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Revised 2018 International Federation of Gynecology and Obstetrics (FIGO) cervical cancer staging: A review of gaps and questions that remain

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ABSTRACT

Recently the revised 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer was published. In this most recent classification, imaging modalities and pathologic information have been added as tools to determine the final stage of the disease. Although there are many merits to this new staging for cervical cancer, including more detailed categorization of early-stage disease as well as information on nodal distribution, the classification falls short in clarifying areas of controversy in the staging system. Many unanswered questions remain and, as such, a number of gaps lead to further debate in the interpretation of relevant clinical data. Factors such as measurement of tumor size, definition of parametrial involvement, ovarian metastases, lower uterine segment extension, lymph node metastasis, and imaging modalities are explored in this review. The goal is to focus on items that deserve further discussion and clarification in the most recent FIGO staging for cervical cancer.

The goal of staging in the management of patients with cancer is to adequately assess the extent of tumor spread in order to more appropriately manage the disease and to allow for more concrete discussion regarding prognosis. It also provides for a means to compare treatment results among different institutions. Therefore, it is imperative that oncologists have a clear and reproducible algorithm for tumor evaluation and staging.

Until recently, cervical cancer International Federation of Gynecology and Obstetrics (FIGO) 2009 staging was based on clinical evaluation, including physical examination and limited imaging modalities, in order to accommodate practitioners in low-resource countries who might not have access to more extensive pathologic and imaging modalities.[1] Such an approach was deemed increasingly more inadequate given the progressive changes in novel imaging modalities and surgical approaches that became part of the routine management of patients with cervical cancer. This disparity left a gap between an outdated clinical staging and a broad range of information available to the oncologist. To that end, a new FIGO staging classification was proposed in 2018 which implemented, in addition to physical examination, information gathered from imaging modalities and surgical histopathological results.[2–4] The latest modification of the staging classification allows incorporation of pelvic ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), and/or positron emission tomography/CT (PET/CT) in order to appropriately assign a stage to the patient. In addition, histopathological findings obtained from the surgical specimen—particularly lymph node status—may be used in order to upstage the patient. The most recent staging also provides a more tangible correlation of risk factors, such as tumor size and lymph node status, with oncologic outcomes. Moreover, it divides pelvic (IIIC1) from para-aortic (IIIC2) nodal disease and tumor size is further classified into three sub-groups (IB1 <2 cm, IB2 ≥2–4 cm, and IB3 ≥4 cm) instead of a dichotomized stage IB1 and IB2 using 4 cm as a cut-off value.

One would consider that, when referring to cancer staging, the details of criteria used are clear and free from variations in both definition and interpretation. Such paradigm would allow physicians to 'speak the same language' and make treatment recommendations based on a unified and concrete system. The new FIGO classification, although commendable for its expansion of the aforementioned criteria, still fails to meet many important goals as there are many questions that remain unanswered leaving clinicians once again to debate the interpretation of relevant clinical data (Table 1).

There are a number of gaps that deserve attention and open an opportunity for discussion.

TUMOR SIZE

The concept of tumor size measurement for any solid tumor is one that certainly remains a topic of heated debate. In cervical cancer one must recognize the inadequacy of physical examination in determining tumor size. Imaging modalities often add valuable information; however, they remain a tool whose

Table 1 Pros and cons of the revised International Federation of Gynecology and Obstetrics (FIGO) 2018 cervical cancer staging system

FIGO 2009		FIGO 2018		
Stage	**Description**	**Stage**	**Description**	**Pros and cons**
I	The carcinoma is strictly confined to the cervix			**Pros** Clarity on depth of invasion and the relationship between the depth of stromal invasion and incidence of lymph node metastases. Rate of positive nodes of 0.1–0.2%, 0.4–1.9%, and 2.1–7.6% for tumors with depth <1 mm, 1–3 mm, and 3.1–5 mm, respectively[18 19]
IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5 mm measured from the base of the epithelium and a horizontal spread of no more than 7 mm. Vascular space involvement, venous or lymphatic, does not affect classification	IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion ≤5 mm*	
IA1	Measured stromal invasion of no more than 3 mm in depth and **no more than 7 mm in horizontal spread**	IA1	Measured **stromal invasion ≤3 mm in depth**	There was limited guidance in previous FIGO staging systems (1995 and 2009) on measuring horizontal spread[20 21] with no correlation of the tumor width and the risk of nodal metastases. Unifocal lesions are straightforward to measure but unclear if a lesion has multiple invasive foci, which can be as high as 25% of stage IA1 carcinomas,[21] and can be located close together or far apart. There is lack of consensus on how measurement is to be performed (adding the maximum horizontal dimension or measuring individually) which can change disease stage from IA1 up to IB[20–22]
IA2	Measured stromal invasion of more than 3 mm but no greater than 5 mm **with a horizontal spread of no more than 7** mm	IA2	Measured **stromal invasion >3 mm and ≤5 mm in depth**	
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2	IB	Invasive carcinoma with measured deepest invasion >5 mm (greater than stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter†	**Pros** The classification of stage IB tumors into three sub-stages improves the discriminatory ability for outcomes.[23] On multivariable analysis, stage IB2 disease is independently associated with a nearly two-fold increased risk of cervical cancer mortality compared with stage IB1 disease (adjusted HR 1.98, 95% CI 1.62 to 2.41, p<0.001).[24] Survival is significantly different between 2018 FIGO stage IB1 and IB2 disease, with a nearly two-fold increased risk in cervical cancer mortality in stage IB2 disease compared with IB1 disease.[24] Five-year survival in the FIGO 2018 schema was 91.6% (95% CI 90.4% to 92.6%) for stage IB1 tumors, 83.3% (95% CI 81.8% to 84.8%) for stage IB2 tumors, and 76.1% (95% CI 74.3% to 77.8%) for IB3 [23]tumors **Cons** Current staging still provides no clarification as to how tumor size should be measured either microscopically or grossly. This is particularly so for specimen demonstrating microscopic tumor in the conization specimen and subsequent additional tumor in final hysterectomy specimen
IB1	Clinically visible lesion no more than 4 cm in greatest dimension	IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤**2 cm in greatest dimension**	
IB2	Clinically visible lesion more than 4 cm in greatest dimension	IB2	Invasive carcinoma **>2 cm and ≤4 cm in greatest dimension**	
		IB3	Invasive carcinoma **>4 cm in greatest dimension**	
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall			
IIA	Tumor without parametrial invasion	IIA	Involvement limited to the upper two-thirds of the vagina without parametrial invasion	
IIA1	Clinically visible lesion no more than 4 cm in greatest dimension	IIA1	Invasive carcinoma ≤4 cm in greatest dimension	
IIA2	Clinically visible lesion larger than 4 cm in greatest dimension	IIA2	Invasive carcinoma >4 cm in greatest dimension	
IIB	Tumor with parametrial invasion	IIB	With parametrial involvement but not up to the pelvic wall	
III	Tumor extends to pelvic wall and/ or involves lower third of vagina, and/ or causes hydronephrosis or non-functioning kidney	III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney **and/or involves pelvic and/ or para-aortic lymph nodes**	**Pros** Stage IIIC1 is independently associated with improved cause-specific survival compared with stage IIIB disease (adjusted HR 0.79, 95% CI 0.74 to 0.85, p<0.001).[24] Stage IIIC1 has been found to have superior cervical cancer-specific survival compared with stage IIIA-B disease[24] Some studies have found micrometastases to have negative impact on prognosis as macrometastases[25] and thus should be considered as positive nodes
IIIA	Tumor involves lower third of vagina, no extension to pelvic wall	IIIA	Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall	
IIIB	Tumor extends to pelvic wall and/ or causes hydronephrosis or non-functioning kidney	IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)	

Continued

Table 1 Continued

FIGO 2009		FIGO 2018		
Stage	**Description**	**Stage**	**Description**	**Pros and cons**
		IIIC	Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases)‡ irrespective of tumor size and extent (with r and p notations)§	**Cons** The staging system fails to describe what is to be considered pelvic positive nodes as a positive parametrial node may potentially be consider as positive pelvic disease. Survival of stage IIIC1 disease significantly differed based on T=stage (5 year rates: 74.8% for T1, 58.7% for T2, and 39.3% for T3) with a 35.3% difference in absolute survival (p<0.001)[24] Survival in stage IIIC1 varies depending on local tumor factors. Stage IIIC1 cervical cancer is not homogenous, and local tumor factors remain salient prognostic factors in cervical cancer[24]
		IIIC1	**Pelvic lymph node metastasis only**	Higher FIGO staging was not consistently associated with worse 5-year survival rates: stage IIIA (40.7%, 95 CI 37.1% to 44.3%), stage IIIB (41.4%, 95% CI 39.9% to 42.9%), stage IIIC1 (positive pelvic nodes) was 60.8% (95% CI 58.7% to 62.8%), and stage IIIC2 37.5% (95% CI 33.3% to 41.7%)[23]
		IIIC2	**Para-aortic lymph node metastasis‡**	Classification of all women with positive lymph nodes into a single stage results in a very heterogeneous group of patients with highly variable survival rates[23] Positive lymph nodes negatively affect survival (IIIC1 HR 2.0, p<0.001, IIIC2 HR 3.9, p<0.001, IIIC1 HR 1.36, p<0.001, IIIC2 HR 2.14, p<0.001). The impact on survival varies by T stage with the greatest effect seen in stage T1B with IIIC2 disease (HR 5.38, p<0.001 vs HR 1.5, p=0.001 for IIIC1 disease)[26] Although no prognostic significance has been found for isolated tumor cells, the precise prognosis of low-volume metastases (isolated tumor cells and/or micrometastases) needs further evaluation.[25 14] Evidence suggests that micrometastasis and isolated tumor cells should be considered as positive nodes as most centers indicate adjuvant treatment[13 14]
IV Tumor has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum (bullous edema does not permit a case to be allotted to stage IV)				
IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as IVA)	IVA	Spread to adjacent pelvic organs	
IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or para-aortic lymph nodes, lung, liver, or bone)	IVB	Spread to distant organs	

*Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages. Pathological findings superseded imaging and clinical findings.
†The involvement of vascular/lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered.
‡Isolated tumor cells do not change the stage, but their presence should be recorded.
§Adding notation of r (imaging) and p (pathology), to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r; if confirmed by pathological findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

contribution is heavily dependent on available technology or the expertise of the radiologist interpreting the study. When combining information from physical examination and imaging studies, one is often left wondering how one arrives at the appropriate tumor size and, thus, the appropriate staging. As an example, a patient who underwent a conization at initial diagnosis that confirmed a 10 mm tumor (positive margins), who then has a 2.5 cm endocervical tumor by pelvic MRI, undergoes a radical hysterectomy and the final specimen shows a 12 mm residual tumor. Should this patient be assigned a FIGO 2018 stage IB1 according to the cone specimen, or is the patient assigned a FIGO 2018 stage IB2 carcinoma as a result of the addition of the two fragments of the tumor specimen (as is frequently done in many centers) totaling 22 mm? This is particularly important at this time when, in the latest version of the FIGO 2018 classification, the size of the primary tumor can be assessed by clinical evaluation (pre- or intra-operative), imaging, and/or pathologic measurement. It goes on to propose that "imaging and pathology can be used, when available, to supplement clinical findings". Such an open-ended recommendation may be prone to higher rates of inaccuracy and misclassification when performing staging designation. In addition, it then opens the question regarding recommendations when clinical examination, pathology, and imaging results show different tumor measurements.

To add to the issue of discrepancy in assessment of tumor size, one should also emphasize and recognize that, to date, we seem to have great discrepancies among institutions, and even among pathologists, as to how to report on tumor size measurements. As an example, the current revised FIGO 2018 classification states in its abstract that stage IB has three sub-groups, where stages IB1, IB2, and IB3 are so determined based on greatest tumor size according to 'diameter'. However, in the body of the manuscript the word 'diameter' is used interchangeably with 'dimension'. Generally, the definition of 'dimension' is the measure of length, breadth, depth, or height, while 'diameter' defines a straight line passing

from side to side through the center of a body or figure, especially a circle or a sphere. Added to this, we must consider that perhaps we see further inconsistencies in measurement based on whether tumors are localized to one region of the cervix, such as the anterior or posterior lip, or whether tumors are circumferential. This calls for further efforts that a more definitive strategy for tumor measurement be used. This inconsistency draws further doubt as to whether we as clinicians are speaking 'the same language' as our pathology colleagues. Would it not make sense that we consider tumor volume, given the three-dimensional nature of cervical tumors to determine tumor size. This further supports the dire need for a consensus statement by an expert committee formed by gynecologic pathologists, radiologists, and gynecologic oncologists to ultimately provide a roadmap for accurate tumor measurement.

PARAMETRIAL INVOLVEMENT

Until the most recent 2018 FIGO classification, parametrial involvement was only routinely established on physical examination. Such criteria, perhaps even more so than tumor size, were prone to misinterpretation and inaccuracy.[5 6] Adding to this uncertainty is the fact that the parametrial tissue contains lymphatic channels and nodes that are often involved, particularly in larger tumors. Unfortunately, the new FIGO 2018 classification fails to provide details regarding the definition of 'parametrial involvement'. As an example, if a patient with a 2 cm cervical tumor undergoes a radical hysterectomy and is found, on final pathology, to have one positive parametrial lymph node (all pelvic nodes are negative), should this patient be assigned a FIGO 2018 stage IIB, as the parametrial tissue is 'microscopically positive' for disease (not up to the pelvic wall) or should this patient be assigned a FIGO 2018 stage IIIC1p given that the parametrial nodes, by definition of location, are in the pelvic region, as are the obturator, internal, and external iliac nodes?

Similarly, patients with positive parametrial tissue by physical examination would be classified as stage IIB, noting, however, that such staging classification may be ascertained based solely on physical examination without a pathologic confirmation of such parametrial involvement while a patient with no detectable parametrial involvement by pre-operative physical examination who undergoes a radical hysterectomy and is then found to have microscopic disease in the parametria would also be classified as a stage IIB. Given that the first patient in the scenario most likely was offered radiation and chemotherapy and the second patient underwent radical hysterectomy followed by radiation and chemotherapy, are we certain that the prognosis for these two patients is the same based on the fact that both are considered stage IIB?

In addition, circumstances of complexity in definition and stage designation may further arise, as in the case of microscopic parametrial involvement that is denoted not from a focus of disease in the parametrial tissue nor from positive lymph nodes in the parametrial tissue, but rather from direct extension of the tumor to the 'cut lateral margin' of the cervical specimen. In such scenarios, is one to designate such patient as having parametrial involvement and therefore assign a stage IIB? Certainly, further clarification is needed.

OVARIAN INVOLVEMENT

Although rare, ovarian metastases in patients with early cervical cancer may be encountered. This clinical scenario is often the source of debate opening discussion for varying management options. There are some who might argue that this scenario completely changes the prognosis of the patient by increasing the risk of intraperitoneal (extra-pelvic) recurrences. In a study by Shimada et al,[7] the authors aimed to determine the frequency and clinicopathological features of ovarian metastastasis in a population of patients with stage IB–IIB cervical cancer. The study population consisted of 3471 patients and the rate of ovarian metastases was 1.5%. In that study, the outcome of patients with ovarian metastases was very poor. The current FIGO 2018 definition of a stage IV tumor is one that 'has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum'. It goes on to identify a FIGO 2018 stage IVA as a tumor that has spread to 'adjacent pelvic organs'. This leaves the question as to whether ovarian involvement is included in this category. In other words, it is unclear if a patient who has a 2.5 cm cervical tumor with negative lymph nodes, negative parametria, but with evidence of microscopic disease in the ovary would be assigned a FIGO 2018 stage IVA. Or is stage IVA exclusively reserved for rectum and/or bladder compromise? If so, would the patient be considered a FIGO 2018 stage IVB? Once again, this is a missed opportunity to provide clarity to this rare but important clinical scenario. Similarly, what should be the stage designation when patients have simultaneous evidence of disease in the ovaries and, in addition, disease in the pelvic nodes? Should these patients be classified as stage IIIC1p or stage IVA?

LOWER UTERINE SEGMENT INVOLVEMENT

Uterine corpus invasion by cervical cancer is found in approximately 5% of patients. Women with cervical cancer whose tumors involve the uterine corpus have been shown to have significantly lower 5-year and 10-year cause-specific survival rates compared with those without uterine corpus invasion. In addition, studies have found that uterine corpus invasion is associated with an increased risk of pelvic lymph node metastases in cervical cancer.[8]

The true rate of lower uterine segment involvement is not well defined as this is a histopathologic finding that may not be routinely reported when present. Certainly, the question remains as to whether uterine corpus involvement should impart major changes in the approach to therapy. Some might argue that, if there is invasion of the lower uterine segment (all remaining findings in the pelvis negative for disease), the patient's staging should be allocated as a stage IVA given that the lower uterine segment is part of an adjacent pelvic organ.

LYMPH NODE METASTASES

One of the most impacting prognostic indicators in the setting of cervical cancer is the lymph node status.[9] Patients with spread of disease to the lymph nodes require additional treatment and, under the new FIGO classification, the status of the lymph nodes impacts the staging for the patient. Interestingly, a recent study examined the prognostic performance of the revised FIGO 2018 staging schema.[10] In that study, the investigators identified 62 212 women from the National Cancer Database. The study showed that

the 5-year survival was 91.6% for stage IB1 tumors, 83.3% for stage IB2 tumors, and 76.1% for stage IB3 tumors. In contrast, for women with stage III tumor, higher FIGO staging was not consistently associated with worse 5-year survival rates: stage IIIA was 40.7%, stage IIIB was 41.4%, stage IIIC1 (positive pelvic nodes) was 60.8% and for stage IIIC2 it was 37.5%. The authors concluded that classifying all women with positive lymph nodes into a single stage results in a very heterogeneous group of patients with highly variable survival rates.

More recently, the role of sentinel lymph node mapping has been shown to be safe and feasible in cervical cancer in the setting of prospective trials and, at the same time, evidence of randomized data shows that sentinel lymph node mapping alone is associated with lower treatment-related morbidity.[11 12] A standard procedure in the setting of sentinel lymph node mapping is routine ultra-staging to detect whether there is evidence of disease and also to determine the size of metastatic disease to the lymph node. One of the major points of debate, particularly in patients with cervical cancer, is whether the size of the metastasis impacts the outcome of the patient. There is a gap in knowledge regarding whether patients with isolated tumor cells require adjuvant therapy in cervical cancer. Although it is standard to recommend adjuvant chemoradiation in patients with macrometastases and micrometastases, some would question whether patients with isolated tumor cells need additional treatment. However, with the current data regarding micrometastases and isolated tumor cells, most groups prefer to treat them as a high-risk group.[13 14] Therefore, the rational question that follows is: if a pathologic finding requires treatment in the form of at least post-operative radiotherapy, why would such finding not change the stage of the patient?

Similarly, when addressing the complex issue of lymph node assessment and processing, the FIGO 2018 classification notes that sentinel lymph node dissection has 'good sensitivity and specificity …with acceptable false negative rates'. However, there is no concrete recommendation for the practitioner as to whether sentinel lymph node assessment is considered appropriate in assigning a stage in patients with cervical cancer. In addition, although understanding that consensus statements such as the FIGO 2018 classification aim to provide the most global and generalizable strategies to manage patients, we must also recognize that there is limited value in the use of language that may be prone to varying interpretation. Statements such as “appropriate facilities and expertise should be available to validate protocol for sentinel approach” and “good backup of pathology for ultrastaging” often fail to provide objective criteria to adequately guide practitioners. In other words, what is the definition of an 'appropriate facility' or 'appropriate expertise' or 'good backup of pathology'. One commonly encountered scenario in low-resource countries is that availability of image-guided biopsies may not be feasible, thus in the setting of a patient with a presumed stage IB1 or IB2 tumor but who has suspicious lymph nodes on CT scan or PET/CT imaging, should that patient be staged IIIC without a pathologic confirmation and be recommended chemotherapy and radiation? One might propose a laparoscopic evaluation of the lymph nodes; however, do we have data that this is oncologically safe, and what to do in the setting where laparoscopic technology is not available?

Given these aforementioned points, one is left wondering whether the new FIGO classification appropriately triages patients with stage IIIC disease to guide treatment recommendations according to risk of recurrence. In other words, should a patient with isolated tumor cells or micrometasis in the sentinel lymph node be considered stage IIIC? Should there be a more detailed classification of this subset of patients to provide a more detailed outcomes profile?

IMAGING MODALITIES

The new FIGO 2018 classification proposes that the methods used for imaging (ultrasound, CT, MRI, PET/CT or PET/MRI) are all considered appropriate modalities of imaging in designating a staging classification. In evaluating tumor size, extension to the surrounding tissue and adjacent organs, and location and characteristics of retroperitoneal lymph nodes, one must consider that the role of imaging modalities is directly dependent on several factors impacting the results of such studies, including but not limited to quality of the technology, quality of the interpretation which may certainly vary according to the expertise of the radiologist and, in the case of ultrasonography, expertise of the person performing the ultrasound. Added to this is the vast literature outlining the differences in diagnostic accuracy among the aforementioned imaging modalities.[15–17] In other words, have we as a community of gynecologic oncologists determined which is the most accurate, available, and reliable imaging modality to evaluate a patient with cervical cancer?

Summary

The revised FIGO 2018 staging represents an impacting step forward in our efforts to determine the best treatment recommendations for our patients and to provide the most accurate information pertaining to disease prognosis. All who took part in the development of the revised staging system ought to be congratulated and recognized for their valiant effort and contribution to improving cancer care for patients with cervical cancer. We must, however, recognize that there is still a great opportunity to improve on this work and should aim to continue exploring strategies to enhance the value of the information that ultimately drives our capacity to deliver the best care possible for women diagnosed with cervical cancer all around the world.

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