# Clear cell carcinoma (CCC) of the cervix is a Human Papillomavirus (HPV)-independent tumor associated with poor outcome. A comprehensive analysis of 58 cases

**Running title:** Clear cell carcinoma (CCC) of the cervix is associated with poor outcome

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## Abstract

Cervical clear cell carcinoma (CCC) is a rare HPV-independent adenocarcinoma. While recent studies have focused on gastric type endocervical adenocarcinoma (GTA), little is known about CCC.

58 (CCCs) were collected from 14 international institutions and retrospectively analyzed using univariable and multivariable methods and compared to 36 gastric type adenocarcinomas (GTA) and 173 HPV-associated (HPVA) ECA regarding overall (OS) and recurrence free survival (RFS).

Most cases were FIGO stage I (70.7%), with Silva C pattern of invasion (75.9%), and histologic grade 3 (96.6%) and the majority were treated with radical surgery (84.5%) and adjuvant therapy (55.2%). Lympho-vascular invasion was present in 31%, while lymph node metastasis (LNM) was seen in 22.4%; 10.3% were associated with abdomino-pelvic 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 p=0.508 respectively), but there were significant differences in both OS and RFS between CCC and HPVA ECA (p=0.003 and p=0.032, respectively). Also, OS and RFS in stage I clear cell and GTA were similar (p=0.632 and p=0.692 respectively). Multivariate analysis showed that OS is influenced by the presence of recurrence (p=0.009), while RFS is influenced by FIGO stage (p=0.025).

Cervical CCC has poorer outcomes than HPVA ECA but similar outcomes to HPV-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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## Introduction

There has been a recent paradigm shift in the classification of endocervical adenocarcinomas (ECA), 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 approximately 85% of cervical adenocarcinomas are caused by HPV. The remaining 15% are caused by other factors independent of HPV[2]. HPV-independent (HPVI) ECA are comprised of

gastric type (most common), clear cell, mesonephric and endometrioid carcinomas. Clear cell carcinoma (CCC) of the cervix is rare, accounting for less than 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.

Clear cell carcinoma 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 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 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 tubo-endometrioid 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. A recent study demonstrated that all cervical CCCs have Silva pattern C destructive stromal invasion; however, we have observed Silva pattern A and B, particularly in small, early-stage tumors, as well as in exophytic lesions[14]. This has important implications regarding the differential diagnosis and management of CCC, since application of the Silva pattern classification system to HPV-independent 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 worse

prognosis than HPVA ECA, no study has looked specifically at a large cohort of CCC as compared to GTA[16]. Some case series have shown that CCCs have poor prognosis in terms of overall survival (OS), disease specific survival (DSS) 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 to advanced stage, but pelvic lymph node involvement was noted in 25% across all stages (stage I-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 in 2014 analyzed 32 cases, demonstrating a 5-year PFS of 72.2% and with early stage (I-IIA) patients having a better 5-year PFS than those with advanced stage (IIB-IVB) (81.5% versus 40.0%)[18]. However, at present little is known regarding the prognosis of CCC compared to HPVA and other HPVI ECA such as GTA.

In this study, we aimed to analyze the clinico-pathologic parameters and outcomes of CCC compared to other HPV-independent (gastric type) and HPV-associated endocervical adenocarcinomas.

## 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, 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, Italy; Centro hospitalar e Universitário de Coimbra, Coimbra, Portugal; Hospital Universitario La Paz: Madrid, Spain; University of Chicago, USA; Brigham and Women's Hospital, Boston, USA; Massachusetts General Hospital, Boston, USA

Memorial Sloan Kettering Cancer Center, USA). 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 clinico-pathologic 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 (LEEP), 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 (H&E) slides containing tumor (an average of 12 slides per case) were examined at a multi-headed microscope and consensus diagnosis reached among three pathologists (RAS, KJP, and SS) 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 (SS and KJP) 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 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 (less than 5mm 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. Subsequent studies have shown HPVI ECAs to be uniformly classified as Pattern C[14,20].

Microscopic grading was performed according to the International Federation of Gynecology and Obstetrics (FIGO) grading system used for endometrial endometrioid carcinomas (grade 1: ≤5% solid growth; grade 2: 6-50% solid growth; and grade 3: >50% solid growth).

In selected cases where the diagnosis was equivocal, immunohistochemical markers (HNF1beta, Napsin A, p53, p16, Vimentin, p63, ER, PR, DNA mismatch repair proteins), as well as HPV testing, were performed (Table 1). 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, lymph node metastases (LNM), metastases in abdomino-pelvic organs, local recurrences, presence of distant metastasis, and survival data. OS was defined as the time from surgery until death by any cause. 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 FIGO grade, Silva pattern and LVI.

***Statistical analysis***

Data were tabulated using Microsoft Excel software and analyzed using SPSS for Microsoft Windows, version 20.0 (Chicago, IL, USA). The Kaplan-Meier test was 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 analyze. $P<0.05$ 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; standard deviation: 19.93; range 10-84)) with 19 patients (32.8%) ≤50 years and 39 patients (67.2%) >50 years old. In utero DES exposure was documented in only 1 patient of 34-year-old.

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: 41 (70.7%) stage I; 8 (13.8%) stage II; 4 (6.9%) stage III; 2 (3.4%) stage IV.

While prior studies have shown that HPVI ECA always show Silva pattern C invasion, we found 3 (5.2%) pattern B and 2 (3.4%) pattern A cases of CCC, with the remaining cases (44, 75.9%) being pattern C. The CCCs with pattern A or B were early stage (I-IIA), some with exophytic growth. Silva pattern was not determined in 9 cases either due to biopsy only specimens or the pattern not being provided by the submitting pathologist. The impact of Silva pattern on prognosis was further analyzed (see below).

The CCCs were mostly grade 3 (56, 96.6%), with only 2 (3.4%) grade 2 and no grade 1 cases. Although histologic grade is not a required element in cervical adenocarcinoma reporting, we analyzed its impact on prognosis (see below).

Lympho-vascular invasion was present in 18 (31%), absent in 33 (55.2%) and not determined in 8 cases (13.8%). Lymph node metastasis (LNM) at the time of diagnosis was present in 13 (22.4%), absent in 42 (72.4%) and not reported in 3 cases (5.2%).

Mean follow up was 64.5 months (1-304 months). Abdomino-pelvic metastases at the time of diagnosis occurred in 6 cases (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 case), uterine corpus (1 case), pelvis (1 case), vagina (1 case), spleen (1 case), omentum (1 case), sacrum (1 case), bladder wall (1 case), perirectal soft tissue (1 case), rectal mucosa (1 case) and para-aortic lymph nodes (1 case). Nineteen cases (32.8%) had recurrences and 34 (58.6%) did not, while no information was available in 5 (8.6%). Eleven (19%) patients died of disease. Sites of recurrences were represented by lungs (6 cases), liver (3 cases), bones (3 cases), brain (1 case), peritoneum (6 cases), retroperitoneum (1 case), mediastinal lymph nodes (2 cases), vagina (3 cases) and sigmoid colon (2 cases) (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 non-block-type positivity in most cases with only 11.5% showing diffuse strong positivity. 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-PCR 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.

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) (Figure 1). 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) (Figure 1). This is in contrast to 5- and 10-year OS in HPVA ECA, 91.9% and 86.7%, respectively (p=0.003) (Figure 2). Similarly, RFS for HPVA ECA at 5 and 10 years was 76.6% and 72.8% (p= 0.032) (Figure 2). In addition, OS and RFS in stage I CCC and GTA were similar (OS at 5 and 10 years 85.3% for CCC and 92.9% for gastric type, p=0.632; RFS at 5- and 10-years for CCC 70.9% and for gastric type 66.8% (p=0.692) (Figure 3). Moreover, OS in stage I CCC was 85.3% at both 5 and 10 years, while in stage II-IV it was 39.7% at 5 years and 0% at 10 years (p=0.00001) (Figure 4). RFS in stage I CCC was 76.1% at both 5 and 10 years, while in stage II-IV was 10% at 5 years and 0% at 10 years (p=0.00001) (Figure 4).

Cox univariate analysis comparing clinico-pathologic 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 in 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) (Table 4, 5).

**Discussion**

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

group of tumors, approximately 15% of which are HPV-independent[1,2]. These HPV-independent tumors have different morphologies, prognoses and molecular pathogenesis and this etiology-based classification has now been incorporated into the 2020 WHO Classification of Tumors of the Female Genital Tract[2]. While there have been some recent studies looking at outcomes of HPV-independent tumors like gastric-type and mesonephric cervical adenocarcinomas, there have been no comparable studies evaluating cervical clear cell carcinomas[22,23]. In this study, we have demonstrated that while CCCs can have Silva A or B pattern of invasion (mostly in early stage and exophytic tumors), it does not affect outcomes, which are similar to gastric-type adenocarcinoma, and worse than that of HPVA ECAs.

CCC is the second most common HPV-independent 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 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 per 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. 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*[25]. Mills et al. did not detect any association with Lynch syndrome, while in an immunohistochemistry-based study, Ueno at el. identified loss of PTEN, positive pAKT and p-mammalian target of rapamycin (mTOR) and HER2 amplification but without molecular correlation[9,26].

All CCC have been classified as Silva pattern C to date and recent recommendations from ISGyP suggest that pattern of invasion should be applied only on HPVA ECA[14]. While we did find 3 (5.2%) pattern B and 2 (3.4%) pattern A cases corresponding to small size, early-stage or

exophytic polyp, and 4 of the 5 cases were not associated with recurrences or death from disease, there was one Silva pattern A case 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, confirming that pattern classification of CCC is not clinically relevant.

While most clinical guidelines state that tumor grade is an important element in pathological tumor evaluation, it is not considered a major prognostic factor in endocervical adenocarcinomas and does not feature in treatment algorithms guiding patient management[27]. CCC is by default a high-grade tumor, although the morphological features may be "low-grade" with bland cytology and predominant or exclusive tubulocystic or papillary architecture. We found only 2 FIGO grade 2 cases with the majority of tumors being grade 3, and therefore, histologic grade is not a significant prognostic parameter in CCCs and grading these tumors is not recommended.

Most studies have reported that CCC is a tumor associated with LVI and LNM. In the largest study by Thomas et al, pelvic lymph node involvement was noted in 25% of cases[17]. Similarly, we found LVI in 31% and LNM in 22.4% of our cases. In addition, 10.3% were associated with abdomino-pelvic 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 lungs (6 cases), liver (3 cases), bones (3 cases), brain (1 case), peritoneum (6 cases), retroperitoneum (1 case), mediastinal lymph nodes (2 cases), vagina (3 cases) and sigmoid colon (2 cases)[22,23].

There are no published data on the difference in prognosis between CCC and GTA and CCC and HPVA ECA. Other than case reports demonstrating that CCC have worse prognosis than usual HPVA ECA, the two largest studies did not correlate CCC survival with those of HPVA and/or with gastric type ECA since these studies were performed prior to the introduction of the etiology-

based classification system[17,18]. The paper by Huo et al suggested that prognoses of CCC and usual type are similar when controlled for stage[24].

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 gastric type ECA 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 in 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-IV CCCs were dead of disease at 10 years.

**Conclusions**

Cervical CCCs have poorer outcomes than HPVA ECAs but similar outcomes to HPV-independent gastric type 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 post-surgery) 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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**Figures legend**

**Figure 1**: Kaplan Meier analysis: OS in Clear Cell Carcinomas versus Gastric type ECA (A); RFS in Clear Cell Carcinomas versus Gastric type ECA (B)

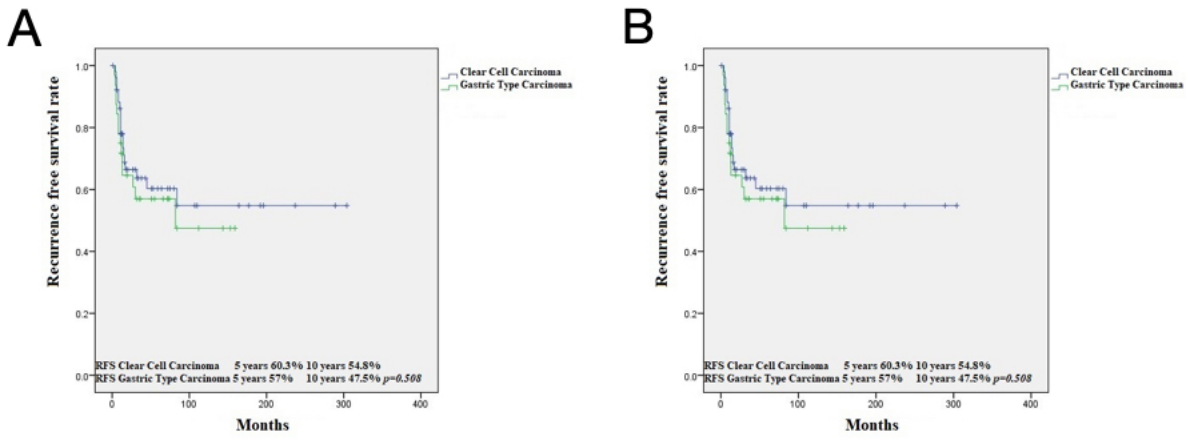


**Figure 2**: Kaplan Meier analysis: OS in CCC versus HPVA related ECA (A); RFS in CCC versus HPVA related ECA

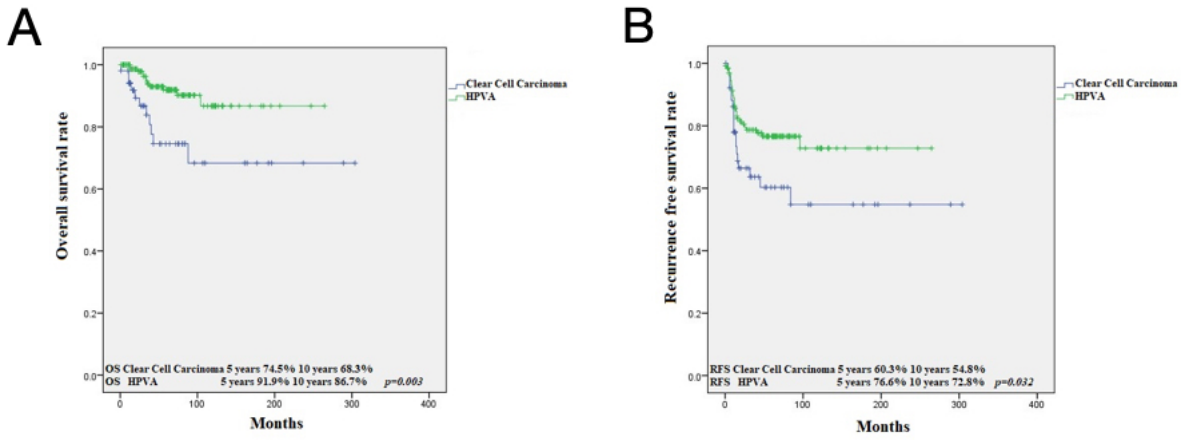


**Figure 3**: Kaplan Meier analysis in FIGO stage I CCC versus stage I Gastric type ECA (A); FIGO stage I CCC versus stage I Gastric type ECA

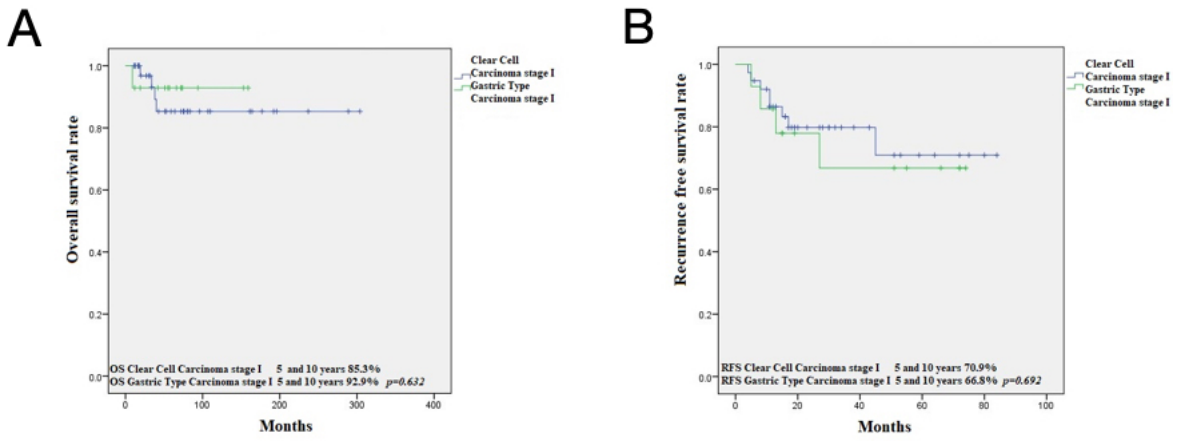


**Figure 4**: Kaplan Meier analysis: OS in CCC stage I versus CCC stage II-IV (A); RFS in CCC stage I versus CCC stage II-IV

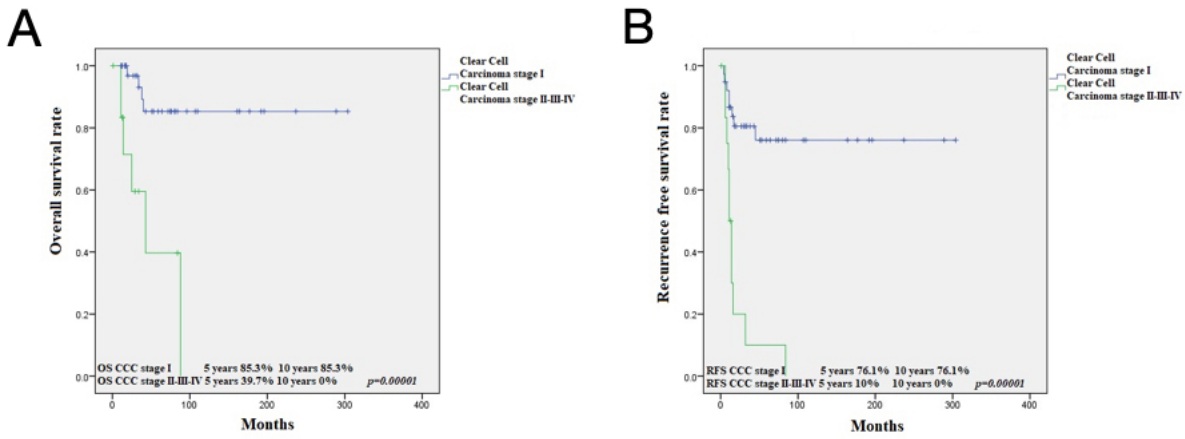

**Table 1: Immunohistochemical profile and Human Papillomavirus (HPV) status in clear cell carcinomas**

| | Positivity (number of cases) | % |
|---|---|---|
| **HNF 1beta** | 12/15 | 80% |
| **Napsin A** | 6/6 | 100% |
| **MMR** | 6/6 | 100% |
| **p53** | 2/19 | 10.50% |
| **p16** | 3/26 | 11.50% |
| **Vimentin** | 0/1 | 0% |
| **p63** | 0/1 | 0% |
| **ER** | 1/6 | 16.70% |
| **PR** | 0/7 | 0% |
| **HPV** | 0/16 | 0% |

**Table 2. Association analysis between clinico-pathologic parameters in 58 cases of clear cell carcinomas of the cervix**

| | **Clear Cell Carcinomas** |
|---|---|
| | Number of cases, (%) |
| **Total** | 58 |
| **Age Means, Median (years)** | 55.5(57.5) |
| **Std. Deviation, Range** | 19.93(10-84) |
| **Age <50 years** | 19(32.8%) |
| **≥50 years** | 39(67.2%) |
| **Surgical Treatment** | |
| **No** | 5(8.6%) |
| **Yes** | 49(84.5%) |
| **N/A** | 4(6.9%) |
| **Adjuvant treatment** | |
| **No** | 21(37.9) |
| **Yes** | 33(55.2%) |
| **N/A** | 4(6.9%) |
| **FIGO Stage** | |
| **Stage 1** | 41(70.7%) |
| **Stage 2** | 8(13.8%) |
| **Stage 3** | 4(6.9%) |
| **Stage 4** | 2(3.4%) |
| **N/A** | 3(5.2%) |
| **Silva pattern** | |
| **A** | 2(3.4%) |
| **B** | 3(5.2%) |
| **C** | 44(75.9%) |
| **N/A** | 9(15.5%) |
| **Histologic grade** | |
| **G1** | 0 |
| **G2** | 2(3.4%) |
| **G3** | 56(96.6%) |
| **LVI status** | |
| **Present** | 18(31%) |
| **Absent** | 33(55.2%) |
| **N/A** | 8(13.8%) |
| **Presence of LNM** | |
| **Yes** | 13(22.4%) |
| **No** | 42(72.4%) |
| **N/A** | 3(5.2%) |
| **Metastasis in abdomino-pelvic organ** | |

| | |
|---|---|
| **Yes** | 6(10.3%) |
| **No** | 41(70.7%) |
| **N/A** | 11(19%) |
| **Recurrences** | |
| **Yes** | 19(32.8%) |
| **No** | 34(58.6%) |
| **N/A** | 5(8.6%) |

**Abbreviations: LVI: lympho-vascular invasion; LNM: lymph node metastases**

**Table 3. Survival analysis by Cox regression (univariate analysis) of parameters that influence overall survival (OS) and recurrence free survival (RFS) in 58 cases of CCC**

| | | **OS** | | | **RFS** | |
|---|---|---|---|---|---|---|
| | HR | CI 95% | p | HR | CI 95% | 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 (performed vs not)** | 1.84 | (0.47-7.14) | 0.38 | **3.66** | **(1.21-11.11)** | **0.022** |
| **FIGO Stage 1 vs 2,3,4** | **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 |
| **Histologic grade 2 vs 3** | 21.31 | (0.01-44323.44) | 0.68 | 1.46 | (0.20-11.07) | 0.715 |
| **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 abdomino-pelvis** | 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** | | | |

**Abbreviations: LVI: lympho-vascular invasion; LNM: lymph node metastases**

**Table 4. Multivariate analysis of factors that influence overall survival (OS) in 58 cases of CCC byCox regression**

| | HR | CI 95% | 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** | **25.40** | **(2.24-288.42)** | **0.009** |

**Abbreviations: LNM: lymph node metastases**

**Table 5. Multivariate analysis of factors that influence recurrence free survival (RFS) in 58 cases of CCC by Cox regression**

| | HR | CI 95% | 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 |

**Abbreviations: LVI: lympho-vascular invasion; LNM: lymph node metastases**