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Clear Cell Carcinoma (CCC) of the Cervix Is a Human Papillomavirus (HPV)-independent Tumor Associated With Poor Outcome

A Comprehensive Analysis of 58 Cases

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Abstract: Cervical clear cell carcinoma (CCC) is a rare human papillomavirus–independent adenocarcinoma. While recent studies have focused on gastric-type endocervical adenocarcinoma (GTA), little is known about CCC. A total of 58 (CCCs) were collected from 14 international institutions and retrospectively analyzed using univariable and multivariable methods and compared with 36 gastric-type adenocarcinomas and 173 human papillomavirus–associated (HPVA) endocervical adenocarcinoma (ECA) regarding overall survival (OS) and recurrence-free survival (RFS). Most cases were FIGO stage I (72.4%), with Silva C pattern of invasion (77.6%), and the majority were treated with radical surgery (84.5%) and adjuvant therapy (55.2%). Lymphovascular invasion was present in 31%, while lymph node metastasis was seen in 24.1%; 10.3% were associated with abdominopelvic metastases at the time of diagnosis; 32.8% had recurrences, and 19% died of disease. We did not find statistically significant differences in OS and RFS between CCC and GTA at 5 and 10 years ($P = 0.313$ and 0.508, respectively), but there were significant differences in both OS and RFS between CCC and HPVA ECA ($P = 0.003$ and 0.032, respectively). Also, OS and RFS in stage I clear cell and GTA were similar ($P = 0.632$ and 0.692, respectively). Multivariate analysis showed that OS is influenced by the presence of recurrence ($P = 0.009$), while RFS is influenced by the FIGO stage ($P = 0.025$). Cervical CCC has poorer outcomes than HPVA ECA and similar outcomes to human papillomavirus–independent GTA. Oncologic treatment significantly influences RFS in univariate analysis but is not an independent prognostic factor in multivariate analysis suggesting that alternative therapies should be investigated.

Key Words: clear cell carcinoma, gastric type, cervix, stage, prognosis

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There has been a recent paradigm shift in the classification of endocervical adenocarcinomas (ECAs), with a move toward categorizing tumors by their etiologic link to human papillomavirus (HPV) infection, as well as morphology. This new system has been adopted by the 2020 World Health Organization (WHO) Classification of Tumors of the Female Genital Tract.[1,2] While nearly all squamous cell carcinomas of the cervix are caused by high-risk HPV infection, only ~85% of cervical adenocarcinomas are caused by HPV. The remaining 15% are caused by other factors independent of HPV.[2] Human papillomavirus–independent (HPVI) ECA are comprised of gastric type (most common), clear cell, mesonephric, and endometrioid carcinomas. Clear cell carcinoma

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(CCC) of the cervix is rare, accounting for <5% of all ECA.[1] While recent studies have focused on the poor outcomes of gastric-type endocervical adenocarcinoma (GTA), little is known about the outcomes of cervical CCC.

CCC of the cervix and vagina have been linked to in utero exposure to diethylstilbestrol (DES), a synthetic estrogen derivative given to millions of pregnant women from the 1940s to the 1970s.[3,4] While a bimodal age distribution has been described in CCC, with peaks at 26 and 71 years, DES-exposed patients tend to be younger with a peak age of 19 years; however, even with DES exposure, not all patients develop malignancies.[5–7] It is also well established that cervical CCC is not caused by HPV infection.[1,8–10] These data suggest that factors other than DES and HPV play an important role in the carcinogenesis of CCC, especially in older patients. However, the etiology and pathogenesis of these tumors are not well established, and no clear-cut precursor lesion has been identified, though a few reports suggest that some CCCs may develop from cervical endometriosis or tuboendometrioid metaplasia.[11–13]

Morphologically, cervical CCC is identical to the endometrial and ovarian counterparts, with solid, tubulocystic, and papillary architecture, often admixed within the same tumor. The tumor cells are characterized by abundant clear, glycogen-rich cytoplasm with prominent cell membranes, hyperchromatic nuclei, and low mitotic rate, and an oxyphilic variant with abundant eosinophilic, rather than clear cytoplasm has also been described as well as cases with tumor cells presenting with a signet-ring appearance (Fig. 1). A recent study demonstrated that all HPVI ECA, including CCCs, have Silva pattern C destructive stromal invasion, though the data were limited for CCC.[14] In addition, we have observed Silva patterns A and B in cervical CCCs, particularly in small, early-stage tumors, as well as exophytic lesions. This has important implications regarding the differential diagnosis and management of CCC since the application of the Silva pattern classification system to HPVI ECA is currently not recommended by the International Society of Gynecologic Pathologists (ISGyP).[15]

The prognosis of cervical CCC is stage-dependent, yet the inherent risk associated with this histology is not well established. While recent work has demonstrated that HPVI ECA have a worse prognosis than HPVA ECA, no study has looked specifically at a large cohort of CCC as compared with GTA.[16] Some case series have shown that CCCs have a poor prognosis in terms of overall survival (OS), disease-specific survival, and progression-free survival (PFS). The largest series of cases published thus far included 34 patients with CCC comprised of 71% stage I, 6% stage II, 17% stage III, and 6% stage IV.[17] That study focused on the optimal management of CCCs and showed that stage I and II CCCs demonstrated superior OS compared with advanced stage, but pelvic lymph node involvement was noted in 25% across all stages (stage I to IV). Moreover, while OS was 75% at 5 years, positive lymph nodes had a negative impact on 5-year OS and PFS in stage I and IIA.[17] The second-largest study published by Jiang et al,[18] in 2014, analyzed 32 cases, demonstrating a 5-year PFS of 72.2% and with early-stage (I to IIA) patients having a better 5-year PFS than those with advanced stage (IIB to IVB) (81.5% vs. 40.0%). However, at present, little is known regarding the prognosis of CCC compared with HPVA and other HPVI ECA such as GTA.

In this study, we aimed to analyze the clinicopathologic parameters and outcomes of CCC compared with other HPVI (gastric type) and HPVA ECAs.

MATERIALS AND METHODS

This study was approved by the institutional review boards of each participating center.

Case Selection

CCCs were collected from 14 international institutions and retrospectively analyzed (University of Medicine, Pharmacy, Sciences and Technology, Targu Mures, Romania; University Hospital of Saint-Etienne, Saint-Etienne, France; Hospital Universitari de Bellvitge-IDIBELL, Barcelona, Spain; Sahlgrenska University Hospital, Gothenburg, Sweden; Vall d'Hebron Hospital, Barcelona, Spain; Universitair Medisch Centrum, Groningen, The Netherlands; Instituto Portugues de Oncologia, Lisbon, Portugal; University of Cagliari, Cagliari, Italy; Centro hospitalar e Universitário de Coimbra, Coimbra, Portugal; Hospital Universitario La Paz, IdiPaz; Center for Biomedical Research in the Cancer Network (CIBERONC); Faculty of Medicine, Universidad Autonoma de Madrid; Madrid, Spain; University of Chicago, Chicago, IL; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Massachusetts General Hospital, Boston, MA, Memorial Sloan Kettering Cancer Center, New York, NY). Cases were also retrieved from International Endocervical Adenocarcinoma Criteria and Classification (IECC) database published in 2018.[1] A live shared spreadsheet was created listing various clinicopathologic parameters into which all participants of this study entered their own data. The study included biopsies (from patients without resection specimens but rather treated with chemo/radiotherapy), as well as loop electrocautery excision procedure, conizations, trachelectomies, and simple/radical hysterectomies with or without lymph node samples. In addition, 36 GTA and 173 HPVA ECA (usual and mucinous types) were retrieved from the IECC database for survival comparisons.[1] In the previously reported IECC cases, hematoxylin and eosin slides containing the tumor (an average of 12 slides per case) were examined at a multiheaded microscope, and consensus diagnosis reached among 3 pathologists (R.A.S., K.J.P., and S.S.) in each case. In cases submitted by the various authors of this study, representative slides of each case were reviewed by the first and senior authors (S.S. and K.J.P.) on either glass slides or digitally scanned images provided by the contributors. Each contributor reviewed full slides sets of their individual cases.

Morphologic Assessment

All cases were classified according to WHO 2020 (derived from the IECC system) as HPVA and HPVI ECA.[1,2] Briefly, HPVA ECA harbor apical mitotic figures and

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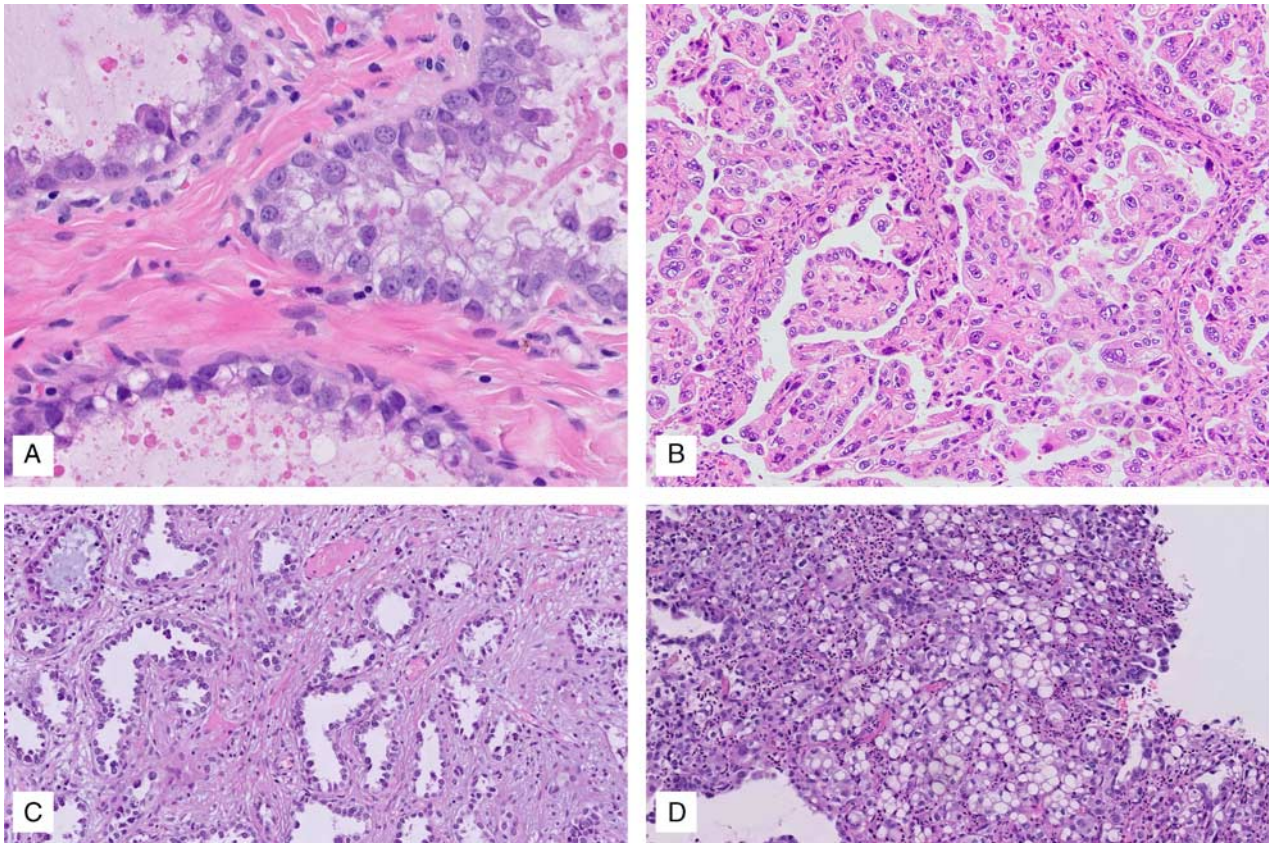

FIGURE 1. CCC: tubular structures lined by atypical tumor cells with abundant clear, glycogen-rich cytoplasm (A); oxyphilic variant of CCC with tumor cells presenting with abundant eosinophilic cytoplasm (B); CCC with hobnail-type tumor cells (C); and with signet-ring tumor cells (D).

apoptotic bodies easily seen at scanning magnification, while in HPVI ECA these features are lacking or limited. CCC was diagnosed by classic morphologic features—solid, papillary, and/or tubulocystic architecture with uniformly atypical polygonal cells harboring clear to eosinophilic cytoplasm with hobnail features and dense stromal hyalinization.[1]

Tumors were also assessed for Silva pattern of invasion.[19] Briefly, pattern A tumors are composed of well-demarcated glands with rounded contours arranged in a vaguely lobular configuration without destructive stromal invasion, single cells, or lymphovascular invasion (LVI); pattern B tumors have only "early/limited" destructive stromal invasion (< 5 mm in diameter) in a background of pattern A, defined as small clusters or individual tumor cells in a focally desmoplastic stroma, and can have LVI; pattern C shows diffusely destructive stromal invasion by glands associated with a desmoplastic stromal reaction and may be associated with LVI. The original Silva pattern classification study was restricted to HPVA ECA and therefore excluded CCC. While subsequent studies have shown HPVI ECAs to be uniformly classified as pattern C, the data are limited for CCC, and we wanted to study a larger cohort of these tumors to determine if they always show pattern C invasion.[14,20]

In the course of routine workup, various immunohistochemical markers (HNF1beta, Napsin A, p53, p16, vimentin, p63, estrogen receptor [ER], progesterone receptor [PR], DNA mismatch repair proteins), as well as HPV testing, were performed as deemed appropriate by the submitting pathologist (Table 1). The HPV in situ hybridization testing method used in the IECC cases has been previously described in detail (1). The other cases tested for HPV used the same RNA-based technique or polymerase chain reaction–based testing. The following clinical parameters were retrieved from the data files of each institution: age at diagnosis, past medical history, 2009 FIGO stage, surgical treatment, adjuvant treatment,

TABLE 1. Immunohistochemical Profile and HPV Status in CCCs

	Positivity, n/N (%)
HNF1beta	12/15 (80)
Napsin A	6/6 (100)
Mismatch repair	6/6 (100)
p53	2/19 (aberrant) (10.5)
p16	2/26 (diffuse, strong) (7.7)
Vimentin	0/1 (0)
p63	0/1 (0)
ER	1/6 (16.7)
PR	0/7 (0)
HPV	0/16 (0)

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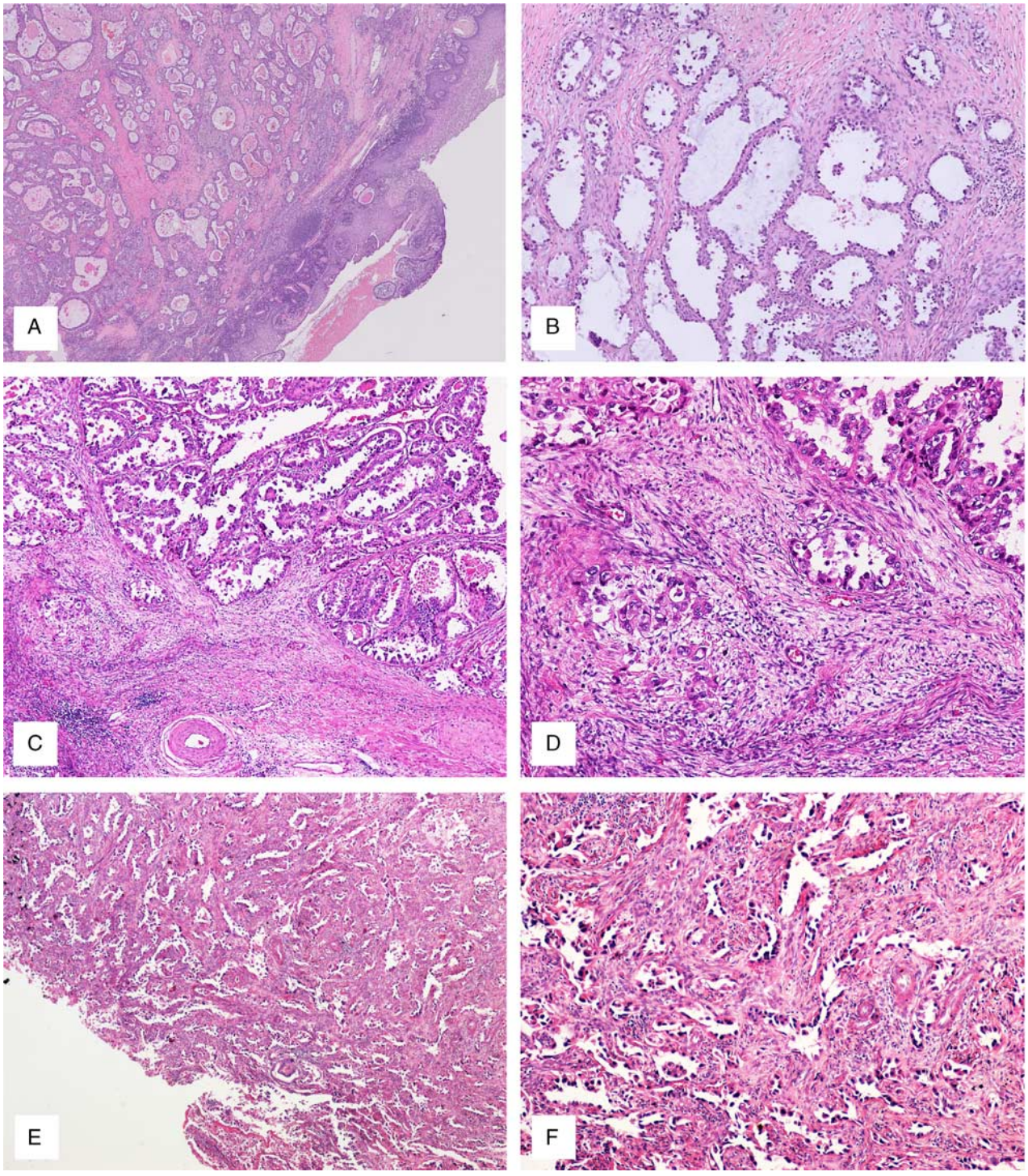

FIGURE 2. Low and high power of Silva A (A, B), Silva B (C, D), and Silva C (E, F) pattern of invasion.

lymph node metastases (LNM), metastases in abdominopelvic organs, local recurrences, presence of distant metastasis, and survival data. OS was defined as the time from surgery until death by any cause. Recurrence-free survival (RFS) was defined as the length of time the patient survived without any signs or symptoms of cervical cancer after completion of primary treatment. Each contributor reviewed full slide sets of their cases to determine Silva pattern and LVI.

Statistical Analysis

Data were tabulated using Microsoft Excel software and analyzed using SPSS for Microsoft Windows, version 20.0 (SPSS Inc., Chicago, IL). The Kaplan-Meier test was

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used for survival curve estimates; and the log-rank Mantel-Cox test was used for group comparisons. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model in univariate and multivariate analysis. *P*-value <0.05 was considered statistically significant.

RESULTS

Fifty-eight cases of CCC were retrospectively analyzed; 10 were retrieved from the original IECC study, while the remaining were submitted from individual authors. Mean age was 55.5 years (median 57.5 y; SD: 19.93 y; range 10 to 84 y) with 19 patients (32.8%) 50 years and below and 39 patients (67.2%) above 50 years old. In utero DES exposure was documented in only one 34-year-old patient.

Most patients (49, 84.5%) were treated surgically (cone, trachelectomy, hysterectomy with or without lymph node sampling), while 5 (8.6%) received definitive chemo/radiotherapy. No data was available regarding surgical treatment in 4 cases (6.9%). Most patients were also treated with adjuvant therapy (33 cases, 55.2%), while 21 (37.9%) were not. There was no data regarding adjuvant treatment in 4 cases (6.9%).

The FIGO (2009) stage breakdown of the 58 cases was as follows: 42 (72.4%) stage I; 9 (15.5%) stage II; 3 (5.2%) stage III; 3 (5.2%) stage IV; the stage was not available in 1 case.

While prior studies have shown that HPVI ECA always show Silva pattern C invasion, we found 5 (8.6%) pattern B and 2 (3.4%) pattern A cases of CCC, with the remaining (45, 77.6%) being pattern C (Fig. 2). The CCCs with pattern A or B were early-stage (I to IIA), some with exophytic growth. Silva pattern was not determined in 6 cases (not available) due to biopsy only specimens. The impact of Silva pattern on prognosis was further analyzed (see below).

Lymphovascular invasion was present in 18 (31%), absent in 34 (55.2%), and not determined in 6 cases (10.3%). Lymph node metastasis (LNM) at the time of diagnosis was present in 14 (24.1%), absent in 42 (72.4%), and not reported in 2 (3.4%).

Mean follow-up was 64.5 months (range: 1 to 304 mo). Abdominopelvic metastases at the time of diagnosis occurred in 6 (10.3%), while there were no metastases in 41 (70.7%); metastasis status was not reported in 11 cases (19%). Sites of synchronous metastases included ovary (1), uterine corpus (1), pelvis (1), vagina (1), spleen (1), omentum (1), sacrum (1), bladder wall (1), perirectal soft tissue (1), rectal mucosa (1), and para-aortic lymph nodes (1) with several patients having multisite involvement (omentum/spleen, ovary/pelvis, and bladder/perirectal/uterine corpus in 3 different patients). Nineteen patients (32.8%) recurred, and 34 (58.6%) did not, while no information was available in 5 (8.6%). Eleven (19%) died of disease. Recurrences occurred in the lungs (6), liver (3), bones (3), brain (1), peritoneum (6), retroperitoneum (1), mediastinal lymph nodes (2), vagina (3), and sigmoid colon (2) (Table 2).

The immunohistochemical profile of cervical CCC was as expected with most cases positive for Napsin A (100%) and HNF1beta (80%); p16 was negative or showed patchy positivity in most cases with only 2 of 26 (7.7%) showing diffuse strong expression (aberrant). These cases were subsequently tested, and negative for HPV by in situ hybridization, and the aberrant p16 expression is likely due to an HPVI mechanism. While ER was negative in most cases, 16.7% showed some ER expression; 10.5% showed aberrant p53 expression (diffuse strong), while no cases showed "null" expression pattern. All tested cases were negative for vimentin, p63, PR, and high-risk HPV (by in situ hybridization, polymerase chain reaction, or both methods), while DNA mismatch repair proteins were retained in all cases (100%) (see Table 1 for details).

Comparison of survival outcomes between CCC and other ECA using Kaplan-Meier analysis showed no statistically significant differences in 5- and 10-year OS or RFS between CCC and GTA; in contrast, there were significant differences between CCC and HPVA ECA.

TABLE 2. Association Analysis Between Clinicopathologic Parameters in 58 Cases of CCCs of the Cervix

	CCCs, n (%)
Total	58
Age, mean (median) (y)	55.5 (57.5)
SD (range)	19.93 (10-84)
Age (y)	
< 50	19 (32.8)
≥ 50	39 (67.2)
Surgical treatment	
No	5 (8.6)
Yes	49 (84.5)
NA	4 (6.9)
Adjuvant treatment	
No	21 (37.9)
Yes	33 (55.2)
NA	4 (6.9)
FIGO stage	
Stage 1	42 (72.4)
Stage 2	9 (15.5)
Stage 3	3 (5.2)
Stage 4	3 (5.2)
NA	1 (1.7)
Silva pattern	
A	2 (3.4)
B	5 (8.6)
C	45 (77.6)
NA	6 (10.3)
LVI status	
Present	18 (31)
Absent	34 (55.2)
NA	6 (10.3)
Presence of LNM	
Yes	14 (24.1)
No	42 (72.4)
NA	2 (3.4)
Metastasis in abdominopelvic organ	
Yes	6 (10.3)
No	41 (70.7)
NA	11 (19)
Recurrences	
Yes	19 (32.8)
No	34 (58.6)
NA	5 (8.6)

NA indicates not available.

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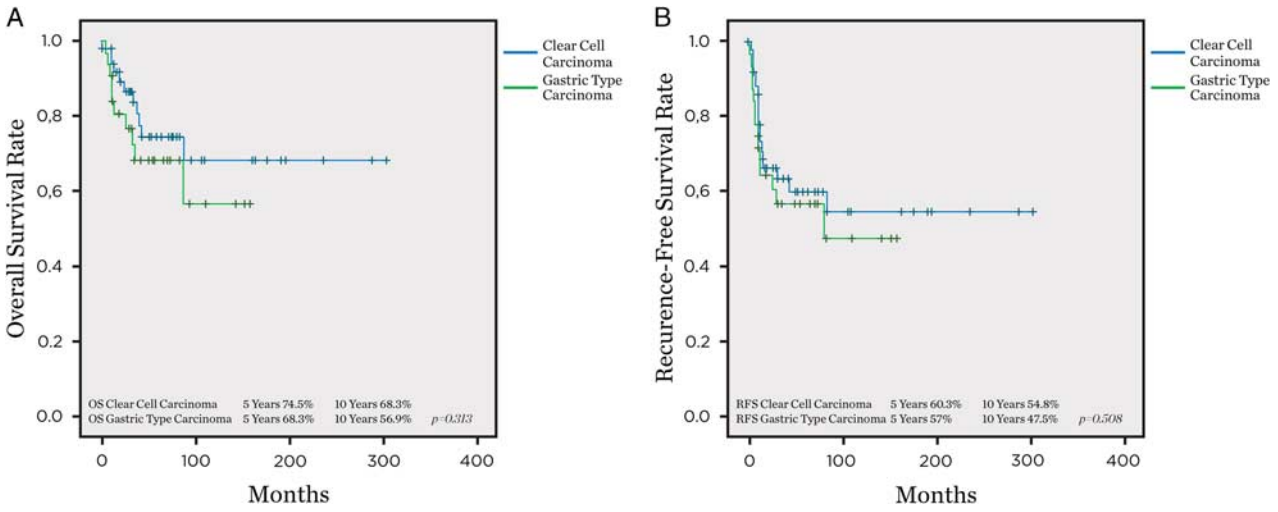

FIGURE 3. Kaplan-Meier analysis: OS in CCCs versus GTA (A); RFS in CCCs versus GTA (B).

OS at 5 and 10 years for CCC was 74.5% and 68.3%, respectively, while for gastric type, it was 68.3% and 56.9% ($P = 0.313$) (Fig. 3). RFS at 5 and 10 years in CCC was 60.3% and 54.8%, respectively, while for GTA, it was 57% and 47.5% ($P = 0.508$) (Fig. 1). This is in contrast to 91.9% and 86.7%, 5- and 10-year OS in HPVA ECA, respectively ($P = 0.003$) (Fig. 4). Similarly, RFS for HPVA ECA at 5 and 10 years was 76.6% and 72.8% ($P = 0.032$) (Fig. 4). In addition, OS and RFS in stage I CCC and GTA were similar (OS at 5 and 10 y 85.3% for CCC and 92.9% for gastric type, $P = 0.632$; RFS at 5 and 10 y for CCC 70.9% and for gastric type 66.8% [$P = 0.692$]) (Fig. 5). Moreover, OS in stage I CCC was 85.3% at both 5 and 10 years, while in stage II to IV, it was 39.7% at 5 years and 0% at 10 years ($P = 0.00001$) (Fig. 6). RFS in stage I CCC was 76.1% at both 5 and 10 years, while in stage II to IV was 10% at 5 years and 0% at 10 years ($P = 0.00001$) (Fig. 6).

Cox univariate analysis comparing clinicopathologic parameters demonstrated that OS is influenced by whether or not the patient was treated surgically (HR = 5.31; 95% CI = 1.11-25.48; $P = 0.037$), FIGO stage (HR = 8.71; 95% CI = 2.41-31.56; $P = 0.001$), presence of LNM (HR = 3.49; 95% CI = 1.02-12.51; $P = 0.05$), and presence of recurrences (HR = 18.68; 95% CI = 2.36-148.07; $P = 0.006$), while RFS is influenced by receiving adjuvant treatment (HR = 3.66; 95% CI = 1.21-11.11; $P = 0.022$), FIGO stage (HR = 7.65; 95% CI = 2.97-19.67; $P = 0.00001$), presence of LVI (HR = 2.98; 95% CI = 1.06-8.34; $P = 0.038$) and LNM (HR = 9.06; 95% CI = 3.46-23.75; $P = 0.00001$) (Table 3). Multivariate analysis showed that OS is influenced by presence of recurrence (HR = 25.4; 95% CI = 2.24-288.42; $P = 0.009$), while RFS is influenced by FIGO stage (HR = 8.56; 95% CI = 1.31-55.94; $P = 0.025$) (Tables 4, 5).

DISCUSSION

Cervical cancer is the fourth most common malignancy among women worldwide and is largely represented

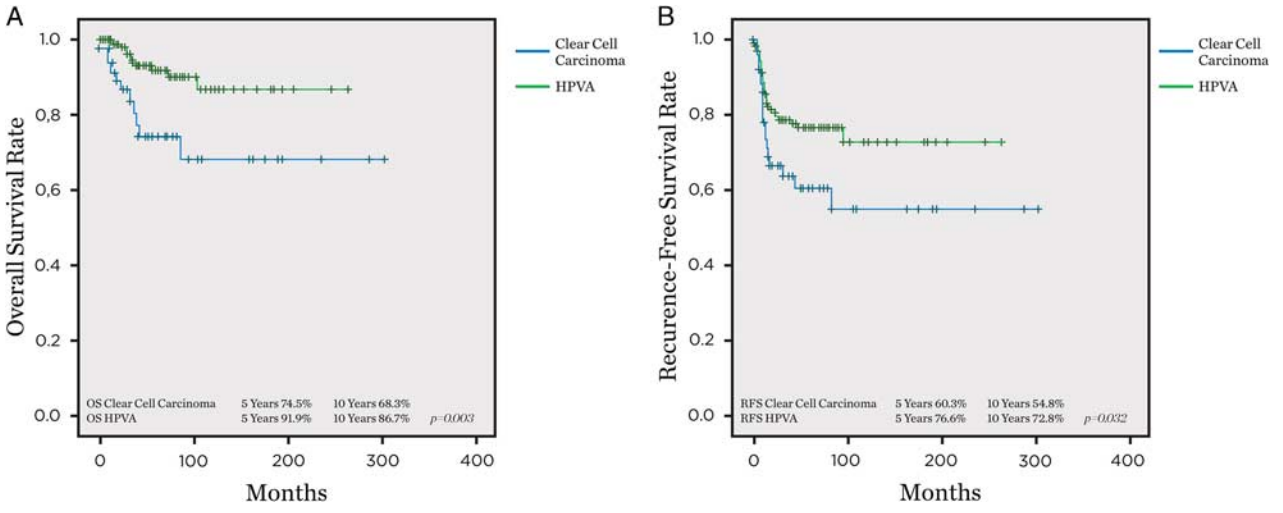

FIGURE 4. Kaplan-Meier analysis: OS in CCC versus HPVA-related ECA (A); RFS in CCC versus HPVA-related ECA (B).

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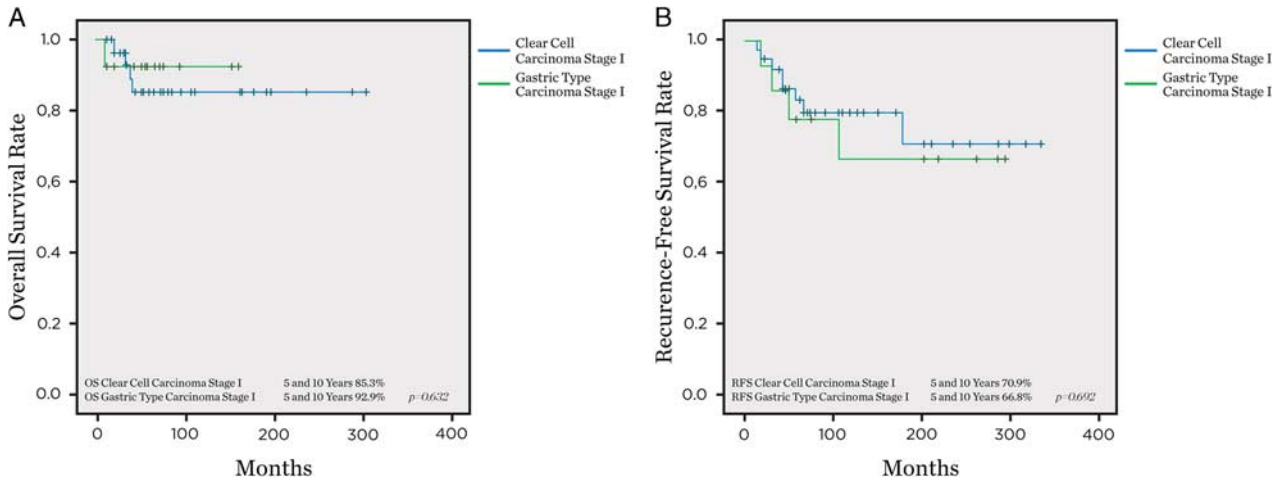

FIGURE 5. Kaplan-Meier analysis in FIGO stage I CCC versus stage I GTA (A); FIGO stage I CCC versus stage I GTA (B).

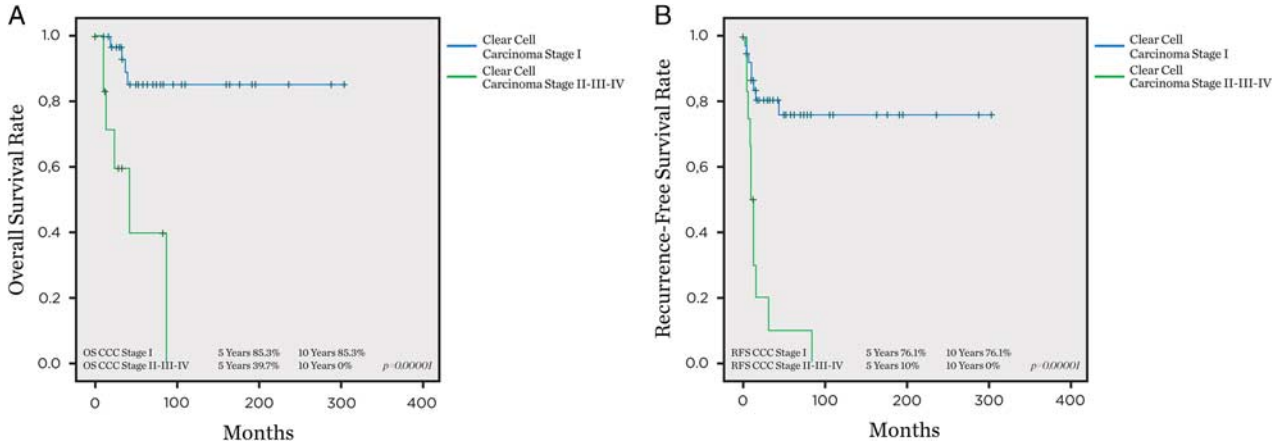

FIGURE 6. Kaplan-Meier analysis: OS in CCC stage I versus CCC stage II to IV (A); RFS in CCC stage I versus CCC stage II to IV (B).

TABLE 3. Survival Analysis by Cox Regression (Univariate Analysis) of Parameters That Influence OS and RFS in 58 Cases of CCC

	OS			RFS		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	2.1	0.45-9.76	0.346	1.21	0.46-3.18	0.71
Surgical treatment (performed vs. not)	5.31	1.11-25.48	0.037	1.83	0.42-7.97	0.423
Adjuvant treatment (received vs. not)	1.84	0.47-7.14	0.38	3.66	1.21-11.11	0.022
FIGO stage I vs. II-IV	8.71	2.41-31.56	0.001	7.65	2.97-19.67	0.00001
Silva pattern A/B vs. C	1.11	0.14-9.16	0.921	2.21	0.29-16.78	0.443
Presence of LVI	1.18	0.29-4.81	0.82	2.98	1.06-8.34	0.038
Presence of LNM	3.49	1.02-12.51	0.05	9.06	3.46-23.75	0.00001
Metastasis in abdominopelvis	3.72	0.74-18.73	0.111	1.89	0.42-8.54	0.408
Recurrences	18.68	2.36-148.07	0.006			

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TABLE 4. Multivariate Analysis of Factors That Influence OS in 58 Cases of CCC by Cox Regression

	HR	95% CI	*P*
Surgical treatment	8.00	0.97-66.33	0.054
FIGO stage	2.04	0.40-10.39	0.389
Presence of LNM	1.81	0.38-8.69	0.458
Recurrences	25.4	2.24-288.42	0.009

TABLE 5. Multivariate Analysis of Factors That Influence RFS in 58 Cases of CCC by Cox Regression

	HR	95% CI	*P*
Adjuvant treatment	2.60	0.51-13.43	0.254
FIGO stage	8.56	1.31-55.94	0.025
Presence of LVI	1.26	0.40-4.00	0.696
Presence of LNM	1.39	0.29-6.72	0.683

by squamous cell carcinoma, a tumor driven by high-risk HPV infection.[21] In contrast, adenocarcinomas comprise up to 25% of all cervical cancers and are a heterogenous group of tumors, ~15% of which are HPVI.[1,2] These HPVI tumors have different morphologies, prognoses, and molecular pathogenesis, and this etiology-based classification has now been incorporated into 2020 WHO Classification of Tumors of the Female Genital Tract.[2] While there have been some recent studies looking at outcomes of HPVI tumors like gastric-type and mesonephric cervical adenocarcinomas, there have been no comparable studies evaluating cervical CCCs.[22,23] In this study, we have demonstrated that rarely CCCs can have Silva A or B pattern of invasion (mostly in early-stage and exophytic tumors), though due to the small number of cases, we cannot comment on whether this affects outcomes in this cohort. We did show that CCC outcomes are more similar to gastric-type adenocarcinoma, being worse than that of HPVA ECAs.

CCC is the second most common HPVI ECA, representing 3% of all cases in the IECC database.[1] These tumors can be associated with in utero exposure to DES but can also occur sporadically. There is a bimodal age distribution with a mean age of 19 in DES-exposed patients and 40 in non–DES-exposed patients.[1,24] However, CCC is rare even among DES-exposed women (with an absolute risk of 1.9 to 2.3/1000); therefore, while DES exposure is an established cause of CCC, it may be an incomplete carcinogen, and other genetic and environmental factors likely play an important role in tumor development.[24] In the present study, only one 34-year-old patient had a history of DES exposure.

Not much is known regarding the etiology and molecular underpinnings of CCCs. Boyd et al[25] showed that microsatellite instability was detected in all DES-exposed and half of non–DES-exposed CCCs, while no mutations were detected in *KRAS*, *HRAS*, *WT1*, *ER*, or *TP53*. Mills et al[26] did not detect any association with Lynch syndrome, while in an immunohistochemistry-based study, Ueno et al[9] identified loss of PTEN, positive pAKT, and p-mammalian target of rapamycin and human epidermal growth factor receptor 2 amplification but without molecular correlation.[9]

All CCC have been classified as Silva pattern C to date, and recent recommendations from ISGyP suggest that the pattern of invasion should be applied only to HPVA ECA.[14] In our study, we did find 5 (8.6%) pattern B and 2 (3.4%) pattern A CCCs corresponding to small size, early-stage, or exophytic polyp, without LNM. Four of the 7 cases were not associated with recurrences or death from disease, and 2 patients died of other causes; however, there was 1 Silva pattern A that developed multiple recurrences within the abdomen, pelvis, retroperitoneal and mediastinal lymph nodes, bone and brain 5 months after the initial diagnosis. Moreover, the pattern of invasion was not found to be an independent prognostic parameter in both univariate and multivariate analysis, supporting that pattern classification of CCC is not clinically relevant, albeit our numbers were small.

Most studies have reported that CCC is a tumor associated with LVI and LNM. In the largest study by Thomas et al,[17] pelvic lymph node involvement was noted in 25% of cases. Similarly, we found LVI in 31% and LNM in 24.1% of our cases. In addition, 10.3% were associated with abdominopelvic metastases, 32.8% had recurrences, and 19% died of disease. The sites of recurrence in our CCC were also very similar to gastric or mesonephric type, represented by lung, liver, bone, brain, peritoneum, retroperitoneum, mediastinal lymph nodes, vagina, and sigmoid colon.[22,23]

There are no published data on the differences in prognosis between CCC and GTA and CCC and HPVA ECA. Other than case reports demonstrating that CCC have a worse prognosis than usual HPVA ECA, the 2 largest studies did not correlate CCC survival with those of HPVA and/or with GTA since these studies were performed before the introduction of the etiology-based classification system.[17,18] The paper by Huo et al[24] suggested that the prognoses of CCC and usual type are similar when controlled for the stage.

We did not find statistically significant differences in OS and RFS between CCC and GTA at 5 and 10 years but there were significant differences in both OS and RFS between CCC and HPVA ECA. OS and RFS in stage I clear cell and GTA were similar.

Cox univariate analysis demonstrated that OS is influenced by FIGO stage, presence of LNM, association with surgical treatment (inextricably linked to stage since early-stage patients have surgery and late-stage get chemotherapy/radiotherapy), and presence of recurrences, while RFS is influenced by FIGO stage, presence of LVI, LNM, and association with adjuvant treatment. However, multivariate analysis showed that OS is influenced by recurrence, while RFS is influenced by FIGO stage. As previously reported, we confirm that stage is an important predictor of OS and RFS, as all patients with II to IV CCCs were dead of disease at 10 years.

CONCLUSIONS

Cervical CCCs have poorer outcomes than HPVA ECAs and similar outcomes to HPVI gastric-type

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adenocarcinoma. Stage is an important factor in prognosis with advanced stage having significantly worse outcomes than stage I. Oncologic treatment (definitive chemotherapy/radiotherapy, adjuvant chemotherapy/radiotherapy postsurgery) significantly influences RFS, and surgical treatment influence OS in univariate analysis but are not independent prognostic factors in multivariate analysis. Since current treatments do not improve outcomes in patients with advanced stage CCCs, further studies on more targeted therapies should be pursued in future studies.

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