



## Clear Cell Carcinoma of the Uterine Cervix: A Case Series of Five Patients

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### Abstract:

**Introduction:** Cancer of uterine cervix, the most common cancer in Indian women where it is second most common cancer and the fifth most common cause of cancer deaths in women. Approximately 80% of cervical cancers occur in developing countries. Clear cell carcinoma of the cervix (CCCC) is a rare subset of adenocarcinomas of the cervix that constitutes 10–20% of all the cervical cancer.

**Objective:** To evaluate the treatment options and their clinical outcome for primary clear cell carcinoma of the cervix.

**Methods:** Retrospective analysis of treatment outcomes and response pattern in patients with primary clear cell carcinoma of the cervix presenting at the department of radiotherapy and oncology from January 2004 till December 2010.

**Results:** Five patients with primary clear cell carcinoma of the cervix with average age 49 years with none of them had a family history of cancer or history of DES exposure. One IIA FIGO stage, one IB FIGO stage and three of patients were IIB FIGO stage. Two patients (IB, IIA) underwent Wertheim's hysterectomy. In view of histopathological revelation of the parametrium involvement, two postoperative patients received adjuvant radiotherapy while three patients received radical concurrent chemo-radiotherapy along with weekly cisplatin. On a follow up of 5 years, one patient showed progressive disease and died after 27 month, one patient defaulted follow up and the remaining three patients had no relapse or metastasis and are on routine follow up.

**Conclusion:** Primary clear cell carcinoma of uterine cervix is a rare disease where patients with low risk early stage may be managed with radical surgery alone, with or without the need for adjuvant chemotherapy or radiation. Advanced stage CCCC should be treated with a combination of platinum based chemo-radiotherapy

**Key words:** Uterine Cervical Neoplasms, Clear Cell adenocarcinoma, Hysterectomy, Radiotherapy, Cisplatin.

### Introduction

Cervical cancer is the commonest cancer in Indian women where it is second most common cancer

and the fifth most common cause of cancer deaths in women [1,2]. Approximately 80% of cervical

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cancers occur in developing countries [3]. Clear cell carcinoma of the cervix (CCCC) is a rare subset of adenocarcinomas that constitutes 10–20% of all the cervical cancer [4]. The diagnosis of the tumor is by histology. Histologically the tumor cells have distinct clear, empty appearing cytoplasm and enlarged, hyper-chromatic nuclei, which project into the apical cytoplasm, the so called hobnail appearance. The clear cytoplasm is attributed to the accumulation of abundant glycogen similar in appearance to that seen in secretory endometrial cells. The cells grow predominantly in tubulocystic, papillary or solid pattern. The most favorable outcome is associated with the tubulocystic pattern, followed by the papillary and solid patterns. In early 1970s, studies showed without any in-utero exposure to diethylstilbestrol (DES), CCCC are rare and generally post-menopausal [5,6]. Radical surgery for localized disease with adjuvant chemo-radiation in patients with high-risk tumor characteristics is the current recommendations for management of adenocarcinoma of the cervix [7,8]. In our case series study, we have evaluated 5 cases of CCCC with the objectives of evaluating the treatment options and their clinical outcome.

### Case Series

This is retrospective analysis of treatment outcomes and response pattern in patients with primary clear cell carcinoma of the cervix presenting at the department of radiotherapy and oncology from January 2004 till December 2010. Total five patients with primary clear cell carcinoma of the cervix were registered.

The average age of females in the study was 49 years ranging from 26 to 66 years, belonging to either middle or lower socio-economic strata with at least one child. None of them had a family history of cancer or history of DES exposure. The most common presenting symptom was bleeding per vagina. Three of patients were IIB-FIGO

stage, one IIA-FIGO stage and one IB-FIGO stage. Two of the patients (IB,IIA) underwent Wertheim's hysterectomy, pathologic examination showed bilateral parametrium involvement in one patients and the right parametrium involvement in other patient. Two postoperative patients received adjuvant radiotherapy while three patients received radical concurrent chemo-radiotherapy along with weekly cisplatin. Out of three, two patients received five courses of chemotherapy with cisplatin at 40 mg/m<sup>2</sup>. All patients were added with intracavitary brachytherapy. On a follow up of 5 years, one patient who showed progressive disease died after 27 months, other patient defaulted follow up and the remaining three patients had no relapse or metastasis and are on routine follow up. The median follow-up was 44.5 months ranging from 27 months to 65 months.

**Case 1:** 66 year old post-menopausal women with no other significant medical or family history presented with the complaints of bleeding and discharge per vagina. Per-vaginal examination showed proliferative growth at cervix measuring around 4 cm involving all fornixes, bilateral parametrium were involved medially but not up to lateral pelvic wall and rectal mucosa was free. CT/USG of abdomen showed a mass of size 3.8x3.3 cm at cervix with thickened endometrium and bilateral parametrial involvement. Clinically it appeared to be of FIGO Stage II-B. The biopsy of cervix confirmed the diagnosis of clear cell carcinoma of cervix. The patient was treated with radiotherapy 50 Gy in 25 fractions and 2 doses ICRT in 50 days and 5 cycles of concurrent injection of cisplatin at the dose of 40mg/m<sup>2</sup>. Follow up after 3 months showed progressive disease and the patient succumbed to death 27 months after the start of therapy.

**Case 2:** A 50 year old post-menopausal woman presented with the complaints of bleeding per vagina and a past history of tuberculosis with allergy to sulfa drugs. No significant family history

was noted. Per-vaginal examination showed proliferative growth at cervix measuring around 4 cm involving right fornix, right parametrium involved medially but not up to lateral pelvic wall, free left parametrium and rectal mucosa. CT/USG report showed 4x4 cm mass at cervix with right parametrial involvement. Clinically it appeared to be of FIGO Stage II-B. The biopsy of cervix confirmed the diagnosis of poorly differentiated carcinoma with clear cell histology. The patient was treated with radical concurrent chemo-radiotherapy 50 Gy in 25 fractions and 2 doses of ICRT in 59 days and 5 cycles of injection cisplatin at the dose of 40 mg/m<sup>2</sup>. The patient showed clinically controlled disease on follow-up visits over 29 months.

**Case 3:** A 43 year old pre-menopausal woman with history of diabetes mellitus presented with leucovaria. Per-vaginal examination showed proliferative growth at cervix measuring around 6 cm hanging into vagina, free bilateral parametrium and rectal mucosa. CT/USG showed a mass measuring 4.3x5.4x5.2 cm. Clinically it appeared to be FIGO Stage IB2. Based on the biopsy reports of the uterine cervix, it was diagnosed as adeno-squamous tumor with 10% clear cell carcinoma of the cervix. The patient underwent Wertheim's hysterectomy for the same, histopathology was reported as 7x7x1.5 cm mass infiltrating more than half thickness of cervical stroma along with free bilateral parametrium, vaginal margins and four pelvic lymph nodes [Fig.1]. She received radiotherapy of 50 Gy in 25 fractions and 2 fractions of CVS brachytherapy in 47 days. The patient was doing well following a five year follow-up.

**Case 4:** A 26 year old pre-menopausal woman presented with bleeding per vagina. Per-vaginal examination showed proliferative growth at cervix measuring around 6 cm hanging into vagina, bilateral parametrium were involved medially but not up to lateral pelvic wall and normal rectal mucosa. CT/USG report showed 5.9x5 cm mass at

cervix. Clinically it appears to be FIGO Stage II-B. The biopsy of the uterine cervix confirmed the diagnosis of clear cell carcinoma. The patient was treated with radical concurrent chemo-radiotherapy 50 Gy in 25 fractions and 2 doses of ICRT in 48 days and 5 cycles of injection cisplatin at the dose of 40 mg/m<sup>2</sup>. The follow up details of the patient is not available, as the patient defaulted.

**Case 5:** A 60 year old post-menopausal woman with history of diabetes mellitus and hemiplegia presented with bleeding per vagina. She also had history of tobacco usage. Per-vaginal examination showed proliferative growth at cervix measuring around 4 cm involving anterior fornix, bilateral parametrium are free, rectal mucosa is normal. A mass of 4.5x3.5x2.5 cm was noted on CT/USG. Clinically it appears to be FIGO Stage II-A. A biopsy of the uterine cervix confirmed clear cell carcinoma. The patient underwent Wertheim's hysterectomy for the same [Fig.2], histopathology were reported as 4.5x3.5x1.5 cm mass infiltrating more than half thickness of cervical stroma. She received radiotherapy of 50 Gy in 25 fractions and 2 fractions of CVS brachytherapy in 50 days. The patient was doing well without clinical evidence of any disease, on a follow-up visit after 5 years and 5 months.

## Discussion

Although most cervical carcinomas are squamous, a significant number are adenocarcinomas. Adenocarcinomas are histologically categorized into mucinous, endometrioid, clear cell, serous and mesonephric subtypes [1]. CCCC were a rare type of adenocarcinomas that affected the older women before the DES era and in the DES era, its incidence increased in the adolescent and young women; whose mothers were exposed to DES during pregnancy. Following the ban on DES, non DES associated CCCC are frequent. The median age of patients affected by this disease is 53 years

and mean age of the patients in this series is 49 years. The common symptom is generally irregular vaginal bleeding and the majority of patients (80%) in the series presented with this symptom. The tumor growth is endophytic and tend to show deep infiltration of the cervix and also extend to the uterine corpus more often than other cervical carcinomas [9]. It is histologically characterized by a mixture of clear and hobnail shaped tumor cells arranged in solid masses and papillary tubule [1]. Early-stage CCCCs have a favourable prognosis and retrospective review has shown that patients with early stage disease are amenable to surgery and have a good overall survival. This review also discussed that CCCC patients with bulky tumor, more than half stromal infiltration, positive lymph nodes are at higher risk of recurrence and would appear to benefit from chemo-radiation [8,9]. The prognosis of patients with early stage CCCC treated surgically and noted to be free of lymphatic dissemination is excellent irrespective of the use of adjuvant therapy. Traditional risk factors (positive lymph nodes, positive surgical margins, parametrial involvement, tumor diameter  $\geq 4$  cm, lymph vascular space involvement, and  $\geq 1/3$  cervical stromal involvement) as indications for chemo-radiation should be applied to patients with early stage CCCC. Similarly in our series, two patients had operable disease hence underwent surgery. In view of high risk for recurrence they received adjuvant radiotherapy; both these patients are on regular follow up more than 5 years.

FIGO stage IIB to IIIB, platinum based chemo-radiation improves the local control and overall survival and is the mainstay of treatment. In our series, three patients were stage IIB where two underwent concurrent chemo-radiotherapy; among them one patient progressed and died eventually after 27 months of treatment while other is having controlled disease till date.

Small observation studies have shown that surgery



**Fig.1:** Hysterectomy specimen (case 3).



**Fig.2:** Wertheim's Hysterectomy specimen (case 5).

combined with chemotherapy with carboplatin and 5-FU or paclitaxel may lead to relatively perfect short-term therapeutic effect [10]. In our series, the chemotherapeutic agent used was cisplatin which showed good response in one of the patient.

## Conclusion

Post Diethylstilbetrol era, primary clear cell carcinoma of uterine cervix is a rare disease where patients with low risk early stage CCCC may be managed with radical surgery alone, with or without the need for adjuvant chemotherapy or radiation. Advanced stage CCCC should be treated with a combination of platinum based chemo-radiotherapy [8].

## References

1. Armstrong EP. "Prophylaxis of Cervical Cancer and Related Cervical Disease: A Review of the Cost-Effectiveness of Vaccination Against Oncogenic HPV Types". *Journal of Managed Care Pharmacy*. 2010;16(3):217–230.
2. World Health Organization February. 2006; "Fact sheet No. 297: Cancer". Retrieved 2007-12-01.
3. Kent, A. "HPV Vaccination and Testing". *Reviews in Obstetrics and Gynecology*. 2010;3(1):33–34.
4. Tamini HK, Figge DC. Adenocarcinoma of the uterine cervix. *Gynecol Oncol*.1982;13:335-338.
5. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med*. 1971;284(15):878–881.
6. Errarhay S, Mamouni N, Mahmoud S, El fatemi H, Saadi H, Mesbahi O, *et al*. Primary Malignant Melanoma of the Female Genital Tract: Unusual Localization. *Journal of Case Reports*. 2013;3(1):169-175.
7. Chaudhari T. Primary clear cell adenocarcinoma of the uterine cervix in a young woman not associated with diethylstilbestrol: A case report and review of literature. Available at <http://www.cci-j-online.org/text.asp> 2012/1/4/239/106278. Accessed on 12 September 2013.
8. M. Bijoy Thomas, Jason D Wright, Aliza L Leiser, Dennis S Chi, David G Mutch, Karl C Podratz *et al*. Clear cell carcinoma of the cervix: A multi-institutional review in the post-DES era; *Gynecologic Oncology*. 2008;109:335–339.
9. T. Hiromura, O Tanaka, T Nishioka, M Satoh, M Tomita. Clear cell adenocarcinoma of the uterine cervix arising from a background of cervical endometriosis; *The British Journal of Radiology*. 2009;82:e20–e22.
10. Tan YT, Zhang X, Lin ZQ, Chen Q, Wang LJ, Zhang BZ. Primary clear cell carcinoma of the cervix: report of five cases and review of the literature. *Zhonghua Fu Chan Ke Za Zhi*. 2008;43(2):120-123.