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Leiden  
The Netherlands

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Concin, N.; Matias-Guiu, X.; Fotopoulou, C.; Creutzberg, C.; Mutch, D.; Gaffney, D.; ... ;  
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## CORRESPONDENCE

## Response: FIGO staging of endometrial cancer 2023

We thank Raspagliesi et al.<sup>1</sup> and Betella et al.<sup>2</sup> for their interest in the new 2023 FIGO staging system for endometrial cancer,<sup>3</sup> supportive feedback, valuable comments, and the important data shared by the European Institute of Oncology (IEO).

Advances in our scientific knowledge that have occurred since the 2009 FIGO staging system (TCGA molecular classification, WHO updates, ESGO-ESTRO-ESP and ESMO guidelines, as well as numerous clinical trials, etc.<sup>4–9</sup>) have confirmed that endometrial cancer is composed of a heterogeneous group of tumors with differing biologic behavior, prognosis, and molecular attributes, which lead to different responses to systemic therapy and radiotherapy. These features underscore the need for individualization of treatment approaches.

In this setting, the development of an informative staging system with the goal of improved prognostic precision (for better treatment planning) is inherently handicapped when staging is exclusively limited to evaluation of anatomic spread. The immediate and distant future will bring greater precision in prognosis and treatment with thorough staging systems for other malignancies that include pathologic and molecular parameters alongside the anatomic extension of the tumors. The integration of multiple parameters that critically reflect tumor biology into a historically surgical-anatomical staging system demonstrates a paradigm shift. FIGO and AJCC started this process by integrating biomarkers, such as estrogen receptor (ER) and progesterone receptor (PR) expression and HER2 expression and/or amplification into the prognostic staging system of breast cancer patients 6 years ago.<sup>10</sup> The TNM staging system for patients with oropharyngeal carcinoma incorporates the finding of human papillomavirus (HPV) into that system.<sup>11</sup> Perineural invasion is incorporated into the TNM staging system as a criterion for T3 tumors in squamous cell carcinoma of the skin. For melanoma, ulceration is also considered.<sup>12,13</sup>

The improved prognostic precision of the 2023 FIGO staging system in comparison to 2009 FIGO has been demonstrated by several peer-reviewed validation studies to date,<sup>14–18</sup> and more confirmational studies are in progress. Two validation studies were published in the most recent issue of *European Journal of Cancer* and accompanied by an editorial.<sup>14–16</sup> Schwameis et al.<sup>14</sup> compared the FIGO 2009 and the FIGO 2023 staging systems in 519 endometrial cancer patients with molecular characterization treated at three ESGO accredited centers. Matsuo et al.<sup>15</sup> compared both staging systems in 5473 patients with advanced (Stage III–IV) endometrial cancer of the National Cancer Institute's Surveillance, Epidemiology

and End Results (SEER) Program. A study by Kobayashi-Kato et al.<sup>17</sup> documented the utility of using the FIGO molecular classification and showed that it improved the discriminatory ability compared with the FIGO 2009 system. A study by Haight and colleagues<sup>18</sup> validated the improved risk-stratification for Stage IV provided by the new 2023 FIGO staging criteria. These validation studies consistently confirm the higher prognostic value of the new 2023 FIGO staging system and demonstrate its statistical superiority to the 2009 staging system.<sup>16</sup> This has significant implications regarding the systemic and radiotherapy treatment choices and the accurate selection of patients for surgery at both the primary diagnosis and at relapse.

Beyond the conventional anatomical and histopathological features, for the past couple of years major European guidelines (ESGO-ESTRO-ESP and the ESMO guidelines)<sup>6,7</sup> have integrated molecular classification and other biological factors (such as LVSI etc.) into the risk group stratification of endometrial cancer patients.<sup>5</sup> Furthermore, these European guidelines provide treatment recommendations based on a molecular profile for specific situations derived from the current level of evidence, even in the absence of Level I prospective trial evidence. While Level 1 evidence is accumulating in clinical trial data,<sup>19–21</sup> the European societies ESGO, ESTRO, ESP and ESMO already felt comfortable with treatment recommendations (with a certain strength) based on pathological/molecular parameters in well-defined situations based on the myriad data from large retrospective studies and post hoc retrospective analyses of prospective randomized trials.<sup>22–24</sup> We are in line with the considerations of Betella et al.<sup>2</sup> that with the FIGO 2023 staging system (and substantial new evidence that includes drug approvals) guidelines will need to be updated, a process which has started for the ESGO-ESTRO-ESP guidelines. Treatment recommendations referring to the 2023 FIGO staging system are expected to be more straightforward and more individualized, as the new FIGO system identifies treatment-relevant subgroups.

Raspagliesi et al.<sup>1</sup> refer to the issue of endometrial carcinomas with ovarian involvement, which is one of the most challenging issues in endometrial cancer. In the 2009 FIGO staging system, all endometrial cancer patients with ovarian metastases were clustered under FIGO stage IIIA, implicating a more adverse prognosis without further differentiation or individualization. Over the past 10 years it has become apparent that low-grade endometrioid carcinoma of the uterus and ovary (following specific criteria) is distinct

from other endometrial carcinomas with metastatic spread to the ovaries, although studies have shown that in both situations the tumors are clonally related in the vast majority of patients.<sup>25</sup> This is now reflected in the new FIGO staging to allow and assist clinicians to make better-informed treatment choices, by distinguishing the low-grade endometrioid carcinomas of the uterus and ovary with indolent behaviors (in 2023 FIGO now classified as FIGO IA3) from other metastatic ECs to the ovary with bad prognosis (in 2023 FIGO now classified as FIGO IIIA1) and endorsing the existing WHO recommendations.<sup>4</sup> Importantly, this discrimination is also treatment-relevant. The ESGO-ESTRO-ESP do not recommend adjuvant treatment in low-grade endometrioid carcinomas of the uterus and ovary that follow specific criteria. The study by Matsuo et al.<sup>15</sup> validated the prognostically relevant split of the old combined 2009 FIGO IIIA category (with a 5-year mortality rate of 24.9%) into the new 2023 FIGO favorable IA3 group (5-year mortality rate of 11%) and the prognostically adverse 2023 FIGO IIIA1 group (5-year mortality rate of 31.8%). This is only one example of the higher prognostic precision of the 2023 FIGO staging system.

There are, nevertheless, still some open questions, such as the impact of the molecular classification in the group of low-grade endometrioid carcinomas of the uterus and ovary, as pointed out by Betella et al.<sup>2</sup> The tumor they mention—a p53 abnormal, low-grade endometrioid carcinoma with limited myometrial invasion and ovarian involvement—is rather unusual, and there are always uncommon cases that pose challenges to any established staging system.

As Raspagliesi et al.<sup>1</sup> mention, the new FIGO staging system introduces tumor volume, namely macro- versus micrometastasis, in the assessment of metastatic lymph nodes, in alignment with the staging system of other organs. The prognostic impact of the differentiation of nodal disease into macrometastasis and micrometastasis in endometrial cancer patients was again validated in the study by Matsuo et al.<sup>15</sup> In view of the current lack of clear evidence on the prognostic impact of isolated tumor cells (ITC), the 2023 FIGO system is in line with major European guidelines considering ITCs as pathologically lymph node negative disease (pNO[i+]).<sup>26</sup> Indeed, ITCs are an evolving subject; however, current evidence does not suggest shifting ITCs into a single category along with micro/macrometastasis of the lymph nodes (pN1).

Betella et al.<sup>2</sup> discuss the new staging system's potential to upstage early-stage tumors, because of the inclusion of lymphovascular space invasion, consideration of high-grade histology, and changes in stage by the inclusion of molecular data. The validation study of Schwameis et al.<sup>14</sup> confirmed stage shift in 27.6% of the patients, with upstage in 23.6%. Of note, these changes resulted in an improved prognostic assessment. As mentioned by Betella et al., among the major reasons for upstaging is the occurrence of a high-grade endometrial carcinoma with any myometrial invasion that now becomes Stage IIC. The results of Schwameis et al.<sup>14</sup> showed that this group of patients have a 5-year progression-free survival (76.4%) similar to the other Stage II patients (overall 70.2%). Moreover, the 5-year overall survival rate for this group (86.8%) is lower than that of low-grade endometrioid carcinomas with cervical involvement

(91.7%). These data are in clear support of the improved prognostication related to this upshift.

Betella et al.<sup>2</sup> raise a concern about *uniformly* upstaging high-grade histologies to 2023 FIGO Stage IIC disease, although it is well established that the prognosis of these tumors can be further differentiated by their molecular profile (particularly in high-grade endometrioid carcinoma). We fully agree that molecular classification is needed for improved prognostication in the group of high-grade tumors, and thus we promote molecular classification in the new FIGO system. However, as access to molecular testing is not always given, 2023 FIGO also provides a staging option purely based on surgical-pathological parameters including histological subtype. For the fortunate situation of known molecular classification, we want to emphasize that, contrary to the statement of Betella et al.,<sup>2</sup> it is not only *POLE* mutations but also p53 abnormalities (with myometrial invasion) that lead to a distinct FIGO stage (other than IIC) in high-grade uterus confined disease according to the 2023 FIGO staging system. These molecularly defined 2023 FIGO stages have been shown to improve the prognostic precision of early-stage disease in two validation studies.<sup>14,17</sup>

Finally, Betella et al.<sup>2</sup> raise concerns about global disparity in resources, and the need for cost-effective analysis. For this reason, the new 2023 FIGO staging system offers two options, one without known molecular classification, and one integrated approach if molecular classification is known. Global resource disparities are of great concern to FIGO, and these are not confined to endometrial carcinoma but reflect a more general social and economic problem. Considerable efforts are needed to make pathologic and molecular tools available in resource-limited countries. Global disparities in resources will increasingly impact treatment of endometrial cancer patients in view of access to the growing number of molecularly targeted treatment options, which critically depend on the determination of molecular status.

Regarding two further distinct challenges targeted by Betella et al.,<sup>2</sup>

1. In disease confined to the uterus, p53 abnormalities do lead to an upstaging to IICm<sub>p53abn</sub> disease, but only in the presence of myometrial invasion. Without myometrial invasion a p53 abnormality does not alter the FIGO stage, and the molecular subgroup is simply recorded (denotation of "m" and subscript on molecular subgroup).
2. With respect to multiple classifiers, the available evidence indicates that MMRd-p53abn tumor should be classified as MMRd, and *POLE*mut-p53abn tumors as *POLE*mut. In the case of *POLE*mut-MMRd-p53abn tumors, scientific evidence is scarce, but it is assumed that they behave as *POLE*mut when the *POLE* mutation is pathogenic.<sup>27</sup> In case *POLE* mutation is not pathogenic, the tumors may behave as MMRd.

We consider the new staging system a step forward for our endometrial cancer patients, as (1) it integrates the myriad and paramount information of the past 14 years; (2) it is associated with a higher prognostic precision; and (3) it promotes individualization of treatment by crucially identifying treatment-relevant patient groups. Our goal in

updating the FIGO endometrial cancer staging is to facilitate improvements in the care and treatment of women with endometrial cancer.

## AUTHOR CONTRIBUTIONS

**Nicole Concin:** Conceptualization, investigation, methodology, project administration, supervision, visualization, writing original draft, review & editing. **Xavier Matias-Guiu:** Conceptualization, investigation, methodology, writing original draft, review & editing. **Christina Fotopoulou:** Conceptualization, investigation, methodology, writing original draft, review & editing. **Carlen Creutzberg:** Conceptualization, investigation, methodology, writing original draft, review & editing. **David Mutch:** Conceptualization, investigation, methodology, writing original draft, review & editing. **David Gaffney:** Conceptualization, investigation, methodology, writing original draft, review & editing. **Kristina Lindemann:** Conceptualization, investigation, methodology, writing original draft, review & editing. **Sean Kehoe:** Conceptualization, investigation, methodology, writing original draft, review & editing. **Jonathan S. Berek:** Conceptualization, investigation, methodology, project administration, supervision, visualization, writing original draft, review & editing.

## CONFLICT OF INTEREST STATEMENT

The authors declare that none of the declared affiliations with the organizations and/or entities in their respective disclosure forms had any influence or financial interest in the writing of this correspondence piece.

Nicole Concin<sup>1</sup>  
 Xavier Matias-Guiu<sup>2</sup>  
 Christina Fotopoulou<sup>3</sup>  
 Carlen Creutzberg<sup>4</sup>  
 David Mutch<sup>5</sup>  
 David Gaffney<sup>6</sup>  
 Kristina Lindemann<sup>7</sup>  
 Sean Kehoe<sup>8</sup>  
 Jonathan S. Berek<sup>9</sup>  
 the FIGO Committee on Women's Cancer

<sup>1</sup>Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria

<sup>2</sup>Department of Pathology, Hospital U. de Bellvitge and Hospital U. Arnau de Vilanova, Universities of Lleida and Barcelona, Institut de Recerca Biomèdica de Lleida, Instituto de Investigación Biomédica de Bellvitge, Centro de Investigación Biomédica en Red de Cáncer, Barcelona, Spain

<sup>3</sup>Gynaecological Oncology, Department of Surgery and Cancer, Imperial College London, London, UK

<sup>4</sup>Department of Radiation Oncology, Leiden University Medical Center, Leiden, The Netherlands

<sup>5</sup>Division of Gynecologic Oncology, Washington University School of Medicine, St. Louis, Missouri, USA

<sup>6</sup>Department of Radiation Oncology, University of Utah, Salt Lake City, Utah, USA

<sup>7</sup>Department of Gynaecological Cancer, Oslo University Hospital, Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

<sup>8</sup>Oxford Gynaecological Cancer Centre, Churchill Hospital, Oxford, UK

<sup>9</sup>Stanford University School of Medicine, Stanford Women's Cancer Center, Stanford Cancer Institute, Stanford, California, USA

## Correspondence

Jonathan S. Berek, Stanford University School of Medicine, Stanford Women's Cancer Center, Stanford Cancer Institute, Stanford, CA, USA.

Email: [jberek@stanford.edu](mailto:jberek@stanford.edu)

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