the cervix to the top of the inner part of the uterine body was less than 8 cm. If it exceeded 8 cm, it was classified as stage Ib. The most significant change in the staging of endometrial cancer was the need to take into account the histological type of adenocarcinoma in stage I of the tumour process: G1 — well-differentiated adenomatous carcinoma; G2 — differentiated adenocarcinoma with areas of solid structure; and G3 — predominantly solid or completely undifferentiated carcinoma.

This approach made it possible to subdivide homogeneous stage I endometrial cancer into six sub-stages based on prognosis. Consequently, the determination of histological type became an integral part of the staging of stage I endometrial cancer.

In 1977, the Gynaecologic Oncology Group (GOG) organised a pilot prospective study aimed at assessing prognostic factors and the course of stage I endometrial cancer, according to the FIGO classification of 1972–1988 [19]. This study was the first to demonstrate that the incidence of lymph node metastases is directly dependent on prognostic factors. In stage IA, metastases to pelvic and para-aortic lymph nodes were detected in 6.2% and 3.8% of patients, respectively. In contrast, in stage IB, metastases to the pelvic and para-aortic lymph nodes were already detected in 18.0% and 11.7% of patients, respectively. Furthermore, a direct correlation was observed between the histological type of adenocarcinoma and involvement of the lymphatic collectors. Metastases to pelvic lymph nodes in well-differentiated adenomatous carcinoma (G1) accounted for 3.1%, and the frequency increased tenfold to 36% in cases of G3 tumour involvement (predominantly solid or completely undifferentiated carcinoma). A similar trend was observed for metastases to para-aortic lymph nodes. Another prognostic factor was the depth of invasion into the myometrium. In tumours confined to the endometrium alone, metastases to pelvic lymph nodes were observed in 3.6% of patients, whereas in patients with deep invasion into the muscular layer of the uterine body, the incidence increased tenfold to 43%, a finding also noted for para-aortic lymph nodes: 1.8% with endometrial involvement and 21% with deep invasion. This study suggested that the nature of disease progression differs from what was previously believed. The notion that uterine body cancer rarely spreads to the lymph nodes in the early stages of the disease is no longer valid. A number of important prognostic factors influence metastasis to the ovaries. And since these factors cannot be assessed prior to surgery, surgical staging must be used to select appropriate treatment for patients with uterine body cancer. In 1984, data from a pilot prospective study of the clinical and morphological features of FIGO stage I endometrioid cancer of the uterine body were published [20, 21]. Risk factors influencing the risk of metastasis to the lymph nodes were clarified. The lowest risk was observed in patients in whom the tumour had not spread to the cervix or adnexa. The group with a good prognosis included tumours confined to the endometrium, regardless of the degree of differentiation (malignancy) (G1, G2, G3), or those with superficial invasion at tumour malignancy grades 1 and 2 (G1, G2), or invasion up to 2/3 of the myometrium at tumour malignancy grade 1 (G1). Conversely, there is a significant risk of metastasis to the lymph nodes in cases of vascular space invasion and tumour spread to the cervix or adnexa. The risk increased when superficial invasion was detected in grade 3 tumours (G3), or intermediate invasion of the myometrium by grade 2 and 3 tumours (G2, G3), or deep invasion of the myometrium by tumours of any grade of differentiation (G1, G2, G3). The

incidence of recurrence/death was associated with the depth of tumour invasion into the myometrium. For patients with stage I tumours without myometrial invasion, the risk of death is 5% and increases to 11% with invasion of up to one-third of the myometrial thickness, 12% with invasion of less than two-thirds, and 36% with deep invasion (more than two-thirds of the thickness) [21].

The results of the pilot study enabled the launch of a larger prospective study to investigate the morphological features of clinical stage 1 endometrial cancer (GOG 33) [22]. Over a 6-year period from 1977 to 1983, 1,180 patients from 43 medical centres were treated, with operations performed by more than 50 surgeons. All patients underwent selective pelvic and para-aortic lymphadenectomy. The number of lymph nodes removed was not taken into account if a lymphadenectomy had been performed. Following screening, 621 patients met the inclusion criteria. The results of this analysis confirmed the findings of the pilot study. The analysis was limited to those factors that predicted metastasis to lymph nodes and were known before or during surgery. The tumour grade is known preoperatively, intra-abdominal tumour spread can be identified during surgical exploration, and the depth of invasion can be determined by intraoperative histology. Using these parameters, the surgeon was able to divide patients into three groups of risk for lymphogenous metastasis during the operation: in the low-risk group, lymphadenectomy was not indicated; in the moderate-risk group, the decision to perform lymph node dissection was left to the discretion of the operating surgeon; and in the high-risk group, lymph node dissection was required. The authors highlighted two points regarding lymphadenectomy: the need for appropriate patient selection to ensure that lymph node dissection is justified; and the fact that the surgeon should not decide whether to perform a lymphadenectomy based on palpation of the lymph nodes, as these are enlarged in fewer than 10% of patients with lymph node metastases. Furthermore, changes in the axillary lymph nodes can only be determined by exploring the retroperitoneal space and removing the lymph nodes themselves.

The factors described above were confirmed once again in 1991, when the long-term results of the GOG-33 study were published [23]. The authors divided them into two groups: the first comprising intrauterine risk factors, and the second comprising extrauterine risk factors. The first risk group included the following parameters: tumour morphological type and differentiation, depth of tumour invasion into the myometrium, tumour invasion into the vascular space, and tumour spread to the cervix. Extrauterine risk factors included metastases to pelvic and/or para-aortic lymph nodes, tumour spread to the uterine adnexa, positive results of cytological examination of abdominal cavity aspirate, and tumour extension to the serous

membrane of the uterus with or without implants. Based on these factors, it was possible to determine the appropriateness and necessity of postoperative treatment, as well as to conduct a well-founded assessment of the prognosis in patients with RE. Five-year recurrence-free survival (RFS) decreases from 92.7% for stage I patients to 69.8% in cases of cervical involvement, and to 57.8% in cases of pelvic lymph node or adnexal involvement. A decrease to 56% was also observed in the presence of tumour cells in abdominal cavity aspirate, to 55% in cases of vascular space invasion, and to 41.2% in the presence of metastases in para-aortic lymph nodes or other macroscopic changes detected during exploration.

Surgical staging as the basis for the classification of endometrial cancer.

Taking into account the studies conducted on the assessment of prognostic criteria and their impact on survival in endometrial cancer, the FIGO Committee on Gynaecological Oncology decided in 1988 to develop a new staging system. The new classification was published in 1989 and incorporated surgical findings as an integral component of staging, based on large-scale clinical and morphological studies of endometrial cancer; it differed from the clinical staging system previously in use [13, 14, 15, 20, 21, 22, 23]. In the 1988 classification, Stage I, as in 1971, was confined to the uterine body; however, the determining criterion for subdivision into substages The absence of invasion into the myometrium corresponded to stage Ia; if the invasion was less than half the thickness of the myometrium, it was defined as stage Ib, and if the invasion was more than half the thickness, it was defined as stage Ic. Patients with tumour spread to the cervix were classified into a separate group; if only the cervical glands were affected, stage IIa was assigned, and if there was invasion into the stroma, stage IIb. Stage III included cases of intra-abdominal tumour spread within the pelvis without involvement of the bladder or rectum. As a result, the group became highly heterogeneous. Thus, stage IIIa included cases of tumour spread to the serosa of the uterus, the adnexa, or a positive cytological analysis of abdominal aspirate. Tumour spread to the vagina corresponded to stage IIIb, whilst involvement of the lymph nodes was classified as stage IIIc. Stage IV remained unchanged in this system compared to the 1962 clinical system; the only difference was the introduction of subgroup ‘a’, which corresponded to involvement of the bladder and/or the rectal mucosa. Subgroup ‘b’ included all other manifestations of the tumour, in particular spread beyond the pelvis to the inguinal lymph nodes. Stage I now comprised 9 substages, and metastasis to lymph nodes corresponded to stage IIIc, even if the invasion of the myometrium was superficial and the histological grade of malignancy was G1 or G2. The proposed system had a number of significant advantages in determining the extent of the disease, the appropriateness and necessity of postoperative treatment, and also allowed

for a well-founded assessment of the disease prognosis. The risk of metastasis to the lymph nodes in the early stages of the disease is very low, and the level of potential complications from lymphadenectomy may outweigh the clinical benefits in patients with endometrial cancer. According to the GOG study, the overall risk of metastasis to pelvic and para-aortic lymph nodes in patients with clinical stage I endometrial cancer is 9% and 6% respectively, and in cases of well-differentiated and moderately differentiated tumours — 3% and 2%.

A tumour confined to the endometrium carries an even lower risk of metastasis — 1% [22, 24]. Thus, determining lymph node status is the most important and most controversial component of the 1988 FIGO staging system [25]. hanks to the use of the 1988 FIGO classification by oncologists and gynaecologists, it has been possible to standardise data collection and subsequently analyse specific prognostic factors for the staging of endometrial cancer []. Thus, since 1999, following the publication of the 23rd volume of the annual report, annual data collection has taken place, recording more than 42,000 patients with endometrial cancer. Thanks to this database and subsequent analysis, the FIGO Gynaecological Oncology Committee decided in 2008 to revise the endometrial cancer staging system [26].

In January 2009, FIGO published a new classification of endometrial cancer,

which identifies four stages of the tumour process: in stages I and II, the tumour is confined to the body of the uterus or does not extend beyond the uterus (localised form); Stage III is characterised by the spread of the tumour beyond the primary site (regional spread), whilst in stage IV, the tumour has invaded adjacent organs or distant metastases are present. Stage III endometrial cancer encompasses a wide range of patterns of metastatic spread. Stages IIIA and IIIB represent metastatic spread to pelvic structures, which differs significantly from stage IIIC, which includes spread to retroperitoneal lymph nodes. Previously considered together as stage IIIC, the current FIGO staging classifies endometrial carcinoma involving pelvic lymph nodes as stage IIIC1, and cancer involving para-aortic lymph nodes as stage IIIC2. This update reflects the understanding that involvement of retroperitoneal lymph nodes, particularly para-aortic lymph nodes, is a poor prognostic indicator [28]. The five-year overall survival rate decreases from 90% in early stages to 60–70% with metastases to pelvic lymph nodes and drops quite sharply to 30–40% with involvement of para-aortic lymph nodes [28, 29]. Based on data from the Centers for Disease Control and Prevention for the period 2016–2020, in the USA, endometrial cancer was diagnosed at stage I/II in 72.6% of patients (195,978), at stage III in 17.3% (46,745) and at stage IV in 10.1% (27,224). The risk of recurrence increases with disease stage, from 6.5% at stage I to 66.7% at stage IV. According to accumulated data, patients with stage I endometrial

cancer had an excellent prognosis. The 5-year overall survival rate for tumours confined to the endometrium can reach 91%, but decreases to 87.3% and 89.2% respectively when the tumour invades less than half the thickness of the myometrium (IB — 1988 and IA — 2009). And in cases of tumour invasion exceeding 1⁄2 the thickness of the myometrium (IC – 1988 and IB – 2009), the 5-year OS is 75.7% and 75.1% respectively. Tumours with a high grade of malignancy (G3, high-grade) had a similar survival rate of approximately 80%, which did not depend on the depth of invasion [38]. Thus, given the similar prognosis, it was decided to combine these subgroups into stage IA according to FIGO 2009. The 1988 stages IA and IB were combined such that stage IA now included tumours confined to the endometrium and/or invasion of less than half the thickness of the myometrium, whilst stage IB involved invasion equal to or exceeding half the thickness of the myometrium. However, the degree of tumour differentiation still had to be taken into account. The number of sub-stages was reduced to 6 compared with the 1988 system, which significantly simplified the classification into risk groups. In the analysis of outcomes, involvement of the cervical glands (stage IIA according to FIGO 1988) had no prognostic significance in a series of studies; tumour invasion into the myometrium is a more significant parameter [29]. Furthermore, the prognosis for stages IC and II, according to FIGO 1988, was equivalent. Upon revision of the classification, stage II, according to FIGO 2009, included only patients with stromal invasion of the cervix. When assessing survival, the rate for tumour spread to the cervix was lower than in all stage I subgroups, which is more logical and reflects an unfavourable prognosis. Thus, in the current classification, stage II no longer had subgroups A and B. Involvement of the endocervical glandular portion of the cervix was now classified as stage I. Involvement of regional lymph nodes is one of the most important prognostic factors in patients with cervical cancer, as reflected in the difference in survival between patients without lymph node involvement and those with metastases to pelvic and para-aortic lymph nodes. According to the literature, the 5-year overall survival (OS) is 58% for patients with involvement of pelvic lymph nodes only and 51% for those with involvement of para-aortic lymph nodes; by comparison, in a cohort of patients with stage I disease, the 5-year OS is approximately 90%. According to the current FIGO 2009 classification, involvement of the pelvic and para-aortic lymph nodes has been separated rather than combined. Consequently, stage IIIC is now classified as IIIC1 (with pelvic lymph node involvement) and IIIC2 (with positive para-aortic lymph nodes regardless of pelvic lymph node status). In addition to the important prognostic significance of determining lymph node status, the distribution of tumours within stage IIIC has important clinical significance, as it directly influences the choice of postoperative treatment [27-29].

Thus, lymphadenectomy is now an integral part of personalised treatment for patients with endometrial cancer. Nevertheless, the role of lymphadenectomy in the early stages of endometrial cancer remains unclear, and there are still conflicting views regarding the indications for the procedure, the extent of lymph node dissection (pelvic and/or para-aortic) and its therapeutic value. Another important factor that needs to be considered is the change in the prognostic significance of cytological examination of abdominal aspirate as a key step in surgical staging for endometrial cancer [30]. FIGO stage IIIA1 (1988) included cases of tumour spread to the serosa of the uterus, the adnexa, or a positive cytological analysis of abdominal aspirate. In this subgroup, the 5-year overall survival (OS) varied and was 55% in cases involving the adnexa or the serosa of the uterus. Where the tumour was present only in the aspirate, survival was significantly higher at 67%. However, for stage IIIA1, regardless of the staging criteria, the prognosis was worse than for tumours confined to the uterine body alone (stages IB and IC). Further observations demonstrated that patients with a positive abdominal washout as the sole criterion for stage IIIA had a better prognosis, whilst unfavourable factors in this situation include the morphological type of tumour and the presence of lymphovascular invasion; with patients deriving the greatest benefit from adjuvant systemic therapy. A Swiss retrospective study assessed the significance of peritoneal cytology in determining the stage of RE. Over a 13-year follow-up period, 170 cases of RE were analysed; patients with positive peritoneal cytology alone had a prognosis as favourable as that of stage 1 patients. The authors note, however, that poor treatment outcomes in other studies may be due to the inclusion of a smaller number of patients who underwent lymph node dissection. In the current FIGO 2009 classification, cytological examination of peritoneal aspirate has been excluded from the staging system; however, a number of authors recommend reporting the presence of tumour cells in peritoneal aspirate [25, 27, 30].

The proposed FIGO 2009 classification system has significantly simplified clinical practice, but its prognostic value has not improved. There are also a number of ‘grey’ areas where the decision on management strategy is based on the treating physician’s personal preferences, convenience (i.e. the patient’s physique, the surgeon’s skills, the operation schedule and ease of access to certain areas via minimally invasive surgery), rather than on evidence-based medicine [30]. For example, the indications for lymph node dissection in endometrial cancer are determined by the risk assessed on the basis of preoperative examination results, where, in cases of intermediate risk, the decision to perform lymph node dissection remains at the discretion of the treating physician. These data highlight the

importance of developing individual risk prediction models and nomograms for endometrial cancer.

Endometrial cancer: from surgical staging to molecular-genetic classification.

A significant achievement in the diagnosis and treatment of endometrial cancer over the last decade has been the development of molecular classification [11]. In 2013, genomic analysis of endometrial cancer was conducted as part of the The Cancer Genome Atlas (TCGA) project. Four main molecular subtypes have been identified in endometrial tumours: POLE-ultramutated; MMR-deficient; p53-mutant; and a non-specific molecular subtype [7, 8, 9, 10]. Further analysis of the molecular subtypes showed that the groups are heterogeneous in terms of prognostic outcomes [31]. The polymerase epsilon (POLE-ultramutant) mutation occurs in 6–9% of endometrial cancers in young and thin women, and is frequently detected in the endometrioid histological subtype and at an early stage of the disease. Studies in the PORTEC cohorts have shown a favourable prognosis regardless of the adjuvant treatment administered. Although tumours with the POLE mutation often exhibit more aggressive morphological features (low grade, lymphovascular invasion), they have the highest 5-year survival rates, around 95–97% [32]. Furthermore, a meta-analysis showed that relapses occur in only 3.7% (11 out of 294) of patients, with a high survival rate of 72%. Thus, patients with a POLE mutation have a low risk of disease recurrence, which is reflected in the most favourable prognosis, regardless of the adjuvant treatment administered.

The ProMisE study revealed that the TP53 gene mutation correlates with abnormal results of immunohistochemical (IHC) testing for the tumour protein p53, which has high inter-laboratory reproducibility and accounts for approximately 13–18% of endometrial cancer cases. The identification of an endometrial tumour with a mutant p53 molecular subtype is associated with a poor prognosis, accounting for approximately 50–70% of mortality in endometrial cancer [53].

The proportion of cases with an abnormal p53 protein expression profile is 93% in serous endometrial cancer, 85% in carcinosarcoma, 38% in clear cell carcinoma, 22% in poorly differentiated endometrioid carcinoma, and only 5% in G1 and G2 endometrioid tumours. In each of these subgroups, this was associated with a poor prognosis. However, when a POLE mutation or MMR deficiency is detected, the tumour is classified into these molecular subtypes, which is associated with no significant differences in prognosis.

The molecular group with MMR deficiency accounts for 20–30% of endometrial cancer cases and is analogous to MSI in the original genomic classification [7, 9]. Detection of this molecular subtype is possible via IHC, making it the most reproducible and least

expensive method. It has been shown that MMR status is associated with an intermediate prognosis for ER and is significant in the prescription of treatment with immune checkpoint inhibitors. Tumours with a non-specific molecular subtype, lacking POLE mutations, characterised by a normal (wild-type) p53 protein expression profile and intact MMR, account for 40–50% of all endometrial carcinomas. Patients in this group typically have a high body mass index (BMI), express oestrogen and progesterone receptors, and show a high response to hormone therapy. However, this classification has not found widespread application in clinical practice due to low reproducibility, high costs of testing, and a lack of reliable data on clinical outcomes in primary patients [33-35].

Based on the data obtained, FIGO proposed the following classification in 2023. Stage I is confined to the uterus and ovary and has 5 sub-stages. Substage IA1 is characterised by a tumour confined to the endometrium or low-grade endometrioid adenocarcinoma; IA2 includes non-aggressive histological types involving less than half the thickness of the myometrium, with or without focal lymphovascular invasion; IA3 includes low-grade endometrioid carcinoma confined to the uterus and ovary. It is worth noting that stage IA3 should be distinguished from extensive spread of RE stage

Stage IB includes non-aggressive histological subtypes of the tumour with invasion of half or more of the myometrial thickness, as well as with no or focal LVSI. Stage IC includes tumours with aggressive histological types that are confined to a polyp or the endometrium. Aggressive histological types include high-grade (G3) endometrioid adenocarcinomas, serous, clear cell, undifferentiated, mixed, mesonephroid, gastrointestinal-type mucinous carcinomas, and carcinosarcomas. Stage II has been subdivided: Stage IIA is diagnosed when there is invasion of the cervical stroma in non-aggressive histological tumour types; Stage IIB is characterised by extensive LVSI in non-aggressive histological tumour types; Stage IIC includes tumours of aggressive histological types with any invasion of the uterine myometrium. Stage III continues to encompass a broad range of disease manifestations, including local and/or regional spread of tumours of any histological subtype. Stage IIIA1 is described above and requires differentiation from stage IA3; whilst stage IIIA2 includes tumour spread to the serosal and subserosal layers of the uterus. Stage IIIB comprises stage IIIB1, in which metastases or direct tumour spread to the vagina and/or parametrium are detected, and stage IIIB2, in which disseminated tumour cells are detected in the pelvic peritoneum. Stage IIIC characterises involvement of lymphatic collectors and reflects the current understanding of lymph node status, with isolated tumour cells (ITC) not considered metastatic and classified as pN0(i+). Stage IIIC1, as in the 2009 FIGO classification, is

characterised by involvement of pelvic lymph nodes. It also includes the status of metastatic involvement of the lymph nodes, in accordance with the classification in the AJCC Cancer Staging Manual. 8th ed. New York: Springer, 2017. Thus, micrometastases in the pelvic lymph nodes are classified as stage IIIC1i according to FIGO 2023, and macrometastases as stage IIIC1ii according to FIGO 2023. A similar distribution of stages applies to involvement of para-aortic lymph nodes, where micrometastases are classified as stage IIIC2i according to FIGO 2023, and macrometastases as stage IIIC2ii according to FIGO 2023. According to the new classification, FIGO 2009 stage IVB has been divided into stage IVB — metastases in the abdominal cavity outside the pelvis — and stage IVC, which includes metastases in any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain or bones.

Conclusion

Endometrial cancer primarily requires surgical staging with a detailed morphological assessment of the tumour, including the mandatory determination of the tumour's morphological type, degree of differentiation and lymphovascular invasion, and possibly in-depth molecular testing to stratify risk groups and factors that may influence the decision regarding adjuvant therapy. Even more significant in terms of surgical staging in the new classification is the mandatory determination of sentinel lymph node (SLN) status, with sentinel lymph node biopsy (SLNB) being an adequate alternative to systematic lymphadenectomy for staging. The new staging system allows the SLN protocol to be applied to all patients with endometrial carcinoma. However, it is worth noting that SLN biopsy should only be performed in conjunction with ultra-staging procedures. Given that incorporating molecular tumour characteristics into the endometrial cancer staging system improves patient selection for surgical, radiotherapy and systemic treatment, a key task in the current context is the implementation of the new endometrial cancer classification into the clinical practice of healthcare institutions.

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