Influence of the New FIGO Classification for Cervical Cancer on Patient Survival: A Retrospective Analysis of 265 Histologically Confirmed Cases with FIGO Stages IA to IIB

Amelie de Gregorio^a Peter Widschwendter^a Florian Ebner^b
Thomas Wolfram Paul Friedl^a Jens Huober^a Wolfgang Janni^a
Nikolaus de Gregorio^a

^aDepartment of Obstetrics and Gynecology, University of Ulm, Ulm, Germany; ^bDepartment of Obstetrics and Gynecology, Amper Hospital Dachau, Dachau, Germany

Keywords

Cervical cancer · New staging classification · Survival · FIGO stage

Abstract

Objective: At the end of the year 2018, a new FIGO classification for cervical cancer was published, mainly revising stage IB and introducing a new stage IIIC, which includes irrespectively of tumor size and local spread all patients with lymph node metastasis. **Methods:** We retrospectively analyzed all cases of cervical cancer stage I to IIB who underwent surgery as primary treatment at our institution from 2000 until 2016 and therefore had a histological confirmation of tumor stage. We reclassified all histologies according to the new FIGO classification and calculated outcome according to the new stages. **Results:** Out of 265 patients, 146 (55%) patients were reclassified into a higher FIGO stage. Most changes appeared within stage IB and from any stage to stage IIIC1. Kaplan-Meier curves for new stages showed a significant difference in disease-free survival (DFS) and overall survival (OS) between stages I versus II versus III (log-rank test, both $p < 0.001$). Overall, patients that were upstaged had a significant worse DFS ($p = 0.012$) and OS ($p = 0.008$) than patients whose stage did not change. Similar observations were made with-

in sub-stages, when node-positive IB or IIB tumors were upstaged to IIIC tumors. **Conclusion:** The new FIGO classification for cervical cancer reflects the strong impact of lymph node metastases on survival and is a clear improvement compared to the old FIGO classification with regard to risk stratification.

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Introduction

Invasive cervical cancer is the 8th most frequent female cancer worldwide. While the incidence in developed countries is low (6–9.5/100,000) and still declining, countries that do not have access to screening programs have a high incidence up to 43.1/100,000. (1) Staging is traditionally done by clinical examination, but MRI, CT, and PET scans are widely used where available and often recommended by contemporary guidelines like the NCCN guideline [1]. The purpose of a staging system is to define

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the extent of disease and allow classification, for example to compare different treatment regimens or recommend therapy strategies based on individual patient's cancer stage. The most widely used staging classification system is the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) classification, which until the last update, strongly relied on clinical examination and not on systemic imaging in order to provide an adequate classification system even in a low-resource setting.

While the precursor of the FIGO classification for cervical cancer was first published in 1929, at that time called the "League of Nations Classification for Cervical Cancer," it saw overall 9 changes to the system until 2014, most of them regarding stage I [2]. In 2018, the recent change of the classification was published [3]. While it now incorporates imaging into the system, one major change was the revision of stage IB. A new stage IB3 was added, including all tumors greater than 4 cm (former stage IB2). Former stage IB1 was split into stage IB1 (tumors <2 cm) and IB2 (tumors >2 cm but smaller than 4 cm). In addition, all tumors with lymph node metastases were included into the new, formerly not existing stage IIIC. Nodal metastases limited to the pelvic lymph nodes are classified into stage IIIC1, and tumors with positive paraaortic nodes are now classified as IIIC2. The aim of these changes was to provide more accurate prognostic groups and thereby help trigger more adequate treatment decisions. In addition, the cervical cancer classification is now more harmonized with the staging systems of endometrial and ovarian cancer. A recently published review describes in detail the underlying reasons that led to applied changes in the classification system [4]. The aim of our study was to describe the changes in FIGO stages by using the revised system and to evaluate the implication of the new FIGO classification with regard to prognosis of the newly defined FIGO stages and their potential for risk stratification.

Material and Methods

Patient Characteristics and Variable Selection

Data from all patients with the diagnosis of invasive cervical cancer that had surgery as their primary treatment in the Department of Gynecology and Obstetrics at the University Hospital Ulm between January 1st, 2000, and December 31st, 2016, were retrospectively reviewed. We identified 265 cases with complete data-sets for our analysis.

We collected data regarding age, weight, body height, initial tumor stage, tumor type and subtype, grade and type of surgical procedure. In addition, outcome parameters as date of first recurrence and death were collected. All data were extracted from the available archived patient's electronic documents and subsequent-

Table 1. Baseline patient and tumor characteristics ($n = 265$)

Age at diagnosis, years	
Median	46
Range	26–84
Body mass index, kg/m ²	
Median	24.7
Range	15.1–50.8
Histological grade	
I	11 (4.2%)
II	128 (48.3%)
III/IV	122 (46.0%)
Missing	4 (1.5%)
Histological subtype	
Squamous	195 (73.6%)
Adeno	48 (18.1%)
Others	22 (8.3%)
Type of surgery	
Open radical hysterectomy	214 (80.8%)
Laparoscopic radical hysterectomy	41 (15.5%)
Open radical hysterectomy with caesarean section	3 (1.1%)
Secondary parametrectomy and upper vaginectomy	7 (2.6%)

ly anonymized. We then used all pathological reports and recalculated the FIGO stage according to the 2018 FIGO classification.

Statistical Analysis

Ordinal and continuous variables were described using medians and ranges, while categorical variables were summarized and described using absolute and relative frequencies. Disease-free survival (DFS; including deaths as event) and overall survival (OS) data were analyzed using the Kaplan-Meier method and presented as Kaplan-Meier survival plots. All time-to-event intervals were measured from the date of surgery to the date of the event. If no event was documented, the data were censored at the date of the last adequate follow-up. Between-group comparisons of DFS and OS were performed with the log-rank test, and hazard ratios (HR) were calculated based on univariable Cox regression models. All statistical analyses were performed using the SPSS statistical software package, version 24 (IBM, New York, NY, USA). All statistical tests were two-sided, and p values below 0.05 were considered significant.

Results

Patient Characteristics

The median age of the patients was 46 years, ranging from 26 to 84 years, and median BMI was 24.7 kg/m² (range 15.1–50.8 kg/m²). 73.6% of patients had a squamous cell carcinoma, followed by adenocarcinoma (18.1%) and others (8.3%). We observed few grade 1 tu-

Fig. 1. Reclassification of cervical cancer cases ($n = 265$) according to the new FIGO classification. Grey arrows indicate no change and black arrows indicate a change (always upstaging). Most changes occurred within stage IB and from any stage to IIIC1.

mors (4.2%), while most patients had either a grade 2 (48.3%) or grade 3 (44.5%) tumor. The majority (80.8%) of patients had radical hysterectomy per laparotomy, while a laparoscopic radical hysterectomy was performed in 15.5%. (Table 1). A pelvic lymphadenectomy was performed in 100% of cases with a median of 35 removed nodes; in 82 cases (30.9%), a para-aortal lymphadenectomy was added. 125 patients (47.2%) had adjuvant chemoradiation, while 11 (4.2%) and 15 (5.7%) patients received adjuvant chemotherapy or radiotherapy only.

Change of FIGO Stage

A change from old to new FIGO stage (only upstaging) occurred in 146 patients (55.1%); in 61 cases (23.0%), this change was due to tumor size, and in 85 cases (32.1%) due to positive lymph nodes. Of those patients that were reclassified, most changes appeared within stage IB (34

from IB1 to IB2, and 25 from IB2 to IB3) and from any stage to stage IIIC1 (10 from IB1, 12 from IB2, 43 from IIB). For more details of the change pattern, see Figure 1.

We conducted further analyses to evaluate the impact of changes in FIGO stage on DFS and OS. We found significant differences with regard to both DFS and OS between the new FIGO classification stages I, II, and III, formerly only stages I and II (both $p < 0.001$). In addition, we observed that patients who were upstaged had a significant worse DFS ($p = 0.012$, HR 2.00, 95% CI 1.16–3.47) and OS ($p = 0.008$, HR 2.32, 95% CI 1.22–4.40) than patients whose stage did not change (Fig. 2). Similar observations were made within sub-stages: FIGO IB patients with positive lymph nodes that were upstaged to new FIGO IIIC had significant worse OS than node-negative patients whose new FIGO stage remained at IB ($p = 0.026$, HR 3.45, 95% CI 1.08–10.95); however, the differ-

Fig. 2. Kaplan-Meier survival plots for patients with cervical cancer that were up-staged within the new FIGO classification and patients whose FIGO stage remained unchanged. **a** Disease-free survival. **b** Overall survival.

ences between these two groups regarding DFS were not significant ($p = 0.279$, HR 1.71, 95% CI 0.64–4.60). Up-staging from IIB to IIIC did significantly impair both DFS ($p = 0.040$, HR 2.05, 95% CI 1.02–4.13; Fig. 3a) and OS ($p = 0.040$, HR 2.20, 95% CI 1.02–4.76; Fig. 3b). No differences in DFS and OS were observed when comparing the new FIGO stages IB1 versus IB2 versus IB3 ($p = 0.361$ and $p = 0.698$ for DFS and OS, respectively). A significant difference was found between the new FIGO stages IIIC1

and IIIC2 with regard to DFS ($p = 0.048$; Fig. 4a) but not with regard to OS ($p = 0.454$; Fig. 4b).

Discussion

The revised FIGO classification system for cervical cancer performs well with regard to the allocation of patients into different risk groups and is a major improve-

Fig. 3. Kaplan-Meier survival plots for patients with cervical cancer that were upstaged from IIB to IIIC within the new FIGO classification and patients whose FIGO stage remained unchanged at IIB. **a** Disease-free survival. **b** Overall survival.

ment compared to the previous system. Especially the implementation of the new FIGO stage IIIC including all patients with lymph node involvement represents an important improvement, as we could show in our study that an upstaging into IIIC is accompanied by a strongly impaired prognosis. We expect that the new classification will be a helpful tool for better risk stratification of cervical cancer patients in future clinical trials and that it will facilitate more personalized treatment recommendations.

Another improvement is the new subdivision of the IB stage into the three stages IB1, IB2 and IB3 according to tumor size. As noted by Park et al. [5], the chance of additional risk factors being present increases with an increase in absolute tumor size. In addition, fertility-sparing surgery (radical trachelectomy) in patients that still wish to bear children is recommended by most authors only in IB1 tumors smaller than 2 cm, which is now displayed as a distinct substage (IB1) in the new staging sys-

Fig. 4. Kaplan-Meier survival plots for patients with FIGO stage IIIC1 or IIIC2 cervical cancer according to the new FIGO classification. **a** Disease-free survival. **b** Overall survival.

tem [6]. While we could not show outcome differences between the newly classified IB1, IB2, and IB3 tumors in our patient cohort, Matsuo et al. [7] reported significant differences with regard to cause-specific mortality among these three groups in their retrospective analysis of cervical cancer patients.

Although our analysis is limited by its retrospective character, a major strength of this study is the availability of a “historic” patient collective, as all patients underwent

surgery and therefore had a histologically confirmed tumor and nodal stage. This gives us a more precise knowledge of detailed tumor stage as compared to different staging modalities such as CT scan or pelvic MRI that have low sensitivities with regard to determination of local tumor spread and nodal involvement [8].

As the validity of imaging is still a subject of debate, the German national guideline (S3 Leitlinie Zervixkarzinom) recommends a surgical lymph node staging for all pa-

tients, even if the primary chemoradiation for, e.g., stage III is planned.

According to current treatment guidelines, the majority of our patient collective would not have been operated anymore, emphasizing the paradigm shift from surgical treatment to chemoradiation within the last decade. However, as there is no differentiation according to the presence of micro- or macrometastases in the new FIGO staging system, and exact tumor size is essential for correct classification, complete histopathological examination is needed for accurate determination of clinical assumed tumor stage and final FIGO stage. Thus, confirmed FIGO stages can be reviewed for predicting patients' outcome. As shown in our analysis, there is a good association of higher FIGO stages with impaired prognosis, and using the revised FIGO classification allows better risk assessment of cervical cancer patients.

A weakness of our study is that we cannot comment on stages IIIa/IIIb and IV, as tumors at those stages are usually not operated on and therefore were not included in our study. However, Matsuo et al. [7] reported a slightly but statistically significantly better prognosis for stage IIIB versus stage IIIC1.

Overall, patients with a changed FIGO stage do have worse OS than those remaining the same stage. This result probably is explained by the upstaged group of lymph node-positive cervical cancer patients. The importance of differentiation between FIGO IIIC1 and IIIC2 is supported by the different outcome in terms of DFS of patients with pelvic only or para-aortic lymph node involvement.

To our knowledge, this is one of the first analyses of a cervical cancer patient collective in which changes in the FIGO stage using the revised system were reported and the implication of the new FIGO classification with regard to risk stratification and prognosis was systematically assessed.

Conclusion

Using the revised FIGO system of 2018, more than 55% of our retrospectively analyzed patient collective were assigned to a different FIGO stage. The majority of patients was "upstaged" (to IIIC) due to lymph node involvement (32.2 %), while the others were upstaged due to tumor size. In addition, this has a dramatic impact on DFS and OS. Thus, the new FIGO classification for cervical cancer reflects the strong impact of lymph node metastases on survival and is a clear improvement compared to the old FIGO classification with regard to risk stratification.

Statement of Ethics

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional committee. Ethical approval of the ethics committee of the University of Ulm was given (133/16).

Disclosure Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Amelie de Gregorio: resources, review and editing; Peter Widschwendter: conceptualization, resources, review, and editing; Florian Ebner: review and editing; Thomas W.P. Friedl: data curation, formal analysis; Jens Huober: supporting and review; Wolfgang Janni: supervision and review; Nikolaus de Gregorio: conceptualization, writing original draft.

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