Diagnosis of Advanced Cervical Cancer, Missed Opportunities?

Jérémie Mattern
Assistance Publique -Hopitaux De Paris
Irène Letendre
Assistance Publique -Hopitaux De Paris
Jeanne Sibiude
Assistance Publique -Hopitaux De Paris
Cécile Pénager
Assistance Publique -Hopitaux De Paris
Asma Jnifen
Assistance Publique -Hopitaux De Paris
Fatoumata Souare
Assistance Publique -Hopitaux De Paris
Sophie Ayel
Assistance Publique -Hopitaux De Paris
Thuy Nguyen
Assistance Publique -Hopitaux De Paris
Laurent Mandelbrot (laurent.mandelbrot@aphp.fr)
Assistance Publique -Hopitaux De Paris

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Abstract

Background

Cervical cancer is common worldwide but despite the existence of primary and secondary prevention strategies, the survival rate is decreasing in France. This survival rate is impacted by the increasing proportion of advanced-stage cancer. Our objective was to determine the factors associated with a diagnosis of advanced-stage cervical cancer in an urban population in France

Methods

A retrospective study was conducted on all consecutive records of patients diagnosed with cervical cancer between January 2006 and December 2018 in a single center in Paris. The data collected were demographic characteristics, medical and gynecological history, circumstances of diagnosis, diagnostic and therapeutic management. The patients were divided into two groups according to the FIGO 2018 stage at diagnosis: group A stages Ia 1 to Ib2 and group B advanced stages Ib3 a to IV.

Results

From 2006 to 2018, among 96 patients who were diagnosed with cervical cancer, 25 (26%) were in group A and 71 (74%) in group B. Women in group B had less frequently received regular gynecological care than in group A (36.9% vs 84.2%, $p < 0.001$) and a fewer had Pap test screening in the previous 3 years (30.4% vs 95.0%, $p < 0.001$). Parity greater than 3 was more frequent in group B (69.6% vs 42.9%, $p = 0.031$). The diagnosis was made during a routine examination or cervical smear in only 9.23% and 16.18% respectively in group B, vs 60 % of cases in 45.82% of cases in group A ($p < 0.001$ and $p = 0.003$). Vaginal bleeding was observed in 85.29% in group B vs 36% in group A ($p < 0.001$). Histological type was squamous cell carcinoma 87.32% of group B and 56% of group A ($p < 0.001$).

Conclusion

Diagnosis of cervical cancers at advanced stages was mostly in women who did not benefit from the recommended screening. Universal access to screening is necessary for the prevention and early treatment of cervical cancer.

Background

Cervical cancer is the fourth most common cancer in women worldwide and the eleventh in France[1], with 3023 new cases and 1102 deaths yearly[2]. Cervical cancer is due to persistent infection with oncogenic subtypes of human papillomaviruses (HPV)[3]. This allows for primary prevention with anti-HPV

vaccination. The progression from low-grade squamous intraepithelial lesions to invasive cancer occurs over a period of several years, thus allowing for secondary prevention. Cervical screening by cytology or HPV testing is used to detect lesions of the cervix and treat if high-grade lesions appear[3,4].

Until recently, screening for cervical cancer in France was based on individual (or spontaneous) initiative. All women aged 25 to 65 were offered cervical cytology testings, yearly and then every 3 years after 2 negative tests.

Despite the existence of these primary and secondary prevention strategies, cervical cancer is one of the only cancers for which the 5-year survival rate is decreasing in France, even though incident cases are decreasing[5]. One of the main prognostic factors is the stage when the disease is discovered. Cervical cancers that are less than 4 cm (up to the FIGO IB2 stage, in the 2018 classification[6]) are said to be localized and with a fairly good prognosis (more than 90% survival at 5 years) whereas tumors larger than 4 cm (FIGO IIa stages and beyond) said to be advanced have a 5-year survival rate of only 50% [6–9]. This difference is largely explained by the first-line treatments possible depending on the stage, namely immediate surgical management for localized cancers versus radio-chemotherapy for advanced stages.

The objective of this study was to analyze the factors associated with the diagnosis of cancer at an advanced stage.

Methods

We performed a retrospective study on medical records in the department of Obstetrics and Gynecology of Louis-Mourier Hospital, a university hospital center of the Assistance Publique-Hôpitaux de Paris (APHP), in the outskirts of Paris, France. All consecutive cases with a diagnosis of cervical cancer were identified over the period 2006 to 2019 from pathology reports on cervical biopsies or surgical samples. The data were extracted from multidisciplinary tumor board files, computerized medical records and paper archives.

The study was approved by the French database security commission (Commission Nationale Informatique et Liberté) and by the Institutional Review Board (Comité d'Evaluation de l'éthique des projets de Recherche Biomédicale, IRB00006477: N°2019-038 January 31, 2020).

The patients were classified into two groups: those diagnosed with cervical cancer at a localized stage (FIGO stage IA1 to IB2) (group A) and those diagnosed with locally advanced or advanced cancer (FIGO stage IB3 to IV) (group B). We chose this classification because the first line of treatment changes beyond stage 1B2 [7,8]. Patients whose files were partly or completely unavailable were excluded, as well as patients who refused access to their data for research purposes.

Variables studied

Demographics and medical history included age, ethnicity, parity and gestation, Human immunodeficiency virus (HIV) status, smoking, psychiatric history, gynecological history (ectopic pregnancy, sexually transmitted infections), professional activity and social deprivation.

Access to care was assessed by whether the patient had regular gynecological examinations (as declared by the patient) and/or a cervical cytology test within the past 3 years. The circumstances of diagnosis were classified as: during a routine gynecological examination, by cytology screening, or due to symptoms such as spontaneous or post coital metrorrhagia. Clinical findings at the time of diagnosis were general symptoms (weight loss, pain), as well as the appearance of the cervix at the time of cancer diagnosis : normal appearance, budding, gross erosion, ulcer or necrosis. The histological type of cancer was classified as squamous cell carcinoma or adenocarcinoma.

The results of pretreatment evaluation PET and MRI and the presence of metastases at the time of diagnosis were noted for each patient as well as the therapies which were used, ie. surgery, radiotherapy, brachytherapy, chemotherapy. We checked for consistency between the stage at diagnosis and care according to the APHP and European Society of Gynaecological Oncology (ESGO) guidelines at the time the woman was treated[7,8].

Statistical analysis

Qualitative variables were compared between groups using a Chi² test or a Fisher test. The quantitative variables were analyzed by Student's t-test. The statistical significance threshold used was $p < 0.05$. The data was analyzed using Stata 14.0 software.

Results

Between 2006 and 2019, 96 patients were diagnosed with cervical cancer in our department. Among them, 25 (26%) had localized cancer and were included in group A and 71 (74%) had advanced cancer and were included in group B.

Patients’ characteristics (Table 1) :

Table 1
Demographic characteristics, history and gynecological care according to diagnosis of cervical cancer at advanced (group B) versus localized (group A) stage

	Group A N = 25	Group B N = 71	p-value
Age	52.4	51.7	
Geographic origin			0.55
- France	3 (23.08%)	14 (40%)	
- Maghreb	6 (46.15%)	13 (37.14%)	
- Other	4 (30.77%)	8 (22.86%)	
Currently employed	4 (36.36 %)	15 (45.45%)	0.60
Psychiatric history	2 (8.33%)	9 (14.29%)	0.37
History of pelvic inflammatory disease or ectopic pregnancy	2 (8%)	3 (4.76%)	0.44
Current smoking	5 (29.41%)	10 (30.30%)	0.95
Social deprivation	3 (20%)	8 (25%)	0.51
Living with HIV	1 (4%)	4 (6.15%)	0.57
Parity > 3	9 (42.86%)	39 (69.64 %)	0.03
Regular gynecological follow-up	16 (84.21%)	17 (36%)	< 0.001
Cervical cytology in the past 3 years	19 (95.00%)	17 (30.36%)	< 0.001

The socio-demographic characteristics did not differ significantly between the two groups, in particular age, professional activity or social deprivation. Parity above 3 was more frequent in group B than in group A (69.64% vs 42.86%, respectively, p = 0.03).

Regular gynecological follow-up was less frequent in group B (36% vs 84.21% in group A, p < 0.001) as well as the presence of cervical cytology in the past 3 years (30.36 vs 95%, respectively, p < 0.001).

The absence of cervical cytology in the past 3 years was not associate with the tabacco smoking (p = 0,31), living with HIV (p = 0,33), professional activity (p = 0,17) or social deprivation (p = 0.27).

Circumstances of cancer diagnosis (Table 2) :

Table 2
Circumstances of diagnosis of cervical cancer at advanced (group B) versus localized (group A) stage

	Group A N = 25	Group B N = 71	p-value
Routine examination	15 (60%)	6 (9.23 %)	< 0.001
Cervical cytology screening	11 (45.82%)	11 (16.18%)	0.003
Colposcopy for the diagnosis	16 (64%)	24 (42.11%)	0.22
Vaginal bleeding, total	9 (36 %)	58 (85.29%)	< 0.001
Vaginal bleeding, post coital	2 (8 %)	9 (13.24%)	0.39
Appearance of cervix :			0.04
- Normal appearance	5 (20.83%)	4 (7.14%)	
- Budding	2 (8.33%)	24 (35.82%)	
- gross erosion. ulcer	13 (54.17%)	26 (38.81%)	
- Local induration	3(12.50%)	8 (11.94%)	
- Necrosis	1 (4.17%)	5 (7.46%)	
General symptoms	0 (0%)	21 (31.34%)	0.001

In group B, the cervical cancer was discovered by routine examination or by cervical cytology in only 9.23% and 16.18% of cases, respectively, whereas in group A the proportions were 60% and 45.82%, respectively ($p < 0.001$ and $p = 0.003$). Spontaneous vaginal bleeding occurred in 85.29% of cases in group B (versus 36% in group A, $p < 0.001$), but post-coital bleeding, although more suggestive of cervical cancer, was noted in just 11 patients, with no significant difference between the two groups. Cervical cancer was discovered with global deterioration in 31.34% of patients in group B

At initial examination, the cervix appeared normal in 7.14% in group B vs 20.83% of cases in group A ; there was budding in more than a third of cases in group B.

Disease staging (Table 3) :

Table 3
Findings of the work-up of cervical cancers at advanced (group B) versus localized (group A) stage

	Group A N = 25	Group B N = 71	p-value
Normal vaginal examination	9 (42.86%)	1 (1.79%)	< 0.001
PET scan findings :			< 0.001
- Local hypermetabolism	14 (93.33%)	14 (26.92%)	
- Hypermetabolism extended in pelvis	1 (6.67%)	31 (59.62%)	
- Hypermetabolism beyond pelvis	0 (0%)	7 (13.46%)	
MRI findings :			< 0.001
- Cervical lesion ≤ 4 cm	13 (61.90%)	3 (4.76%)	
- Cervical lesion > 4 cm	0 (0%)	7 (11.11%)	
- Extension to parametrium and/or pelvic lymph nodes	3 (14.29%)	37 (58.73%)	
- Extension to parametrium and pelvic, iliac and para-aortic lymph nodes	0 (0%)	8 (12.70 %)	
- Extension to bladder. ureters or rectum	0 (0%)	8 (12.70 %)	
- No MRI lesions	5 (23.81%)	0 (0%)	
- Distant metastases	0 (0%)	11 (21.57%)	0.013
Pathology			
- Squamous cell carcinoma	14 (56%)	62 (87.32%)	0.001
- Adenocarcinoma	11 (44%)	9 (12.68%)	0.001

By definition, there were marked differences between the two groups in local extension and metastases.

Pathology findings differed, with squamous cell carcinoma in 56% of group A patients vs 87.32 % of group B ($p < 0.001$).

Treatments (Table 4) :

Table 4
Treatment for cervical cancer at advanced (group B) versus localized (group A) stage

	Group A N = 25	Group B N = 71	p-value
Total hysterectomy with adnexectomy	11 (44%)	9 (13.64%)	< 0.001
Total hysterectomy with adnexectomy + lymph node dissection	14 (56%)	14 (21.21%)	
No surgery	0 (0%)	43 (65.15%)	
Chemotherapy	6 (25%)	64 (91.43%)	< 0.001
Radiation therapy	8 (33.33%)	53 (80.30%)	< 0.001
Brachytherapy	11 (45.83%)	24 (40%)	0.62

The management of patients followed existing guidelines, although the recommended management changed over the study period. Thus only 35% of patients in group B had a hysterectomy vs 100% of patients in group A. For a large period of our study, post-irradiation hysterectomy was usually recommended for advanced cancers.

Discussion

Main findings

We found that lack of gynecological care and cytological screening were associated with a diagnosis of cervical cancer at advanced stages. Conversely, most advanced stage cancers were discovered following symptoms, in particular bleeding, as reported in other studies[10].. It should be noted that the cervix was clinically abnormal in over 75% of cases in group A, confirming the importance of screening and systematic clinical examinations to diagnose asymptomatic cancers at an early stage[3]. Also, we observed a higher proportion of adenocarcinomas in cases diagnosed at advanced stages.

We found no association between most socio-demographic variables such as age, ethnic origin, and social deprivation, with diagnosis at advanced stages. Contrary to our hypothesis that socially and economically disadvantaged women would have poorer access to care, this was not the case in our

population regarding cytological screening. This contrasts with findings from the United States[11], which may be related to the differences in health care coverage between countries.

Parity was significantly associated with late diagnosis. The literature suggests that there me pathophysiological reasons for this association[12] , because the concentration of estrogens and progesterone during pregnancy alters the epithelial junction, which is the transformation zone which is most vulnerable to HPV infection. In addition, this junction is maintained in the exocervix longer in multiparous women. We found no differences between groups regarding smoking and HIV status, which are known to be risk factors for cervical cancer.

Strengths and weaknesses

Most patients were cared for entirely in our center from the first visit, through diagnostic and staging procedures, therapy and comprehensive follow-up. This decreases the risk of recruitment bias in some dedicated pelvic cancer centers where patients are referred after diagnosis and assessment. Our recruitment was through gynecologic clinics as well as emergency room, thus closer to a population-based study. Also, the number of patients was relatively large for a single-center study.

The main weaknesses of our study are inherent to its retrospective nature, including potential selection bias due to missing data. These were numerous for certain socio-demographic variables and social deprivation was not assessed with a systematic scale, such as the EPICES score[13,14] , because not all of the variables were routinely collected. The power was also limited, so we could not perform a multivariate analysis.

Interpretation in view of the literature

In previous studies[15–19], mainly from Africa, where health infrastructures for screening and prevention differ, the factors associated with a diagnosis at an advanced stage of cervical cancer were high parity as in our study, and also low education level, long distance from the health center, and young age at first sexual intercourse, variables which were not available in our study, as well as living with HIV. The number of women with HIV in our population was insufficient to conclude, but it should be noted that we offer yearly gynecologic visits for these patients in our center.

In France, the coverage of cervical cytology was estimated in 2016 at 61.9%[20]. It was recommended every 3 years for women between 25 and 65 years of age. However, despite information campaigns on screening and the relative accessibility of gynecological follow-up by general practitioners, midwives or gynecologists, in the office or hospital, a large proportion of patients do not access such care.

In our center there is a structured network, with close collaboration allowing physicians and midwives to refer patients to our cervical diseases clinic through a dedicated channel, with access to colposcopy for low grade lesions within 1 month and for high grade lesions within 2 weeks of the cytology results. None

of the patients diagnosed at an advanced stage accessed the cervical diseases channel. It is therefore essential to reinforce training for general practitioners, midwives, and healthcare providers in general.

Nevertheless, the performance of cytological screening is imperfect, with a sensitivity of only 58%[21]. Because the HPV subtype is highly associated with cervical transformations and cancer, and because the reproducibility of HPV testing is better than for cytology, the most recent guidelines recommend HPV testing as the first line of screening for all women between ages 30 and 64, with cytologic screening maintained in women from ages 24 to 29[22]. Also, whereas the incidence of squamous carcinoma of the cervix has declined in countries with cytologic screening, the proportion of adenocarcinoma of the cervix has increased[23], which is less amenable to prevention through cervical screening by cytology[24].

Conclusion

Non-engagement in care or screening stands out as the main factor for cervical cancer diagnosed at advanced stages. This should encourage us to better identify missed opportunities for prevention and to take action on these factors. More recently, guidelines are increasingly recommending screening with HPV testing. Simple messages remain to be communicated more effectively in mass information campaigns, in an outreach to women and systematic discussion on screening and vaccination during all types of medical visits.

Abbreviations

HPV
human papillomaviruses
HIV
Human immunodeficiency virus
EPICES
Evaluation de la précarité et des inégalités de santé dans les Centres d'examens de santé
APHP
Assistance Publique-Hôpitaux de Paris
ESGO
European Society of Gynaecological Oncology

Declarations

Ethics approval and consent to participate:

All methods were performed in accordance with the relevant guidelines and regulations(Declaration of Helsinki). The study was approved by the French database security commission (Commission Nationale Informatique et Liberté) and by the Institutional Review Board (Comité d'Evaluation de l'éthique des

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Consent for publication

No personally identifiable data.

Availability of data and materials :

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

L.M. and I.L. conceived the study, J.M., L.M. and I.L. wrote the main manuscript text, F.S, J.M., A.J., S.A., C.P. and T.N. collected the data, J.S. performed the analysis. All authors reviewed the manuscript.

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