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Paraskevaidis, Evangelos

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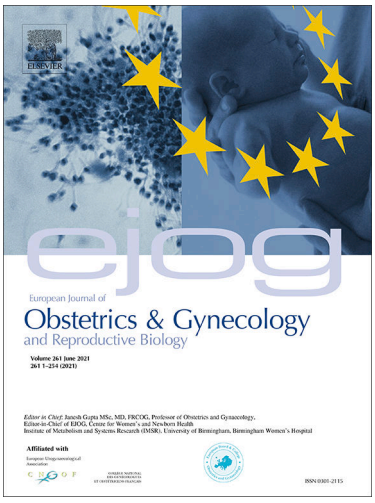

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Invasive cervical cancer following treatment of pre-invasive lesions: a potential theory based on a small case series

Evangelos Paraskevaidis[1], Antonios Athanasiou[2], Ilkka Kalliala[2,3], Anna Batistatou[4], Maria Paraskevaidi[2,5], Evripidis Bilirakis[6], Maria Nasioutziki[7], Minas Paschopoulos[1], Deirdre Lyons[8], Marc Arbyn[9], Margaret Cruickshank[10], Pierre Martin-Hirsch[11], Maria Kyrgiou[2]

[1]*Department of Obstetrics and Gynaecology, University Hospital of Ioannina, Ioannina, Greece*

[2]*Institute or Reproductive and Developmental Biology, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK*

[3]*Department of Obstetrics and Gynaecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*

[4]*Department of Pathology, University Hospital of Ioannina, Ioannina, Greece*

[5]*Department of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, UK*

[6]*Department of Obstetrics & Gynaecology, IASO Hospital, Athens, Greece*

[7]*Second Department of Obstetrics & Gynaecology, University Hospital of Thessaloniki, Thessaloniki, Greece*

[8]*Department of Obstetrics and Gynaecology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK*

[9]*Unit of Cancer Epidemiology, Belgian Cancer Centre, Sciensano, Brussels, Belgium*

[10]*Department of Obstetrics & Gynaecology, University of Aberdeen, Aberdeen, Scotland, UK*

[11]*Department of Obstetrics and Gynaecology, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK*

Corresponding Author:

Evangelos Paraskevaidis, MD, PhD

Professor in Obstetrics & Gynaecology, University of Ioannina, Ioannina, Greece

President of the Hellenic Society of Colposcopy & Cervical Pathology (HSCCP)

Tel: +30 6944981000, email: vangelispar@hotmail.com

ABSTRACT

Purpose: The aim of this study is to present a single department's experience on cervical cancer cases following previous excision of cervical intraepithelial neoplasia (CIN) and to discuss potential pathogenesis.

Methods: Nine cervical cancer cases meeting the inclusion criteria, with available pathological and follow-up data, were considered eligible for this study.

Results: The majority (7/9) have had clear excisional margins. The interval between initial treatment and cancer diagnosis ranged from 7 to 17 years. In all cases cancer diagnosis was "unexpected", as the prior cytological and/or colposcopic evaluation was not suggestive of significant cervical pathology. All cancers were squamous, and 5/9 at stage I.

Conclusion: The long interval between initial CIN treatment and final diagnosis as well as the normal post-treatment follow-up may suggest a 'de novo' underlying but 'hidden' carcinogenesis process. It might be that dysplastic cells entrapped within crypts (or normal metaplastic affected by the same predisposing factors) continue undergoing their evolution, undetectable by cytology and colposcopy until they invade stroma and surfaces (endo- and/or ectocervical) approximately a decade later. Heavy cauterisation of cervical crater produced post excision might be a potential culprit of this entrapment.

Keywords: CIN; excision; carcinogenesis; cervical cancer; cervical crypts

INTRODUCTION

After successful treatment of cervical intraepithelial neoplasia (CIN), it would be expected that the risk of future invasive cervical cancer would be the same compared to the general population. However, all available data shows that women with a history of treatment for cervical intraepithelial neoplasia remain at substantially increased risk of cervical cancer. Soutter et al[1] first published a large, robust population-based study in 1997 which illustrated this increased risk (4-5 greater than the general population); this finding was subsequently confirmed by many other studies[2-9]. A recent systematic review and meta-analysis from our group[10] estimated this risk at over three times, and another recent large population-based study[11] at over two times greater, respectively, than the general population. The increased risk of subsequent cancer persists over at least 20 years and this finding is often cited as the justification for recommendations to keep women during two decades under intensified surveillance (United States guidelines[12]). However, almost none of the available studies provides a history of post-treatment cytology, HPV status and/or colposcopic findings and therefore any possible explanation of this increased risk remains rather obscure or arbitrary.

The aim of this study was to present a 24-year experience with cases of invasive cervical cancer that were referred to or diagnosed in an academic hospital department having had previous treatment of cervical intraepithelial neoplasia, in whom the interval cytology and colposcopy data were available at large. To the best of our knowledge, this is the first study to provide individual history interval data, carefully collected over such a long period of time.

METHODS AND MATERIALS

Setting

Women who presented with cervical cancer from 1997 to 2020 in the University Hospital of Ioannina, Greece, with a history of local excisional treatment for high-grade CIN [cold knife conisation (CKC), laser conisation (LC), or large loop excision of the transformation zone (LLETZ)]. Initial CIN treatment could have been performed either regionally or elsewhere in Greece.

Eligibility criteria

Women who did not comply with follow-up scheme after CIN treatment according to national guidelines, were excluded. To eliminate the possibility of underdiagnosed micro-invasive cervical cancer at the time of initial treatment, only women in whom the diagnosis of cervical cancer had

been made after the first two post-operative years were included. We chose a two-year 'lag period' because the majority of residual disease is identified during this interval[13, 14]. Finally, we excluded patients treated with ablation due to lack of cone specimen and subsequent histological examination of the whole transformation zone as in patients treated with excision.

Collection of data

Clinical characteristics, histological type and stage of cervical cancer were prospectively recorded. Data on initial treatment of CIN (date, technique, CIN grade, margin status and crypt involvement) and post-treatment follow-up (intervals and results) were retrospectively collected. National guidelines for post-treatment surveillance recommend follow-up with cytology and colposcopy every six months for the first two years, and annually thereafter if this initial period is negative for residual/recurrent disease. In the last ten years, hrHPV (high-risk HPV) testing as test-of-cure is also recommended at 6 months after treatment, but since none of the cases had been treated for CIN after 2010, test-of-cure HPV status was not available.

RESULTS

26 women with cervical cancer after previous treatment of high-grade CIN were identified. Of these, we excluded women with diagnosis of cervical cancer in less than two years after treatment (n=8), women without regular follow-up after treatment (n=5) and women with ablative treatment (n=4). Therefore, the women fulfilling the eligibility criteria were nine. None of these individuals had co-morbidities or immunodeficiency. Smoking history was reported in five cases.

Treatment for CIN, histological evaluation of excised cone and follow-up surveillance had been performed in four academic hospitals in seven cases (two in our own hospital, and five in three other academic hospitals), and in two private hospitals in two cases. Five women had been treated with LLETZ, three with CKC and one with LC. Final histopathological diagnosis was CIN2 in three and CIN3 in six cases. Endo- and ectocervical margins were clear in seven cases, but in one out of seven, a clear endocervical margin was achieved after a repeat excision; margin status was not available in two cases. Crypt involvement was present in three cases and absent in one case. The pathologist did not make any comments regarding crypts in the remaining five cases. We were able to contact with the clinician who had performed the conisation for seven patients and we were advised that endocervical curettage (ECC) at the time of treatment had not been performed and that the crater of the excision had been cauterised for control/prevention of bleeding in all seven cases.

The interval between CIN treatment and diagnosis of cervical cancer ranged from 7 to 17 years. Cytology within the last 2 years before cancer diagnosis was normal in all but one case where cytology showed atypical squamous cells of undetermined significance (ASC-US). In two cases with normal cytology, there was a lack of endocervical cells on the smear due to post-operative cervical stenosis. HPV testing within the last 2 years prior to cancer diagnosis was available in four cases, where it was positive in three of them despite a concomitant unimpressive cytology (≤ASC-US). Cervical cancer was squamous in all cases (stage I: 5; stage II: 1; stage III: 3). Table 1 presents the main characteristics of the eligible patients, by chronological order of cervical cancer diagnosis.

Table 1: Main characteristics of eligible patients diagnosed with cervical cancer after treatment for CIN

Case	CIN treatment technique	Histological CIN grade	Margin status	Crypt involvement	Interval between CIN treatment and cancer diagnosis (in years)	Most recent cytology prior to cancer diagnosis	HPV testing prior to cancer diagnosis	Stage
1	CKC	CIN3	NA	NA	11	WNL	-	SCC IIB
2	LC	CIN2	Clear	NA	11	WNL	-	SCC IB1
3	LLETZ	CIN3	Clear	Yes	9	WNL (lacking endo-cervical cells)	-	SCC IA2
4	LLETZ	CIN2	NA	NA	8	WNL (lacking endo-cervical cells)	-	SCC IB2
5	CKC	CIN3	Clear	NA	17	WNL	Positive (16)	SCC IIIA
6	LLETZ	CIN3	Clear	Yes	13	WNL	Negative	SCC IA2
7	CKC	CIN3	clear	NA	7	ASC-US	Positive (16)	SCC IIIB
8	LLETZ (2)	CIN3	Clear (in second LLETZ)	Yes (in first LLETZ)	13	WNL	-	SCC IIIB

9	LLETZ	CIN2	Clear	No	7	WNL	Positive (45)	SCC IA1

Abbreviations:
ASC-US; atypical squamous cells of undetermined significance; CIN: cervical intraepithelial neoplasia; CKC: cold knife conisation; LC: laser conisation; LLETZ: large loop excision of the transformation zone: NA: not available; SCC: squamous cell carcinoma; WNL: within normal limits

DISCUSSION

Main findings

The aim of this study is to provide a potential explanation of cervical carcinogenesis after previous CIN treatment, based on a limited number of cervical cancer cases with a history of CIN treatment. In our cases, the facts that the interval from initial CIN treatment to diagnosis of invasion was almost a decade and that five out of nine cancers were early stages, may fit well with the established natural history of the *de novo* cervical carcinogenesis, according to which cervical cancer occurs from a persistent HPV infection/pre-invasive lesion over an interval of 10-20 years[15, 16]. It may be quite likely that cervical cancer arose from precursors which had not been completely removed during treatment and subsequently progressed to cancer. We suggest that cytology/colposcopy failed to detect these precursors on time because these might have been entrapped inside cervical crypts under a thick thermal plaque, caused by cauterisation of the crypts along with the rest of the crater's surface during treatment, and under subsequent extended metaplasia of the new transformation zone. As a result, they might have remained undetected until they progressed to cancer and reached the endo- and/or ectocervical surface. Another explanation for the emergence of cervical cancer after previous CIN treatment is a new HPV infection. However, we would expect that regular follow-up would have detected HPV-related pre-invasive lesions before progression to cancer, therefore a new HPV infection is less likely to account for the cervical cancer development in our case series.

The 'crypt theory' could explain why the risk is greater with more conservative treatment methods, since shallow excision/ablation is not deep enough to remove/destroy all crypts. Optimal excision dimensions to ensure minimum risk of cervical carcinogenesis and minimum risk of reproductive morbidity is yet to be determined, probably in an individualised fashion[17-19].

There are several practical implications ensuing from the 'crypt theory'. Firstly, cauterisation of the crypts as well as at the whole crater created after cone excision, should be limited to the bare minimum in order to minimise the risk of affected cells being buried inside the crypts. An

alternative to cauterisation would be the use of haemostatic solutions, such as Monsel's. Secondly, treated women with high-grade histology or other unfavourable characteristics such as crypt involvement, satellite lesions[20] or aggressive HPV types might benefit from a rigorous (longer and more frequent) follow-up after treatment even if initial excisional margins were clear. Nonetheless, this is not practised in most countries, and some guidelines, such as in the UK, even support discharge to general population screening as early as at 6 months[21]. Thirdly, clinicians should be aware of the possibility of cervical cancer after CIN treatment and be alert especially if a previously treated woman presents with otherwise unexplained vaginal bleeding. Fourthly, it might be plausible that HPV testing, due to its higher sensitivity than cytology and colposcopy[22, 23], would also feature better long-term sensitivity for the diagnosis of these hidden lesions inside the crypts, and indeed HPV testing has been included in the post-treatment follow-up guidelines of many countries such as the UK, USA and Finland[21, 24, 25]. Of course, this is only a hypothesis since entrapped lesions inside the crypts might not exfoliate cells and HPV genetic material, thus HPV DNA or mRNA testing might be negative as well.

Strengths and limitations

Our explanation is unproven but is plausible and original. Also, review of the initial histology specimen and interval cytological smears, in order to rule out false negatives, was not feasible in half of the cases. However, treatment of CIN2+ and follow-up took place in academic hospitals in most cases (7/9), with experienced pathologists, cytologists and colposcopists involved. Additionally, post-treatment high-risk HPV testing as test of cure was not available since all cases had been treated before its introduction. Finally, we were not able to calculate the cervical cancer incidence rate after CIN treatment because some cases were referred to us by other clinicians, but our aim was not to calculate the prevalence but to suggest a potential explanation for the increased incidence as already shown in other studies.

CONCLUSION

Until better evidence may sometime appear, the original data of this small series could probably allow someone to consider the endocervical crypts as the origin of these 'hidden' and suddenly appearing carcinomas after CIN treatment. Apart from awareness regarding intra-operative technicalities, clinicians should also have at least an average index of suspicion particularly in symptomatic cases with a history of treatment for CIN, performing endocervical dilation and curettage (E&C) or even repeat excision. After all, most of these women would have had already completed their families.

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