Thieme

New FIGO 2023 Staging System of Endometrial Cancer: An Updated Review on a Current Hot Topic

Neues FIGO-2023-Staging-System für das Endometriumkarzinom: eine aktualisierte Übersicht über ein aktuelles Topthema

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ABSTRACT

The International Federation of Gynaecology and Obstetrics (FIGO) introduced a new staging system for endometrial carcinoma FIGO 2023 in June 2023. The new staging system differs significantly from previous versions by incorporating other non-anatomical parameters (histological type of tumour, tumour grade and the presence of massive lymphovascular space involvement as well as the molecular classification of the tumour). The FIGO 2023 staging system enhances the accuracy of prognostic assessments for patients at a specific stage with better options for targeted treatment. Another objective was to synchronise staging as much as possible with the European oncogynaecological ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma established in 2021. However, several changes are controversial. Routine molecular classification of endometrial carcinomas is not yet commonly available in most countries of the world. Another limitation of the FIGO 2023 staging system of endometrial cancer is the inclusion of variables whose definitions are still evolving, as well as variables that are subject to considerable interobserver variability in their assessment. Advantages, controversies, and limitations for clinical practice of the new FIGO 2023 endometrial cancer staging system are discussed.

ZUSAMMENFASSUNG

Im Juni 2023 hat die Internationale Vereinigung für Gynäkologie und Geburtshilfe (FIGO) ein neues Staging-System für das Endometriumkarzinom – FIGO 2023 – eingeführt. Das neue Staging-System unterscheidet sich signifikant von früheren Versionen, da nun auch andere nicht anatomische Parameter

(z. B. histologischer Tumortyp, Tumorgrad, ausgedehnter Befall des lymphatischen Raums sowie die molekulare Klassifikation von Tumoren) einbezogen wurden. Das FIGO-2023-Staging-System verbessert die prognostische Genauigkeit bei Patientinnen in einem bestimmten Tumorstadium mit einer besseren Auswahl an gezielten Behandlungsmöglichkeiten. Zweck des neuen Systems ist es auch, das FIGO-Staging weitmöglichst mit dem Staging der gynäkologisch-onkologischen Europäischen Leitlinien der ESGO/ESTRO/ESP, die im Jahre 2021 für das Management von Patientinnen mit Endometriumkarzinom aufgestellt wurden, in Einklang zu bringen. Allerdings werden mehrere Änderungen immer noch kontrovers diskutiert. So ist in den meisten Ländern der Welt die routinemäßige molekulare Klassifikation von Endometriumkarzinomen nicht allgemein üblich oder erhältlich. Eine weitere Einschränkung des FIGO-2023-Staging-Systems für das Endometriumkarzinom ist die Einbeziehung von Variablen, deren Definitionen noch im Entstehen begriffen sind, bzw. von Variablen, die eine erhebliche Interobserver-Variabilität aufweisen. Die Vorteile, Kontroversen und Einschränkungen des neuen FIGO-2023-Staging-Systems in der klinischen Praxis werden hier diskutiert.

Introduction

Endometrial cancer is the sixth most common malignancy in women worldwide and the most common gynaecological cancer in Europe, with a continuous increase in incidence [1]. The lifetime risk of endometrial cancer is close to 3 %; in patients with Lynch syndrome, it reaches 40–60 % [2, 3, 4]. In June 2023, the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique, The International Federation of Gynaecology and Obstetrics) Women's Cancer Committee officially introduced a new updated staging system for endometrial cancer, replacing the last version from 2009 [5, 6]. The international team was chaired by Professor Nicole Concin from ESGO (European Society of Gynaecological Oncology), Professor Carien L Creutzberg from ESTRO (European Society for Radiotherapy and Oncology) and Professor Xavier Matias-Guiu from ESP (European Society of Pathology) [6]. The new staging system differs significantly from the previous versions, as it includes other histopathological parameters (histological type of tumour, the presence of substantial lymphovascular space involvement) and molecular classification of the tumour in the definition of individual stages, in addition to the traditional anatomical extent of the tumour. The FIGO 2009 and FIGO 2023 staging systems are shown in ▶ **Table 1**. The staging system for carcinosarcoma remains identical to that for endometrial cancer.

Stage I

Stage IA, originally reserved for tumours with myometrial invasion < 50 % of any histological types, now includes endometrial carcinomas of non-aggressive histological types only, i.e. LG (low-grade, grade 1 and 2) endometrioid carcinomas with no LVSI or focal LVSI (lymphovascular space involvement). Stage IA is divided into three following substages: IA1 – non-aggressive histological type without invasion of the myometrium; IA2 – non-aggressive histological type with myometrial invasion < 50 %; IA3 – non-aggressive histological type with myometrial invasion < 50 % with simultaneous low-grade endometrioid ovarian involvement and with other conditions (see Comment below). Tumours classified as Stage IB are non-aggressive histological types without evidence of substantial/extensive LVSI and with myometrial invasion ≥ 50 %. Stage IC is reserved only for tumours that are limited to an endometrial polyp or confined to the endometrium of aggressive histological types, i.e., high-grade (HG, grade 3) endometrioid and non-endometrioid carcinomas (serous, clear cell, mixed, undifferentiated, carcinosarcoma, mesonephric-like, gastrointestinal mucinous types).

Comment: In patients with both endometrial and ovarian involvement, great emphasis has been placed in the past on the distinction between metastases and two synchronous primary endometrial and ovarian cancers. Recent studies suggest that the origin of concomitant LR endometrioid and ovarian cancer is overwhelmingly from the same clonal cell lineage, suggesting that the primary tumour from the endometrium spreads secondarily to the ovary [7, 8]. These patients are classified in the new Stage IA3 if the following criteria are met: 1) myometrial invasion < 50 % 2) the absence of substantial/extensive LVSI; 3) the absence of additional metastases 4) tumour limited to one ovary without capsule invasion/rupture (equivalent to pT1a). Cases that do not meet these criteria should be classified as Stage IIIA1 (metastasis of endometrial carcinoma to the ovary).

Stage II

Stage II originally included all endometrial carcinomas with infiltration into the cervical stroma, now at least one of three conditions must be met: 1) an invasion of the cervical stroma without extrauterine spread or 2) the presence of substantial LVSI in a non-aggressive histological type or 3) aggressive histological type with myometrial invasion. Stage IIA now represents non-aggressive histological types without substantial LVSI with an invasion of the cervical stroma. Stage IIB includes non-aggressive histological types with substantial LVSI regardless of local tumour spread (non-aggressive histological type without substantial LVSI and without myometrial invasion corresponds to Stage IA, with myometrial invasion means Stage IB and with an invasion of the cervical stroma is Stage IIA). Stage IIC is reserved for aggressive histological types with myometrial and/or cervical stroma invasion (an aggressive histological type without myometrial invasion corresponds to Stage IC).

Comment: Stage II now includes some tumours confined to the endometrium and tumours with infiltration of the cervical stroma. These changes will significantly increase the number of patients with Stage II endometrial cancer. On the other hand, in a retrospective analysis comparing the PFS (progression-free survival) of patients with endometrial cancer according to the 2009

▶**Table 1** Staging FIGO 2009 and 2023 of endometrial cancer (new stages based on the result of molecular classification are highlighted).

FIGO 2009	FIGO 2009 stage definitions	FIGO 2023	FIGO 2023 stage definitions
I	Tumor confined to the uterine corpus	I	Confined to the uterine corpus and ovary[1]
IA	Disease limited to the endometrium or invasion < 50 % myometrium	IA	Disease limited to the endometrium or non-aggressive histological type, i.e., low-grade endometrioid, with invasion < 50 % myometrium, with no or focal LVSI[2] or good prognosis disease
		IA1	Non-aggressive histological type limited to an endometrial polyp or confined to the endometrium
		IA2	Non-aggressive histological types with invasion < 50 % myometrium with no or focal LVSI[2]
		IA3	Low-grade endometrioid carcinomas limited to the uterus and ovary[1]
		IAm$_{POLEmut}$	**POLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type**
IB	Invasion ≥ 50 % myometrium	IB	Non-aggressive histological types with invasion ≥ 50 % myometrium, and with no or focal LVSI[2]
		IC	Aggressive histological types[3] limited to a polyp or confined to the endometrium
II	Tumor invades cervical stroma, but does not extend beyond the uterus (endocervical glandular involvement only should be considered as stage I)	II	Invasion of cervical stroma without extrauterine extension or with substantial LVSI[2] or aggressive histological types[3] with myometrial invasion
		IIA	Invasion of the cervical stroma of non-aggressive histological types
		IIB	Substantial LVSI[2] of non-aggressive histological types
		IIC	Aggressive histological types[3] with any myometrial involvement
		IICm$_{p53abn}$	**p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type**
		IIC2m$_{p53abn}$	**p53abn non-aggressive endometrial (grade 1 and 2 endometrioid) carcinoma confined to the uterus regardless of the degree of LVSI**
III	Local and/or regional spread of the tumor (positive cytology has to be reported separately without changing the stage)	III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexa	IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
		IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[1]
		IIIA2	Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Vaginal and/or parametrial involvement	IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
		IIIB1	Metastasis or direct spread to the vagina and/or the parametria
		IIIB2	Metastasis to the pelvic peritoneum
IIIC	Metastases to pelvic and/or para-aortic lymph nodes	IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both
IIIC1	Positive pelvic nodes	IIIC1	Metastasis to the pelvic lymph nodes
		IIIC1i	Micrometastasis[4]
		IIIC1ii	Macrometastasis[4]
IIIC2	Positive para-aortic lymph (suprapelvic) nodes up to the renal vessels with or without positive pelvic lymph nodes	IIIC2	Metastasis to para-aortic (suprapelvic) lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
		IIIC2i	Micrometastasis[4]
		IIIC2ii	Macrometastasis[4]

▶Table 1 continued

FIGO 2009	FIGO 2009 stage definitions	FIGO 2023	FIGO 2023 stage definitions
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases	IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Tumor invasion of bladder and/or bowel mucosa	IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone	IVB	Abdominal peritoneal metastasis beyond the pelvis
		IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Comments:
[1] Low-grade (LG) endometrioid adenocarcinomas (grade 1 and 2) involving both the endometrium and the ovary, when the following criteria are met 1) invasion < 50 % myometrium; 2) absence of extensive/substantial LVSI (lymphovascular space involvement); 3) absence of additional metastases; 4) the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).
[2] LVSI (lymphovascular space involvement) as defined in WHO 2021: extensive/substantial, ≥ 5 vessels involved
[3] Aggressive histological types are serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, carcinosarcomas, and high-grade (HG, grade 3) endometrioid adenocarcinomas
Non-aggressive histological types are low-grade (grade 1 and 2) endometrioid adenocarcinomas.
[4] Micrometastases are considered to be metastatic involvement (pN1[mi]). The prognostic significance of ITCs (isolated tumor cells) is unclear. The presence of ITCs should be documented and is regarded as pN0(i+). Macrometastases are > 2 mm in size, micrometastases are 0.2–2 mm and/or > 200 cells, and isolated tumor cells are ≥ 0.2 mm and ≤ 200 cells

and 2023 FIGO staging systems, the 5-year PFS for patients with Stage II (as opposed to Stage I) was comparable in both groups (70.2 % vs. 71.2 %) [9].

Stage III

The basic definition of Stage III remains unchanged: local and/or regional spread of the tumour of any histological type. Stage IIIA newly distinguishes between adnexal (IIIA1) and uterine serosa infiltration (IIIA2). Stage IIIB1 indicates vaginal and/or parametrial involvement, which corresponds to the previous Stage IIIB. Involvement of the pelvic peritoneum is now classified as IIIB2 (previously Stage IVB). Stage IIIC, with an identical definition for both FIGO 2009 and FIGO 2023 staging (metastasis to pelvic and/or para-aortic lymph nodes), now distinguishes between micrometastases (IIIC1i, IIIC2i) and macrometastases (IIIC1ii, IIIC2ii) in the lymph nodes.

Comment: Fallopian tube tumours are always classified as Stage IIIA1, unlike LR endometrioid carcinomas with synchronous involvement of the endometrium and one ovary (see Stage IA3). In serous carcinoma, secondary tubal involvement should always be distinguished from the concurrent presence of primary serous tubal intraepithelial carcinoma (STIC). In these cases, it is appropriate to examine the tubes histologically according to the SEE-FIM protocol, and immunohistochemically [6]. The presence of intraluminal tubal free floating tumour fragments is a controversial issue, particularly in serous carcinoma, but is not decisive for staging. The same applies for positive washing cytology [6]. Differentiation of nodal involvement into macrometastases (size > 2 mm) and micrometastases (0.2–2 mm and/or number > 200 affected cells) in accordance with the approach adopted by the AJCC (American Joint Committee on Cancer) will significantly refine the prognosis. This change reflects better prognosis in patients with micrometastases in lymph nodes [6, 10, 11]. The prognostic significance of ITCs (isolated tumour cells) remains unclear and is not considered a metastasis (pN0[i+]) [6, 10, 12].

Stage IV

The general definition of Stage IV is the same (spread to the bladder mucosa and/or intestinal mucosa and/or distant metastasis). Local invasion of bladder mucosa and/or intestinal/ bowel mucosa remains Stage IVA. However, an additional substage was added for patients with extrapelvic peritoneal metastasis (Stage IVB), patients with involvement of the pelvic peritoneum belong to Stage IIIB2. Stage IVC means the presence of distant metastases.

Comment: Isolated peritoneal carcinomatosis (new Stage IIIB2) is rare (approximately 2 % of all patients with endometrial carcinomas) and these patients should be distinguished from those with distant metastases, because, unlike in Stage IV of endometrial cancer, they are usually indicated for primary surgical treatment [6, 10, 13, 14]. The level of lymph nodes involvement between Stage III and IV remains the same. Distant metastases mean involvement of intra-abdominal nodes above the renal vessels and/or any extra- or intra-abdominal lymph nodes.

FIGO 2023 Staging with Molecular Classification

Molecular classification allows to classify endometrial cancer into four prognostic groups: *POLE*mut, MMRd (mismatch repair deficient), NSMP (non-specific molecular profile) and *p53*abn [2, 3, 4, 15].

1. **POLEmut** (inactivation of DNA polymerase ε POLE); a large number of somatic mutations is typical (ultramutated endometrial carcinomas). The proportion of this group in endometrial carcinomas ranges from 6 to 12 % [2, 3, 4, 15].
2. **MMRd** (synonym of microsatellite instable); includes carcinomas with microsatellite instability (MSI) with a high number of mutations (so-called hypermutated endometrial carcinomas). The proportion of these carcinomas is estimated at 30 to 35 % [2, 3, 4, 15].
3. **NSMP**; these endometrial carcinomas with a non-specific molecular profile show a low number of somatic alterations with low copy number variation (CNV) and low, somatic copy-number alteration low, SCNA-low). This group is the largest (30 to 60 %), genetically very heterogeneous and will probably be further subdivided in the future [2, 3, 4, 15].
4. **p53abn** (p53 abnormal); in addition to the defining *TP53* aberration, a high number of copy number alterations (copy number high, somatic copy-number alteration high/serous like, SCNA-high) are present. These tumours account for 12 to 25 % of all endometrial cancers [2, 3, 4, 15].

According to the recommendations of the CGA (The Cancer Genome Atlas), at least three immunohistochemical markers (p53, MSH6, and PMS2) and one molecular test (analysis of pathogenic *POLE* mutations) should be performed for the correct evaluation of molecular classification [2, 3, 4, 15]. Stages I and II change only when *POLE*mut ($IAm_{POLEmut}$) or p53abn ($IICm_{p53abn}$) is detected, while FIGO stage does not change when MMRd or NSMP is detected (▶ **Table 1**). Stages III and IV are retained when any molecular marker is detected, but the result of the molecular classification should always be recorded in the stage for data collection and evaluation purposes (e.g., $IA3m_{MMRd}$, $IIBm_{NSMP}$, $IIIA2m_{POLEmut}$, $IVCm_{p53abn}$, etc.). If molecular classification has been performed, the stage designation shall always be followed by the letter "m". If the result of the molecular classification is not available, the stage should be assigned according to traditional histopathological criteria, which remain important prognostic parameters for the indication of adjuvant therapy [6, 10].

FIGO 2023 Staging System Controversies

The introduction of molecular classification results is the main and most discussed change in the new staging system. The molecular classification of endometrial cancer and its clinical relevance is rapidly evolving, which could lead to some contradictions in the future [6, 10, 16]. Moreover, there is a lack of recent prospective studies addressing the integration of molecular classification into FIGO 2023 EC staging. The methodology for determining the molecular group is not specified in the 2023 FIGO update, which may cause differences in the interpretation of results between laboratories. However, the WHO has specified and approved the methodology for performing immunohistochemistry in detail [17, 18]. Based on current evidence, a combination of immunohistochemistry and separate *POLE* testing appears to be the preferred approach [3, 4, 15, 19]. Nevertheless, these auxiliary tools can exhibit a variability in the possible workflow and interpretation of results. Previous papers comparing immunohistochemistry (IHC) and polymerase chain reaction (PCR) in endometrial tumours have shown discordance rates as high as 5 to 10 %. However, recent studies have indicated that next-generation sequencing (NGS) can help resolve discrepant results when selecting the appropriate tumour tissue for both IHC and molecular is ensured [20]. The introduction of new sequencing panels for NGS to extend the testing of *POLE* mutations has on the one hand also provided information on new pathogenic or likely pathogenic *POLE* mutations, but on the other hand identified new variants of unknown significance. There are currently twelve known mutations of the *POLE* gene that are proven to be pathogenic [19]. This spectrum will undoubtedly continue to expand. The distinction between pathogenic and non-pathogenic *POLE*mut may not be clear-cut. Due to the high mutational load, non-pathogenic *POLE* mutations are mostly found in the group of hypermutated MMRd tumours as a secondary genetic event and the biological behaviour is consistent with the characteristics of this group. Since a positive *POLE* mutation result often changes the stage of the disease and thus the indication for adjuvant therapy, knowledge of the correct pathogenic *POLE* mutations is essential for the classification of endometrial cancer as a "*POLE*mut" [16].

Immunohistochemical detection of abnormal p53 expression is very sensitive with respect to detection of *TP53* gene mutation status; only a minority of cases with mutations show normal expression type on immunohistochemical level. A study on ovarian carcinomas showed that with proper validation, immunohistochemical testing has a concordance with *TP53* gene mutation status of 100 % specificity and 95.9 % sensitivity [21]. However, unlike ovarian cancer, endometrial carcinoma can have abnormal, mostly clonal expression patterns, which are particularly common in patients with MMRd or *POLE* mutations [21]. Patients with *TP53*-mutated cancers are the only ones among 4 molecular groups to benefit from chemoradiotherapy [22]. Misclassification of the tumour as *TP53*abn has significant negative consequences for the patient. Some experts believe that p53 immunostaining is not a perfect surrogate of *TP53* mutations [23]. A study on 132 patients with endometrial cancer observed sensitivity, specificity, positive (PPV), and negative predictive values (NPV) of IHC for MSI status in 89.3 %, 87.3 %, 78.1 %, and 94.1 %, and for p53 in 92.3 %, 77.1 %, 60.0 % and 96.4 % of cases, respectively. The authors concluded that the moderate concordance (Cohen's kappa coefficient of 0.59) between IHC and NGS for p53 status implies that they cannot be used interchangeably [24]. Singh et al. found the concordance between p53 IHC and *TP53* mutation in 92.3 % (155/168) of cases overall, and in 95.1 % (117/123) after excluding MMRd and POLEmut endometrial cancers [25]. Matsumoto et al. demonstrated the concordance of p53 IHC and NGS for *TP53* mutation status in 100 % (43/43) of high-grade endometrial cancers [26]. A meta-analysis assessing the diagnostic accuracy of p53 immunohistochemistry as surrogate for *TP53* sequencing included 13 studies with 727 endometrial cancers. Immunohistochemical criteria used to define aberrant p53 expression were "overexpression" and "overexpression or complete absence". Both "overexpression" and "overexpression or complete absence" showed high diagnostic accuracy (area under the curve, AUC = 0.9088 and 0.9030, respectively). The subgroup with "overexpression" and NGS showed the best results, with very high diagnostic accuracy

(AUC = 0.9927). The conclusions of this meta-analysis confirmed that IHC is a highly accurate surrogate of *TP53* sequencing [27].

In addition, 3 to 6% of all endometrial carcinomas have more than one molecular characteristic (referred to as multiple classifier) [2, 3, 4, 15, 28, 29]. The most common is the "double classifier" (e.g., POLEmut and p53abn or MMRd and p53abn), but there are also "triple classifiers" (POLEmut and MMRd and p53abn simultaneously). In these cases, p53abn is a secondary manifestation of the ultramutated state in *POLE* mutation or within the microsatellite instability in MMRd. The prognosis of these tumours is then based on the *POLE* mutation or MMRd and the appropriate stage is assigned accordingly [29]. The current consensus is that in tumours with a pathogenic mutation of the *POLE* gene, this mutation is superior to all other abnormalities, and such tumours should be classified as POLEmut [4]. However, data are limited for tumours that exhibit both the common molecular characteristics of POLEmut and MMRd and in these cases more detailed investigation should be considered to exclude Lynch syndrome [15].

Although molecular classification is not a mandatory part of the new FIGO staging, its inclusion appears problematic for several reasons, including the varying availability across different countries. In addition, there are other immunohistochemical markers (mainly estrogen [ER] and progesterone receptor [PR] expression) that are more affordable and significantly improve prognosis [30], but have not been included in the staging or in the ESGO/ESTRO/ESP guidelines at all. This was confirmed, for example, in a prospective study of 132 patients [31]. In the preoperative stratification of low- or high-risk patients, the authors evaluated the importance of the presence of certain immunohistochemical biomarkers (L1CAM, ER, PR and p53) in addition to standard criteria (age, stage, histological type, grade, lymphovascular invasion). The results of immunohistochemical markers significantly improved the sensitivity for determining the high-risk group (48.4% vs. 75.8%, $p < 0.001$) with a statistically insignificant decrease in specificity to 80% ($p = 0.238$). The positive predictive value (PPV) was similar for the two methods, whereas the negative predictive value (NPV) (i.e., the probability of extremely low risk in negative test cases) improved statistically significantly (66.0% vs. 78.9%, $p < 0.001$) [31]. Another study of 763 EC patients showed that abnormal expression of p53, L1CAM, ER or PR was significantly associated with a higher risk. Moreover, ER-/PR-negative status and p53abn were independently associated with reduced disease-specific survival (HR 2.74; 95% CI 1.48–5.07; $p = 0.001$ and HR 1.88; 95% CI 1.00–3.51; $p = 0.048$, respectively) [32].

Another limitation of the FIGO 2023 staging system of endometrial cancer is the inclusion of variables whose definitions are still evolving, as well as variables that are subject to considerable interobserver variability in their assessment. The presence of substantial LVSI plays a significant role in tumour prognosis, and therefore this parameter has been implemented in staging [6, 33, 34, 35]. The problem remains that several different definitions are used to quantify LVSI. FIGO 2023 as well as the WHO Classification of Female Genital Tumours [17, 18, 36] and ESGO/ESTRO/ESP guidelines [10] define substantial (or extensive) LVSI as involvement of ≥ 5 lymphovascular structures (focal LVSI < 5 vessels involved, negative LVSI is without vessel involvement). However, other organisations use different definitions. The NCCN (National Comprehensive Cancer Network) defines substantial LVSI as involvement of ≥ 4 lymphovascular structures on a single hematoxylin-eosin-stained section [37] and the ICCR (International Collaboration on Cancer Reporting) [38], ISGyP (The International Society of Gynaecological Pathologists) [39], CAP (College of American Pathologists) [40], DGGG (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, German Society for Gynecology and Obstetrics) and DKG (Deutsche Krebsgesellschaft, German Cancer Society) [41], only ≥ 3 vessels are sufficient to define massive LVSI involvement. Additionally, most definitions (including FIGO 2023) do not specify whether the extent of LVSI is based on the maximum involvement in a single tissue section or the cumulative involvement across all examined sections of the affected tissue. This ambiguity may lead to the assignment of different stages in oncologically identical patients with different outcomes of identical therapy [16].

Another example is the renewed requirement for a histological distinction between tumours confined to the endometrium and those with minimal invasion of the myometrium. This distinction is particularly problematic in non-aggressive (low grade endometrioid) carcinomas. Accurate histological assessment is often difficult because of the presence of adenomyosis and the irregular interface between the endometrium and myometrium. Consequently, the description of tumour invasion into the myometrium can vary considerably from one institution to another [16, 23, 39]. Another issue is the histopathological determination of uterine serosa tumour involvement, which is listed as "uterine subserosa" for the definition of Stage IIIA2. ISGyP includes submesothelial fibrous tissue as part of the definition of serous invasion [39]. The definition of subserous (as opposed to serous) invasion lacks clearly defined histopathological criteria and is not included in any professional guidelines or other source documents and cannot be clearly interpreted [16, 23].

Already in 2021, ISGyP conducted a questionnaire survey addressing many of the questions that were later integrated into the 2023 FIGO staging system among ISGyP and International Gynecologic Cancer Society members and received responses from 172 pathologists and 135 clinical oncogynaecologists [42]. Relatively few questions elicited a consensus response, defined as at least 75% agreement. Consensus agreement was reached on differentiating nodal involvement into micro- and macrometastases, defining criteria for categorizing cases of simultaneous uterine body and ovarian cancer LR endometrioid cancer, and the importance of LVSI expression as an independent risk factor. However, only half of pathologists (48%) and two thirds of oncogynaecologists (61%) agreed with the implementation of LVSI results in the staging system, and there was similar support for the inclusion of molecular classification (48% of pathologists and 63% of oncogynaecologists) or histological type of tumour (52% of pathologists and 65% of oncogynaecologists) in staging [42]. Interestingly, while two thirds of clinical oncologists agreed with these changes, approximately half of pathologists were in favour while the other half were not. This reflects current opinions on the FIGO 2023 staging of endometrial cancer [42]. While pathologists tend to criticise it [16, 23], clinicians have embraced the changes, although they raise some questions [43]. The parameters needed to determine the specific stage, with indication of appropriate

therapy, largely depend on histopathological parameters. Some experts believe that the lack of representation of the pathology community was a major shortcoming in the design of the FIGO 2023 staging [16].

Many of the implemented changes and recommendations are presented without any citations to the original peer-reviewed literature. An example is the inclusion of grade 3 endometrioid carcinoma in the group of "aggressive" histological types, alongside other non-endometrioid carcinomas, although it is a markedly molecularly and clinically heterogeneous group. This stratification is not substantially supported by the cited literature, and the 2021 ESGO/ESTRO/ESP guidelines also separate grade 3 endometrioid carcinoma from other aggressive non-endometrioid carcinomas (▶ **Table 2**) [10, 16, 36].

Discussion

The last change to the endometrial cancer staging system was adopted by FIGO in 2008 and published in 2009. Two years later, similar changes were implemented in the TNM system [5]. The traditional concept of staging system was based on the description of the anatomical extent of the disease at the time of diagnosis based on clinical, radiological and possibly histopathological examination. Staging is the key and often the strongest prognostic factor for an individual patient. The new FIGO 2023 staging system aims to define individual stages with a more accurate prognosis by incorporating additional important prognostic factors that simple anatomical spread cannot capture. This approach, which includes histological-pathological and molecular data, has already been applied to staging systems of breast, head and neck, and prostate carcinomas [16, 44]. The 2021 joint ESGO/ESTRO/ESP guidelines follow the same principle and categorise patients with endometrial cancer into several risk groups (low, intermediate, medium-high and high risk). This principle is also used in the joint guidelines for endometrial cancer of the German-speaking professional societies [41, 45]. The definition of risk groups varies on whether the result of molecular classification of the tumour is known (▶ **Table 2**) [10].

Some experts find the FIGO 2023 staging system complicated and non-intuitive, with difficulty to facilitate correspondence with the 2009 FIGO staging [23]. This can make it significantly more difficult to adopt more widely in regions with different levels of healthcare. Incorporation of cancer molecular classification results into FIGO 2023 staging essentially precludes staging in under-resourced areas. This will fundamentally complicate the collection of health data for clinical, epidemiological and research purposes, including clinical trials. For existing clinical trials, it is not clear how the inclusion criteria could be adapted to fit the new FIGO staging system [16]. Also, the stage can change several times in one patient in a relatively short period of time. For example, the histology from a hysterectomy may show Stage IIC (aggressive histological type with myometrial invasion), but after review at the local cancer centre the resulting stage changes to, for example, $IAm_{POLEmut}$ (evidence of a pathogenic POLE mutation). It is still a matter of debate whether the stage of the disease should be an auxiliary component in the calculation of the patient's risk stratification, or whether the stage, by incorporating other prognostic parameters beyond the anatomical extent of the tumour, should reflect the most accurate risk of a particular patient, i.e. whether the staging system should be the defining model itself, expressing the most accurate risk. The phase of refining the prognosis of a specific stage by incorporating various histopathological and molecular variables makes the determination of this stage significantly more complicated. Therefore, maintaining definitions of individual stages based on anatomical spread seems to be a better solution worldwide. Paradoxically, the sudden transition to the full FIGO 2023 staging system as proposed by FIGO may hinder progress towards a more accurate prognosis for individual stages [42].

The new FIGO 2023 endometrial cancer staging system has some undeniable advantages over the previous version. The new FIGO 2023 staging system reflects that endometrial cancer is not a single disease. The undisputed fact remains that the implementation of new histopathological parameters and molecular classification results for endometrial cancer will significantly improve the prognosis of a specific patient at a specific stage [2, 4, 6, 15]. This was confirmed by an international retrospective study from three oncogynaecology centres in Austria and Italy comparing the FIGO 2009 and FIGO 2023 staging systems [9]. In this study, all applied statistical tests confirmed more accurate prediction of PFS and OS (overall survival) using the FIGO 2023 staging system compared to FIGO 2009 [9]. A retrospective analysis of 519 patients with endometrial cancer showed a significantly higher 5-year PFS in Stage I according to the FIGO 2023 staging system compared to FIGO 2009 (93.0% vs. 87.4%). Two new molecularly defined sub-stages $IAm_{POLEmut}$ and $IICm_{p53abn}$ according to 2023 FIGO showed completely different oncological results [9].

Molecular classification can define patients with an excellent prognosis (*POLE*mut) from a group with a poor prognosis (*p53*abn) [3, 4, 15, 29]. This is a major advance in the diagnosis and treatment of endometrial cancer in the last 10 years [6]. MMRd testing plays an important role in screening for Lynch syndrome and is also a predictor of response to immunotherapy in advanced tumours using immune check point inhibitors (ICI). Two randomised phase III trials (ENGOT-en6/GOG-3031/RUBY and NRG-GY018/Keynote-868) have demonstrated a statistically significant PFS advantage with the addition of an immune checkpoint inhibitor (ICI) (dostarlimab or pembolizumab, respectively) to standard carboplatin/paclitaxel chemotherapy followed by ICI maintenance therapy in MMRd patients with a hazard ratio (HR) of 0.28 (95% confidence interval [CI] 0.16–0.5) and 0.30 (95% CI 0.19–0.48), respectively [46, 47]. Similarly, phase III trial (AtTEnd) observed significantly increased PGS in patients with advanced or recurrent endometrial cancer (especially those with MMRd cancers) treated with ICI atezolizumab added to standard carboplatin/paclitaxel chemotherapy (HR 0.4; 95% CI 0.61–0.91; $p = 0.022$) compared to controls [48]. Recent trial (phase III DUO-E) showed statistically significant PFS benefit in ICI durvalumab (plus standard carboplatin/paclitaxel chemotherapy) (HR 0.71; 95% CI 0.57–0.89; $p = 0.003$) and durvalumab + olaparib (plus standard chemotherapy) arms (HR 0.55; 95% CI 0.43–0.69; $p < 0.0001$) versus standard chemotherapy arm among advanced or recurrent endometrial cancer patients. The PFS benefit was higher in MMRd subjects (HR 0.42; 95% CI 0.22–0.80 and HR 0.41; 95% CI 0.21–0.75, respectively) [49].

▶**Table 2** Definition of prognostic risk groups according to ESGO/ESTRO/ESP guidelines.

Risk group	Molecular classification not performed	FIGO 2023	Known molecular classification result	FIGO 2023
Low	Stage IA (FIGO 2009) low-grade (LG)[1] endometrioid ca + LVSI negative or focal[2]	IA1 IA2 IA3	Stage I–II (FIGO 2009, 2023) POLEmut endometrioid ca	$IAm_{POLEmut}$
			Stage IA (FIGO 2009) MMRd/NSMP + LG[1] endometrioid ca + LVSI negative or focal[2]	$IA1m_{MMRd}$ $IA1m_{NSMP}$ $IA2m_{MMRd}$ $IA2m_{NSMP}$
Intermediate	Stage IB (FIGO 2009) LG[1] endometrioid ca + LVSI negative or focal[2]	IB	Stage IB (FIGO 2009) MMRd/NSMP + LG[1] endometrioid ca + LVSI negative or focal[2]	IBm_{MMRd} IBm_{NSMP} ICm_{MMRd} ICm_{NSMP}
	Stage IA (FIGO 2009) high-grade (HG)[3] endometrioid ca + LVSI negative or focal[2]	IIC	Stage IA (FIGO 2009) MMRd/NSMP + HG (grade 3)[1] endometrioid ca + LVSI negative or focal[2]	ICm_{MMRd} ICm_{NSMP} $IICm_{MMRd}$ $IICm_{NSMP}$
	Stage IA (FIGO 2009) non-endometrioid[3] ca without myometrial invasion	IC	Stage IA (FIGO 2009) p53abn + and/or non- endometrioid[3] ca without myometrial invasion	$IICm_{p53abn}$ $IIC2m_{p53abn}$ ICm
High–intermediate	Stage I (FIGO 2009) endometrioid ca + substantial LVSI[2] regardless of grade and depth of invasion	IIB	Stage I (FIGO 2009) MMRd/NSMP + endometrioid ca + substantial LVSI[2] regardless of grade and depth of invasion	$IIBm_{MMRd}$ $IIBm_{NSMP}$
	Stage IB (FIGO 2009) HG[3] endometrioid ca + regardless of LVSI status	IIB IIC	Stage IB (FIGO 2009) MMRd/NSMP + HG[3] endometrioid ca + regardless of LVSI status	$IICm_{MMRd}$ $IICm_{NSMP}$
	Stage II (FIGO 2009)	IIA, IIB IIC	Stage II (FIGO 2009) MMRd/NSMP + endometrioid ca	$IIAm_{MMRd}$ $IIAm_{NSMP}$
High	Stage IIIA–IVA (FIGO 2009) with no residual disease	IIIA–IVA	Stage III–IVA (FIGO 2009) MMRd/NSMP + endometrioidní ca, bez rezidua průkaz MMRd/NSMP + endometrioid ca + no residual disease	Identical stage with "m_{MMRd}" or "m_{NSMP}"
	Stage IA–IVA (FIGO 2009) non-endometrioid[3] + no residual disease	IIC–IVA	Stage I–IVA (FIGO 2009) p53abn endometrial ca + myometrial invasion + no residual disease	$IICm_{p53abn}$ $IIC2m_{p53abn}$ $IIIm_{p53abn}$ – $IVAm_{p53abn}$
			Stage I–IVA (FIGO 2009) NSMP/MMRd + serous, undifferentiated ca, carcinosarcoma + myometrial invasion + no residual disease	Im_{MMRd} – $IVAm_{MMRd}$ Im_{NSMP} – $IVAm_{NSMP}$
Advanced metastatic	Stage III–IVA (FIGO 2009) with residual disease	IIIA-IVA	Stage III–IVA (FIGO 2009) + any molecular type	Identical stage with "m_{MMRd}" or "m_{NSMP}" or "$m_{POLEmut}$" or "m_{p53abn}"
	Stage IVB (FIGO 2009)	IVB, IVC	Stage IVB (FIGO 2009) + any molecular type	

Comments:
[1] Low-grade (LG) endometrioid adenocarcinomas have grade 1 or 2, high-grade (HG) endometrioid adenocarcinomas have grade 3
[2] LVSI (lymphovascular space involvement) as defined in WHO 2021: extensive/substantial, ≥ 5 vessels involved
[3] Non-endometrioid adenocarcinomas (serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, carcinosarcomas)

Molecular classification is particularly important in aggressive histological types. HG endometrioid carcinoma benefits most from molecular classification because it is a clinically, molecularly and prognostically very heterogeneous disease [36]. Without molecular classification, HG endometrioid carcinoma cannot be stratified into the appropriate risk group. Due to early symptomatology, almost two thirds of patients with endometrial cancer are diagnosed at early stages allowing for primary surgical treatment, and a relatively small proportion of patients are then indicated for adjuvant therapy, sometimes based solely on molecular classification results. Patients with *POLE*mut group cancers significantly benefit in a reduction of postoperative adjuvant radiotherapy in terms of elimination of adverse effects while maintaining the same prognosis [3, 4, 6, 10]. In contrast, the detection of *p53*abn has a significantly worse prognosis and extensive adjuvant therapy may be beneficial. However, according to our own experience in clinical practice, some clinical oncologists may have difficulty relying solely on the outcome of pathogenic *POLE*mut. They prefer to administer adjuvant therapy even in *POLE*mut carcinomas that are considered very aggressive by other criteria. The use of molecular classification is also likely to be used to determine the risk of disease for fertility preserving procedures in young women with endometrial cancer who meet the prescribed criteria. Furthermore, molecular classification is feasible in routine practice for all patients with endometrial cancer and does not prolong the time needed to decide on adjuvant therapy [50]. The largest study in Central Europe included a total of 270 molecularly classified endometrial cancers [51]. In total, 6.6% (18/270) of subjects had *POLE*mut, 31.5% (85/270) had MMRd, 11.1% (30/270) had *TP53*mut, and 50.7% (137/270) had no specific molecular profile. Thirteen cases (4.8%) were classified as "multiple classifiers". The NSMP group was often characterised by multiple genetic alterations, the most common being mutations in the *PTEN* (44%), *PIK3CA* (30%), *ARID1A* (21%) and *KRAS* (9%) genes [51].

NSMP endometrial carcinomas are a heterogenous group of tumours and comprise both aggressive and low-risk ECs; therefore NSMP does not change the stage. Within the NSMP cancer group, certain features significantly affect the patient's prognosis. Grade 3 and/or ER-negative status were responsible for most of the disease-specific deaths at 5 years (HR 16.3; 95% CI: 8.4–31.7) compared with low-risk NSMP endometrial cancers (grade 1–2, ER-positive) [52]. A study on 648 cases revealed that only ER-positivity was independently associated with a reduced risk of recurrence (HR 0.33, 95% CI: 0.15–0.75) in high-risk NSMP endometrial cancers [53]. Treatment de-escalation could be considered in ER-positive NSMP ECs, which constitute the vast majority of NSMP ECs [52]. Assessment of ER status in high-risk NSMP EC is feasible in clinical practice and can improve risk stratification and treatment.

Multiple classifier endometrial cancers are at a higher risk of being classified into a different molecular group with a different prognosis estimate. In cases analysed solely by Sanger sequencing of the *POLE* gene, which has lower analytical sensitivity than NGS testing, pathogenic mutations in the *POLE* gene may go undetected, leading to misclassification of the EC as p53abn or MMRd. The clinical outcomes of patients with MMRd-p53abn and POLEmut-p53abn endometrial carcinomas, exhibiting a 5-year recurrence-free survival (RFS) of 92.2% and 94.1% for Stage I, respectively, were significantly different from those of single-classifier p53abn endometrial carcinomas, which had a Stage I RFS of 70.8% ($p = 0.024$ and $p = 0.050$, respectively) [29]. The authors of a prospective study with a follow-up duration of 24.7 months state that "multiple classifier" endometrial carcinomas have the potential to behave aggressively, and their categorization as POLEmut EC with treatment de-escalation may therefore not be safe [51]. However, the recent cohort study observed no recurrences in 15 POLEmut-p53abn cases, 2 POLEmut-MMRd and 3 POLEmut-MMRd-p53abn ECs during a median follow-up of 12.8 and 17.0 months, respectively. In contrast, recurrences were noted in 7.1% (2/28) of MMRd-p53abn cases at 5.0 and 6.9 months post-surgery, while MMRd and p53abn recurred in 4.0% (4/99) and 34.2% (25/73) cases, respectively, with a median time to recurrence of 8.8 and 8.4 months [54]. Collaborative prospective multi-institutional studies are needed to evaluate the prognostic significance of multiple classifiers, since current results are based on a limited number of patients. The experts also welcomed the creation of Stage IA3 for LR cancer with synchronous involvement of the endometrium and one ovary, as these cancers have a good prognosis if the defined criteria are met [7, 34, 35, 36]. According to the WHO 2020 classification [18] and also according to the ESGO/ESTRO/ESP guidelines [10], conservative management without adjuvant therapy is recommended for these patients [6, 34, 36, 55, 56]. On the other hand, in aggressive types of tumours (mainly serous carcinoma), there is a significant difference in patient prognosis between tumours limited to the polyp and those affecting the adjacent endometrium [57]. The creation of new Stages IC and IIC (▶ **Table 1**) is therefore justified from this perspective. Additionally, the extension of the definitions of Stages II, III and IV with more precise differentiation of different types of tumour spread outside the uterus, and thus more precise prognosis of individual sub-stages has been generally well received by the professional community. Another development well received by oncologists and pathologists was the differentiation of nodal involvement into micro- and macrometastases in accordance with the AJCC [16, 40]. Various techniques of sentinel node detection with detailed histological examination using ultrastaging are now standard in Central Europe [58, 59, 60].

Conclusion

The new staging system for endometrial cancer FIGO 2023 differs significantly from previous versions, as it includes additional histopathological parameters and molecular classification of the tumour in the definition of individual stages, alongside the traditional anatomical extent of the tumour. This change has further strengthened the role of the pathologist in staging. The inclusion of these parameters has significantly refined the prognosis estimation of each stage, enabling the indication of targeted therapy. On the other hand, the FIGO 2023 staging system may appear overly complex, and its implementation in daily practice requires the full involvement of all stakeholders.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Sung H, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209–249. DOI: 10.3322/caac.21660

[2] Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013; 497: 67–73. DOI: 10.1038/nature12113

[3] Stelloo E, Nout RA, Osse EM et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res 2016; 22: 4215–4224. DOI: 10.1158/1078-0432.CCR-15-2878

[4] León-Castillo A, de Boer SM, Powell ME et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol 2020; 38: 3388–3397. DOI: 10.1200/JCO.20.00549

[5] Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet 2009; 105: 109. DOI: 10.1016/j.ijgo.2009.02.010

[6] Berek JS, Matias-Guiu X, Creutzberg C et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet 2023; 162: 383–394. DOI: 10.1002/ijgo.14923

[7] Anglesio MS, Wang YK, Maassen M et al. Synchronous Endometrial and Ovarian Carcinomas: Evidence of Clonality. J Natl Cancer Inst 2016; 108: djv428. DOI: 10.1093/jnci/djv428

[8] Hájková N, Tichá I, Hojný J et al. Synchronous endometrioid endometrial and ovarian carcinomas are biologically related: A clinico-pathological and molecular (next generation sequencing) study of 22 cases. Oncol Lett 2019; 17: 2207–2214. DOI: 10.3892/ol.2018.9855

[9] Schwameis R, Fanfani F, Ebner C et al. Verification of the prognostic precision of the new 2023 FIGO staging system in endometrial cancer patients – An international pooled analysis of three ESGO accredited centres. Eur J Cancer 2023; 193: 113317. DOI: 10.1016/j.ejca.2023.113317

[10] Concin N, Matias-Guiu X, Vergote I et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Radiother Oncol 2021; 154: 327–353. DOI: 10.1016/j.radonc.2020.11.018

[11] Mueller JJ, Pedra Nobre S, Braxton K et al. Incidence of pelvic lymph node metastasis using modern FIGO staging and sentinel lymph node mapping with ultrastaging in surgically staged patients with endometrioid and serous endometrial carcinoma. Gynecol Oncol 2020; 157: 619–623. DOI: 10.1016/j.ygyno.2020.03.025

[12] Krizova A, Clarke BA, Bernardini MQ et al. Histologic artifacts in abdominal, vaginal, laparoscopic, and robotic hysterectomy specimens: a blinded, retrospective review. Am J Surg Pathol 2011; 35: 115–126. DOI: 10.1097/PAS.0b013e31820273dc

[13] Burg L, Timmermans M, van der Aa M et al. Incidence and predictors of peritoneal metastases of gynecological origin: a population-based study in the Netherlands. J Gynecol Oncol 2020; 31: e58. DOI: 10.3802/jgo.2020.31.e58

[14] Li H, Zhang R, Chen C et al. Prognostic value of different metastatic sites for patients with FIGO stage IVB endometrial cancer after surgery: A SEER database analysis. J Surg Oncol 2020; 122: 941–948. DOI: 10.1002/jso.26102

[15] Piulats JM, Guerra E, Gil-Martín M et al. Molecular approaches for classifying endometrial carcinoma. Gynecol Oncol 2017; 145: 200–207. DOI: 10.1016/j.ygyno.2016.12.015

[16] McCluggage WG, Bosse T, Gilks CB et al. FIGO 2023 endometrial cancer staging: too much, too soon? Int J Gynecol Cancer 2024; 34: 138–143. DOI: 10.1136/ijgc-2023-004981

[17] WHO Classification of Tumours Editorial Board. Female Genital Tumours. Accessed August 09, 2024 at: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Female-Genital-Tumours-2020

[18] Cree IA, White VA, Indave BI et al. Revising the WHO classification: female genital tract tumours. Histopathology 2020; 76: 151–156. DOI: 10.1111/his.13977

[19] Cui J, Chen X, Zhai Q et al. A novel somatic mutation in POLE exonuclease domain associated with ultra-mutational signature and MMR deficiency in endometrial cancer: a case report. Diagn Pathol 2023; 18: 19. DOI: 10.1186/s13000-023-01287-y

[20] Smithgall MC, Remotti H, Hsiao SJ et al. Investigation of discrepant mismatch repair immunohistochemistry and microsatellite instability polymerase chain reaction test results for gynecologic cancers using next-generation sequencing. Hum Pathol 2022; 119: 41–50. DOI: 10.1016/j.humpath.2021.10.004

[21] Köbel M, Ronnett BM, Singh N et al. Interpretation of P53 Immunohistochemistry in Endometrial Carcinomas: Toward Increased Reproducibility. Int J Gynecol Pathol 2019; 38 (Suppl 1): S123–S131. DOI: 10.1097/PGP.0000000000000488

[22] Corr B, Cosgrove C, Spinosa D et al. Endometrial cancer: molecular classification and future treatments. BMJ Med 2022; 1: e000152. DOI: 10.1136/bmjmed-2022-000152

[23] Espinosa I, D'Angelo E, Prat J. Endometrial carcinoma: 10 years of TCGA (the cancer genome atlas): A critical reappraisal with comments on FIGO 2023 staging. Gynecol Oncol 2024; 186: 94–103. DOI: 10.1016/j.ygyno.2024.04.008

[24] Streel S, Salmon A, Dheur A et al. Diagnostic Performance of Immunohistochemistry Compared to Molecular Techniques for Microsatellite Instability and p53 Mutation Detection in Endometrial Cancer. Int J Mol Sci 2023; 24: 4866. DOI: 10.3390/ijms24054866

[25] Singh N, Piskorz AM, Bosse T et al. p53 immunohistochemistry is an accurate surrogate for TP53 mutational analysis in endometrial carcinoma biopsies. J Pathol 2020; 250: 336–345. DOI: 10.1002/path.5375

[26] Matsumoto N, Manrai P, Rottmann D et al. Correlative Assessment of p53 Immunostaining Patterns and TP53 Mutation Status by Next-Generation Sequencing in High-Grade Endometrial Carcinomas. Int J Gynecol Pathol 2023; 42: 567–575. DOI: 10.1097/PGP.0000000000000930

[27] Raffone A, Travaglino A, Cerbone M et al. Diagnostic accuracy of p53 immunohistochemistry as surrogate of TP53 sequencing in endometrial cancer. Pathol Res Pract 2020; 216: 153025. DOI: 10.1016/j.prp.2020.153025

[28] Talhouk A, McConechy MK, Leung S et al. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer 2017; 123: 802–813. DOI: 10.1002/cncr.30496

[29] León-Castillo A, Gilvazquez E, Nout R et al. Clinicopathological and molecular characterisation of „multiple-classifier" endometrial carcinomas. J Pathol 2020; 250: 312–322. DOI: 10.1002/path.5373

[30] Visser NCM, van der Wurff AAM, IntHout J et al. Improving preoperative diagnosis in endometrial cancer using systematic morphological assessment and a small immunohistochemical panel. Hum Pathol 2021; 117: 68–78. DOI: 10.1016/j.humpath.2021.08.006

[31] Weinberger V, Bednarikova M, Hausnerova J et al. A Novel Approach to Preoperative Risk Stratification in Endometrial Cancer: The Added Value of Immunohistochemical Markers. Front Oncol 2019; 9: 265. DOI: 10.3389/fonc.2019.00265

[32] Vrede SW, van Weelden WJ, Visser NCM et al. Immunohistochemical biomarkers are prognostic relevant in addition to the ESMO-ESGO-ESTRO risk classification in endometrial cancer. Gynecol Oncol 2021; 161: 787–794. DOI: 10.1016/j.ygyno.2021.03.031

[33] Bosse T, Peters EEM, Creutzberg CL et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer–A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer 2015; 51: 1742–1750. DOI: 10.1016/j.ejca.2015.05.015

[34] Veade AE, Foote J, Ehrisman J et al. Associations between lymphovascular space invasion, nodal recurrence, and survival in patients with surgical stage I endometrioid endometrial adenocarcinoma. World J Surg Oncol 2019; 17: 80. DOI: 10.1186/s12957-019-1620-x

[35] Tortorella L, Restaino S, Zannoni GF et al. Substantial lymph-vascular space invasion (LVSI) as predictor of distant relapse and poor prognosis in low-risk early-stage endometrial cancer. J Gynecol Oncol 2021; 32: e11. DOI: 10.3802/jgo.2021.32.e11

[36] Bosse T, Nout RA, McAlpine JN et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol 2018; 42: 561–568. DOI: 10.1097/PAS.0000000000001020

[37] Abu-Rustum N, Yashar C, Arend R et al. Uterine Neoplasms, Version 1.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2023; 21: 181–209. DOI: 10.6004/jnccn.2023.0006

[38] Matias-Guiu X, Selinger CI, Anderson L et al. Data Set for the Reporting of Endometrial Cancer: Recommendations From the International Collaboration on Cancer Reporting (ICCR). Int J Gynecol Pathol 2022; 41: S90–S118. DOI: 10.1097/PGP.0000000000000901

[39] Singh N, Hirschowitz L, Zaino R et al. Pathologic Prognostic Factors in Endometrial Carcinoma (Other Than Tumor Type and Grade). Int J Gynecol Pathol 2019; 38 (Suppl 1): S93–S113. DOI: 10.1097/PGP.0000000000000524

[40] College of American Pathologists. Homepage. Accessed August 26, 2024 at: https://www.cap.org/

[41] Emons G, Steiner E, Vordermark D et al. Endometrial Cancer. Guideline of the DGGG, DKG and DKH (S3-Level, AWMF Registry Number 032/034-OL, September 2022). Part 1 with Recommendations on the Epidemiology, Screening, Diagnosis and Hereditary Factors of Endometrial Cancer, Geriatric Assessment and Supply Structures. Geburtshilfe Frauenheilkd 2023; 83: 919–962. DOI: 10.1055/a-2066-2051

[42] Kayraklioglu N, Katsakhyan L, Cohen PA et al. Perceptions of Controversies and Unresolved Issues in the 2014 FIGO Staging System for Endometrial Cancer: Survey Results From Members of the International Society of Gynecological Pathologists and International Gynecologic Cancer Society. Int J Gynecol Pathol 2024; 43: 242–252. DOI: 10.1097/PGP.0000000000000977

[43] Betella I, De Vitis LA, Calidona C et al. Letter to the editor-The new FIGO staging system for endometrial cancer: Is the paradigm shift clinically feasible? Int J Gynaecol Obstet 2024; 164: 364–365. DOI: 10.1002/ijgo.15265

[44] Amin MB, Greene FL, Edge SB et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017; 67: 93–99. DOI: 10.3322/caac.21388

[45] Emons G, Steiner E, Vordermark D et al. Endometrial Cancer. Guideline of the DGGG, DKG and DKH (S3-Level, AWMF Registry Number 032/034-OL, September 2022) – Part 2 with Recommendations on the Therapy of Precancerous Lesions and Early-stage Endometrial Cancer, Surgical Therapy, Radiotherapy and Drug-based Therapy, Follow-up Care, Recurrence and Metastases, Psycho-oncological Care, Palliative Care, Patient Education, and Rehabilitative and Physiotherapeutic Care. Geburtshilfe Frauenheilkd 2023; 83: 963–995. DOI: 10.1055/a-2066-2068

[46] Mirza MR, Chase DM, Slomovitz BM et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med 2023; 388: 2145–2158. DOI: 10.1056/NEJMoa2216334

[47] Eskander RN, Sill MW, Beffa L et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. N Engl J Med 2023; 388: 2159–2170. DOI: 10.1056/NEJMoa2302312

[48] Colombo N, Biagioli E, Harano K et al. Atezolizumab and chemotherapy for advanced or recurrent endometrial cancer (AtTEnd): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2024; 25: 1135–1146. DOI: 10.1016/S1470-2045(24)00334-6

[49] Westin SN, Moore K, Chon HS et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. J Clin Oncol 2024; 42: 283–299. DOI: 10.1200/JCO.23.02132

[50] Bednaříková M, Hausnerová J, Minář L et al. Molecular testing of endometrial carcinoma in real-world clinical practice. Klin Onkol 2023; 36: 215–223. DOI: 10.48095/ccko2023215

[51] Michalová K, Presl J, Straková-Peteříková A et al. Advantages of next-generation sequencing (NGS) in the molecular classification of endometrial carcinomas – our experience with 270 cases. Ceska Gynekol 2024; 89: 349–359. DOI: 10.48095/cccg2024349

[52] Jamieson A, Huvila J, Chiu D et al. Grade and Estrogen Receptor Expression Identify a Subset of No Specific Molecular Profile Endometrial Carcinomas at a Very Low Risk of Disease-Specific Death. Mod Pathol 2023; 36: 100085. DOI: 10.1016/j.modpat.2022.100085

[53] Vermij L, Jobsen JJ, León-Castillo A et al. Prognostic refinement of NSMP high-risk endometrial cancers using oestrogen receptor immunohistochemistry. Br J Cancer 2023; 128: 1360–1368. DOI: 10.1038/s41416-023-02141-0

[54] De Vitis LA, Schivardi G, Caruso G et al. Clinicopathological characteristics of multiple-classifier endometrial cancers: a cohort study and systematic review. Int J Gynecol Cancer 2024; 34: 229–238. DOI: 10.1136/ijgc-2023-004864

[55] Zhan X, Li L, Wu M et al. The prognosis of stage IA synchronous endometrial endometrioid and ovarian carcinomas. Arch Gynecol Obstet 2019; 300: 1045–1052. DOI: 10.1007/s00404-019-05288-5

[56] Turashvili G, Gómez-Hidalgo NR, Flynn J et al. Risk-based stratification of carcinomas concurrently involving the endometrium and ovary. Gynecol Oncol 2019; 152: 38–45. DOI: 10.1016/j.ygyno.2018.10.033

[57] Assem H, Rottmann D, Finkelstein A et al. Minimal uterine serous carcinoma and endometrial polyp: a close clinicopathological relationship. Hum Pathol 2021; 118: 1–8. DOI: 10.1016/j.humpath.2021.09.001

[58] Brych O, Drozenová J, Pichlík T et al. Preoperative and postoperative staging in endometrial cancer – a prospective study. Ceska Gynekol 2024; 89: 5–10. DOI: 10.48095/cccg20245

[59] Michal M, Valha P, Velemínský M. Sentinel lymph node mapping in endometrial cancer – robotic vs. laparoscopic detection system. Ceska Gynekol 2023; 88: 157–161. DOI: 10.48095/cccg2023157

[60] Vinklerová P, Minář L, Weinberger V et al. Change in the trend of surgical treatment and staging of lymph nodes in endometrial cancer – results of the Oncogynecology Center, Department of Gynecology and Obstetrics, University Hospital Brno and Masaryk University in the years 2012–2021. Ceska Gynekol 2022; 87: 308–316. DOI: 10.48095/cccg2022308