South Afr J Gynaecol Oncol. 2023;15:24-27
https://doi.org/10.36303/SAJGO.385

South Afr J Gynaecol Oncol
ISSN 2074-2835 EISSN 2220-105X

OPINION PIECE

Simplicity sacrificed in the FIGO 2023 endometrial cancer staging: Demystifying the complexity of twelve stages and seventeen substages

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Introduction

Endometrial cancer incidence is rapidly rising globally, and in recent years, research has gained significant momentum. Surgical techniques, histopathology classification, risk stratification and understanding of different adjuvant modalities have progressed a great deal since the last endometrial cancer FIGO (The International Federation of Gynecology and Obstetrics) staging revision in 2009.[1] Simultaneous rapid advances in the development of targeted therapies, accompanied by improved molecular and genetic diagnostics have contributed to a significant change in our understanding of the disease.

These changes were discussed in depth in the 2021 FIGO cancer report, which formed the basis for inclusion in the recently published 2023 FIGO endometrial cancer staging.[2,3] Four histopathological criteria were recommended to define high-risk disease, namely: poor differentiation grade, substantial lymphovascular invasion (LVI), non-endometrioid histology types, and cervical stromal involvement. These and other markers of high risk, as well as a binary division of histology type and grade all gain importance in the current update of stages I & II.

In the last decade, molecular markers have become significant in determining prognosis and adjuvant treatment in endometrial cancer patients.[4] In tandem with existing histological and oncological prognostic factors, molecular marker information provides clinicians the opportunity to make more sophisticated decisions regarding adjuvant treatment and prognostic predictions. Morphology remains important as predictor of behaviour, but particularly the high-grade endometrioid cancer group consists of well-behaved and aggressive cancers, which can be better differentiated. In the 2023 FIGO classification, molecular classification can override anatomical spread and histotype in staging.[3]

The patient-centred benefits of minimally invasive surgery (MIS) (via standard laparoscopy or the robotic platform) have been established beyond doubt. In patients with presumed early-stage endometrioid endometrial cancer, similar oncological outcomes are achieved compared to open surgery (level IA evidence).[5] Sentinel lymph node biopsies were introduced as part of MIS to enable lymph node diagnosis but limit surgical complexity, time, and morbidity. Its diagnostic accuracy is now established, provided the algorithm is respected, and it has become the preferred method.[6] Sentinel node sampling is permitted and considered diagnostic of nodal staging under stage III in the 2023 update (isolated tumour cells remain node negative) while the details of lymph node and peritoneal invasion and other metastatic disease has been refined.

The 2009 FIGO staging retained the surgical nature of the 1988 staging, but was based on anatomical divisions and easily memorised.[1] In contrast, the 2023 FIGO classification is extensive, complex, non-anatomical and goes beyond surgical and histological staging.[3] Here, we outline and briefly discuss changes that were made and aim to summarise and simplify the new classification to some extent.

Disease confined to the uterus – the staging of early disease

Stages I and II now have more sub-divisions, and many changes have been implemented along the lines of prognosis, risk categories and adjuvant therapy recommendations rather than anatomical divisions. Most noticeable additions are that firstly, there is a division into "*non-aggressive*" (grade 1 and 2 endometrioid, including non-gastrointestinal mucinous variant) and "*aggressive*" (grade 3 endometrioid as well as all other histotypes) histological types. Secondly, "*substantial LVI*" gains importance in early-stage non-aggressive types and is now integrated into staging as a reason to upstage disease. Lastly, *new sub-stages* were created and stage II was expanded to accommodate the mentioned additions.

For non-aggressive types, it is interesting that the pre-2009 division into disease confined to the endometrium (now also specifying polyps) **(stage IA1)** and early myometrial invasion of less than ½ **(stage IA2)** is brought back. Low-risk concomitant uterine/ovarian disease with single unilateral ovarian stromal implant is downstaged **(stage IA3)** under some strict criteria (unilateral ovarian involvement without infiltration or rupture of the capsule, and without any findings, making it more than stage IA). Invasion of more than ½ myometrium remains **(stage IB)** but only for non-aggressive types without LVI.

Markers of risk for loco-regional recurrence include invasion of the cervical stroma and LVI, now somewhat illogically brought together under stage II. Cervical stromal invasion is retained **(stage IIA)** for non-aggressive types and cervical glandular

Table I: Summary of changed staging for early disease – disease confined to the uterus

Stage	Group name with description of substages	Comments
Stage I A and B	**Low-risk types without other markers of risk:** Non-aggressive endometrioid carcinoma without LVI confined to the endometrium (IA1) or inner ½ myometrium (IA2) or ovary (low risk) (IA3) or deep ½ myometrium without sub-serosa (IB).	$IAm_{POLE\ mut}$
Stage I C	**High-risk types not invading the myometrium:** Aggressive endometrial carcinoma confined to endometrium.	
Stage II A and B	**Low-risk types with other markers of risk:** Non-aggressive endometrioid carcinoma with spread to the cervical stroma (IIA) or with LVI (IIB).	
Stage II C	**High-risk types invading the myometrium:** Aggressive endometrial carcinoma confined to the myometrium.	$IICm_{p53\ abn}$

invasion is now established as not relevant to recurrence risk and is not even mentioned anymore. All non-aggressive stage I tumours with substantial LVI are upstaged **(stage IIB)**. The World Health Organization (WHO) 2021 definition of "substantial" LVI (5 or more vessels involved) is accepted, and a binary division is implemented: substantial vs. negative, which includes everything less-than-substantial and "focal". This definition makes it easier to classify not-mentioned LVI as negative.

Aggressive types are now separately staged, and early-stage disease is simply divided into either confined to a polyp or endometrium **(stage IC)** or confined to the uterus but with any myometrial involvement **(stage IIC)**. In aggressive histotypes, LVI status and depth of myometrial invasion does not further differentiate stage, and it is uncertain where to stage aggressive types with cervical stromal invasion, but without myometrial invasion.

Disease outside the uterus – the staging of advanced disease

Stages III and IV are also significantly amended with more sub-divisions but the overall structure was retained, and at first glance it seems simpler and more anatomical than the earlier stages. Noticeable additions include that of *uterine subserosal spread* as a high-risk event, as well as the new divisions of *pelvic and extra-pelvic peritoneal spread,* of nodal involvement into *isolated tumour cells (equals no spread), micro- and macro-metastases*, of *pelvic and para-aortic nodes vs. distant nodes ("above renal vessels" or extra-abdominal),* and of different *categories of distant spread*.

Local spread is still divided into stage IIIA and stage IIIB. The earlier group is newly divided into adnexal spread **(stage IIIA1)**, and full-thickness uterine wall invasion with involvement of sub-serosa or serosa **(stage IIIA2)**. Later, local spread is divided into vaginal/parametrial spread **(stage IIIB1)** and the new category of pelvic peritoneal spread **(stage IIIB2)**.

Regional nodal spread is still divided into pelvic **(stage IIIC1)** and para-aortic nodes **(stage IIIC2)**, but now also subdivided into micro-metastases if < 2 mm and macro-metastases IIIC2 **(shown respectively with "I" and "ii")**. Isolated tumour cells (< 0.2 mm/< 200 cells) as found on ultra-staging of sentinel nodes is acknowledged. At present, these should be mentioned to assist future analysis of its prognostic significance, but should be considered as negative nodes.

Extensive intra-abdominal spread to the mucosa of the bladder or any bowel remains the same **(stage IVA)**, and intra-abdominal metastasis to the extra-pelvic peritoneum (assumed to include omental disease) also remains in the same stage **(stage IVB)**.

Distant metastatic disease is now given a separate stage **(stage IVC)** and includes any metastasis to nodes above the renal vessels, any parenchymal metastasis (liver, lung, bone, etc.) or any disease outside the abdominal cavity.

Molecular assessment, classification and staging

One of the major advances in the past decade is the ability to classify endometrial cancer using molecular profiling, rather than just morphologically. The Cancer Genome Atlas (TCGA) uses four categories, namely: *POLE* mutated tumours/ultramutated (*POLE*mut); microsatellite instability high/hypermutated tumours (mismatch repair deficient group) (MMRd); somatic copy-number alteration high or serous-like tumours (95% has *TP53* mutations) (SCNA/p53abn); and somatic copy-number

Table II: Summary of changed staging for advanced disease – disease outside the uterus

Stage	Group name with description of substages	Comments
Stage III A and B	**Local pelvic spread:** Adnexae (IIIA1), the subserosa/serosa (IIIA2), vagina or parametrium (IIIB1) or pelvic peritoneum (IIIB2).	Differentiate IIIA1 from IA3
STAGE III C	**Regional nodal spread:** Pelvic (IIIC1) or para-aortic (IIIC2) nodes; up to renal vessels, more than isolated tumour cells (ITC).	i = Micrometastasis ii = Macrometastasis N0(i+) = isolate tumour cells
STAGE IV A and B	**Extensive local spread:** Bowel/bladder mucosa (IVA) or intra-abdominal, extra-pelvic peritoneum (IVB).	Malignant ascites not included
STAGE IV C	**Distant metastasis:** Extra-abdominal or parenchymal metastasis or supra-renal nodes (IVC).	

Table III: Summary of molecular classification and its impact

Name	Characteristics; surrogate marker	Prognosis	Staging
*POLE*mut	Pathogenic mutation in *POLE;* no surrogate marker.	Excellent	All early stage: downstage to IA
MMRd	Microsatellite instability; abnormal IHC staining for MSH6 or PMS2 protein.	Intermediate; consider Lynch syndrome	Stage is not affected
p53abn	Somatic copy-number alterations high or *TP53* mutation; abnormal IHC staining for p53 protein.	Unfavourable; increase adjuvant	All early stage with myometrial invasion: upstage to IIC
NSMP	No specific molecular profile; none of the above.	Intermediate	Stage is not affected

alteration low tumours where no driver mutation is found (no specific molecular profile [NSMP]).[7]

Simplified surrogate testing is now available and has been validated to improve risk assessment, which allows the TCGA classification to be clinically useful. Immunohistochemical (IHC) markers can identify abnormal gene expression (p53, MSH6 and PMS2) but mutation analysis is needed for pathogenic *POLE* mutations. Tests can be performed on any tumour tissue material, including formalin-fixed paraffin embedded. Molecular markers tested preoperatively on biopsy material do not need to be repeated on the resection specimen. The recommendation is that, where feasible, all patients with endometrial cancer should undergo testing that allows complete molecular classification.

Molecular markers add clinically important information, which will increase in the future. The following changes in management should currently be implemented where it is possible:

- *POLE*mut: postoperative adjuvant treatment may be omitted. *POLE*mut in stage I and II results in downstaging to stage IA;
- MMRd: early-stage patients with this molecular type requiring adjuvant treatment will benefit from pelvic radiation but not from chemotherapy; advanced or recurrent disease patients may benefit from the addition of immune checkpoint inhibitors to standard chemotherapy;
- p53abn: because of the unfavourable prognosis of this group, intensive postoperative adjuvant therapy might be indicated. p53 in stage I results in upstaging to stage II.

About 5% of tumours will test positive for more than one molecular marker (multiple classifiers). The available data suggests in these cases, the more favourable marker determines prognosis: patients with both p53abn and *POLE*mut should be managed as *POLE*mut, MMRd tumours with p53abn should be regarded as MMRd. Data is limited for patients with both *POLE*mut and MMRd, and they should be screened for Lynch syndrome.

When performed, molecular classification should be recorded in all cases by adding the letter "m" and the molecular subtype as a subscript to the stage. Changes to the stage applies only to endometrial cancer surgically staged as I or II, for those with a *POLE* mutation (becomes stage $IAm_{POLEmut,}$ regardless of lymph-vascular space invasion (LVSI) or histological type) and those with a P53 abnormality (becomes stage $IICm_{p53abn}$ if there is any myometrial invasion). For MMRd, NSMP and stages III and IV molecular profiling do not modify stage and should only be recorded for the purpose of data collection.

Conclusion

Endometrial cancer used to be regarded as a simple disease with an excellent prognosis. The staging was also simple and easily memorisable, with the large majority of patients diagnosed in stage I. Gradually we realised that all "early-stage disease" was not, in fact, early-stage. The 1988 staging then included findings from comprehensive surgical staging, and more patients were staged accurately. The 2009 update confirmed and firmly established surgical staging.[1] But even after the upstaging of node-positive patients, patients with "early-stage disease" still had heterogenous risks and outcomes. This group ended up being split into various risk categories for decision-making about adjuvant treatment using information not included in the FIGO staging.

The current update attempts to include (almost all) these factors into the staging, ending with a risk-based continuum, which include more surgico-pathological information.[3] This resulted in a far more complex staging, which necessitates surgical sampling more than ever, followed by comprehensive histopathological morphological and molecular review. Early-stage disease remains primarily treated by hysterectomy (MIS is preferred in early-stage including those with nodal micro-metastases), bilateral salpingo-oophorectomy, diagnostic lymph node dissection or sentinel biopsy where appropriate, and infracolic omentectomy for certain histological types. In late-stage disease the surgical approach is similar to that for ovarian cancer, aiming at confirming the stage and reaching a complete cytoreduction. Thorough preoperative assessment is essential to characterise the disease, to arrive at a presumed stage, and to advise on the best staging and therapeutic approach.[8] Endometrial cancer is, therefore no longer a cancer that can or should be treated outside the subspecialty of gynaecological oncology.

Adding the molecular classification is ground-breaking, and it is brave to migrate stages according to genetic profile. Costs and local availability of molecular tests will limit the immediate introduction of universal testing. The estimated cost at the time of writing for IHC testing is R5 000.00, and mutation analysis R14 000.00. We recommend that molecular testing should be done where it is clinically indicated using both the IHC and mutation analysis. Currently, that is in surgically staged I and II endometrial carcinomas, especially in poorly differentiated endometrioid type, where tumour behaviour seems discordant with type and grade, as well as where targeted therapy is considered.

Above, we attempted to simplify the changes. The substages of early disease form a continuum of risk rather than separate

logical or anatomical divisions. In late stage, the new divisions and definitions bring important clarification and add value by being intuitively logical and clinically relevant. The 2023 endometrial cancer staging will probably become known as a complex, even confusing, staging system and difficult to memorise. On the other hand, it will probably serve its main purpose, namely, to assist with treatment recommendations and prognostic classification. Clinical treatment guidelines now need to be updated to use alongside the new staging.

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