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Clear cell carcinoma of the cervix: A multi-institutional review in the post-DES era

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Abstract

Objective—To conduct an outcome analysis of patients with cervical clear cell carcinoma (CCCC) in the post-DES era.

Methods—A retrospective review was conducted at 3 major gynecologic cancer centers of all primary CCCC between 1982 and 2004.

Results—CCCC was confirmed in 34 patients. Median age was 53 years. DES exposure was confirmed in 2 (6%) patients. A history of smoking was elicited in 22%, and of abnormal Pap smear 18% patients. Primary surgical resection was performed in all stage I or IIA patients ($n=26$); they displayed superior 3-year overall survival (OS) compared to advanced stage ($n=8$) patients (91% vs. 22%, $p<0.001$). Pelvic lymph node involvement was noted in 25%; all patients with positive *para*-aortic nodes (20% of patients sampled) had positive pelvic nodes. All node positive patients were treated with adjuvant radiation, but nevertheless displayed reduced progression free (31% vs 92%, $p<0.001$) and overall survival (80% vs. 100%, $p=0.02$). Adjuvant radiotherapy did not appear to impact OS in patients with negative lymph nodes.

Discussion—This series provides insight into the management of early stage CCCC in the post-DES era. Although these patients may be at slightly higher risk of nodal spread, clear cell histology by itself does not appear to portend a worse prognosis than squamous cell carcinoma of the cervix in the absence of traditional risk factors. Our data suggest that patients with low risk early stage CCCC may be managed with radical surgery alone, without the need for adjuvant chemotherapy or radiation.

Keywords

Cervical clear cell carcinoma; Radical hysterectomy; Systematic lymphadenectomy; Radiation therapy

Introduction

Diethylstilbestrol (DES) was used by 2–4 million American women during pregnancy in the 1950s and 1960s in an attempt to prevent adverse pregnancy outcomes. In 1971 a case-

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control study showed a highly significant association between in utero exposure to DES and subsequent development of vaginal and cervical clear cell adenocarcinoma in adolescents and young women [1,2]. Heretofore, this disease was extremely rare and generally affected older women. In 2007, over thirty years after the ban on DES, DES-associated clear cell carcinoma of the cervix (CCCC) is observed much less frequently than non-DES-associated CCCC. Previous studies suggested important differences in patterns of metastasis and recurrence in these two populations and no clear recommendations for optimal management exist [3–6]. As per the registry for research on Hormonal Transplacental Carcinogenesis, as of 1999, 705 patients with clear cell adenocarcinoma of the cervix and vagina were accessioned among women born after 1948. Among DES-exposed women, clear cell adenocarcinoma occurs in 1 in 1000 [4]. Current recommendations for squamous cell and adenocarcinoma of the cervix include radical surgery for localized disease with adjuvant chemoradiation in patients with high-risk tumor characteristics [7]. It is unclear if these recommendations are in need of modification for patients with CCCC.

The aim of this investigation was to conduct an outcomes analysis of patients diagnosed with CCCC in the post-DES era at 3 major gynecologic cancer centers. We sought to assess the outcomes of radical surgery in patients with early stage disease. We also investigated the role of systemic chemotherapy (CT) and radiation (RT) in CCCC.

Materials and methods

A retrospective review was conducted at 3 major gynecologic cancer centers: Mayo Clinic, Rochester, MN, Washington University School of Medicine, St. Louis, MO, and Memorial Sloan-Kettering Cancer Center, New York, NY. All primary CCCC diagnosed and treated between 1982 and 2004 were collected and characteristics including demographics, pathology, treatment, and follow-up were recorded. The Institutional Review Board of the respective institutions approved this investigation. Assignment to stage was in accordance with the International Federation of Gynecology and Obstetrics (FIGO) criteria for staging cervical cancers [8]. Central pathologic review was conducted at each institution for histologic confirmation.

Surgical treatment consisted of type III, type II, or type I hysterectomy with or without removal of adnexae. Pelvic with or without *para*-aortic lymphadenectomy was performed at the discretion of the attending surgeon. The decision to administer adjuvant RT or CT was predicated on the extent of disease, medical co-morbidities, and institutional practices at that time.

The follow-up period was defined as the time interval between the date of surgery (or diagnosis in non-surgical patients) and either the date of death or the latest date of confirmed survival. We considered as censored all patients who were alive (with or without disease) at the time of follow-up or who died of a cause not related to the disease; patients who died of disease were considered uncensored. Recurrences were designated as vaginal (VR), pelvic (PR), lymphatic (LR), and distant (DR).

JMP statistical package version 5.1 was used for all the analyses (SAS Institute, Inc., Cary, NC 27513). Student's *t* test was used to analyze quantitative data, and Chi square test was used for categorical data. Survival estimates were determined by Kaplan Meier method and comparison between groups was assessed by Log Rank test. A *p*-value <0.05 was considered statistically significant.

Results

CCCC was confirmed in 34 patients. Median age at time of diagnosis was 53 years with 3 patients (9%) diagnosed before age 30. Median BMI was 26.5. Vaginal bleeding was the presenting symptom in 85% of patients; 15% were asymptomatic and diagnosed at routine gynecologic examination. The distribution of DES exposure was as follows: confirmed exposure in 2 patients (6%), confirmed non-exposure in 10 patients (29%), and unknown exposure status in 22 patients (65%). A history of smoking was elicited in 8 (22%). A past history of abnormal Pap smear was noted in 6 (18%) of 31 patients with available information. The stage distribution was 71% ($n=24$) stage I, 6% ($n=2$) stage II, 17% ($n=6$) stage III, and 6% ($n=2$) stage IV. Median follow-up of censored patients was 39 months.

All stages I and IIA patients ($n=26$: IA=2, IB=22, IIA=2) underwent surgery with or without adjuvant RT or CT and are considered separately here. A single patient received preoperative RT. Hysterectomy types were defined as described by Piver et al. [9]. In our series Type I hysterectomies were performed in 3 (12%) patients, type II in 11 (42%), and type III in 12 (46%) patients. On pathologic review of the 26 stages I and IIA tumors, distribution of largest tumor diameter was as follows: 4 (15.5%) no residual tumor, 4 (15.5%) 1 cm, 3 (11%) >1 cm but 2 cm, 8 (31%) >2 cm but 4 cm, and 7 (27%) >4 cm. The 4 patients with no residual disease included 2 patients each with stages IA and IB disease (1 of the IB patients had received preoperative RT, the other had preoperative diagnostic cone).

Pelvic lymphadenectomy (PLND) was performed in 24 (92%) stage I or IIA patients yielding a median of 27 nodes (range 7 to 63). *Para*-aortic lymphadenectomy (PALND) was performed in 15 (58%) patients yielding a median of 4 nodes (range 1 to 14). Metastatic pelvic lymph nodes were present in 6 patients (25%), 4 of whom demonstrated lymphovascular space involvement, 2 parametrial involvement, and 1 a metastatic implant in the cul-de-sac. The rate of lymph node involvement progressively increased with tumor size, from 21% for those measuring less than 4 cm to 29% for those measuring 4 cm or more. Mean tumor diameter of patients with positive lymph nodes was 3.5 cm. *Para*-aortic lymph nodes were involved in 3 (20%) patients, all of whom also had positive pelvic lymph nodes.

There were 3 immediate postoperative complications: 1 ureteral obstruction that required nephrostomy tube placement and eventually permanent intermittent self-urinary catheterization, 1 wound infection, and 1 prolonged ileus. There were 3 late complications: 1 patient who required permanent intermittent self-urinary catheterization (described above), 1 with lower extremity lymphedema, and 1 small bowel obstruction. All 3 patients with late complications had undergone type III hysterectomy without adjuvant RT.

Adjuvant RT (13 pelvic RT with or without *para*-aortic boost, 1 vaginal brachytherapy (VB)) was administered in 14 (54%) stages I and IIA patients. The median dose of pelvic RT was 5040cGy, and 7 (50%) received concomitant chemo-sensitization. Chemotherapy was platinum based with or without 5-fluorouracil. All 6 patients with positive lymph nodes received post-operative RT and 4 also received CT.

The 5-year progression free survival (PFS) and overall survival (OS) for all 34 patients were 65% and 75% respectively. As expected, stage I or IIA patients had a better 3-year OS compared to stage III or IV patients (91% vs. 22%, $p<0.001$) (Fig. 1). Tumor size, grade, and ovariectomy had no impact on PFS or OS. The presence of positive lymph nodes had a negative impact on 5-year PFS (31% vs. 92%, $p<0.001$) and 5-year OS (80% vs. 100%, $p=0.02$) in the stages I and IIA CCCC patients (Fig. 2).

There were 5 documented recurrences among the 26 early stage CCCC patients (Table 1). There were 3 VR and 2 DR. No residual tumor was noted in the hysterectomy specimen in 2 of these 5 patients, but 3 patients had positive lymph nodes. The stage IA patient with no residual tumor and a negative lymph node assessment was diagnosed with a vaginal recurrence 47 months following surgery. This patient also had a history of vaginal adenosis, and thus it is unclear if this represented a true recurrence or a new primary vaginal cancer. A second patient with a VR had stage IB disease and no residual tumor after hysterectomy. She received pre-operative radiation and the lymph nodes were not assessed at simple hysterectomy. The remaining three patients all had metastatic lymph nodes and all received adjuvant RT, 2 with concomitant CT. The median time to recurrence was 12 months (range 7 to 47).

18 patients who underwent hysterectomy and LND for stage I or IIA CCCC had negative lymph nodes. Adjuvant RT was nonetheless given to 5 patients while the remainder received no adjuvant therapy. Adjuvant radiation therapy did not impact PFS or OS in stage I or IIA patients with CCCC and negative lymph nodes.

Advanced CCCC (6 stage III, and 2 stage IV) was diagnosed in 8 patients. All received RT and 5 received platinum based CT. 2-year OS for stages III and IV was 50% and 0% respectively. 5 patients died of disease, 2 were with no evidence of disease at last follow-up, and 1 was alive with disease. Of the 5 patients who died of disease, distant recurrences occurred in 3, progression of pelvic disease occurred in one, and progression of both pelvic and distant disease occurred in another. Two patients without evidence of disease at 30 and 40 months follow-up were stage III at diagnosis and had received RT.

Discussion

An association between in utero DES exposure and clear cell adenocarcinoma of the vagina was identified in the early 1970s, leading to a ban on its use in pregnancy [1,2]. Herbst and Hanselaar et al. have reported on large series of clear cell carcinomas of the vagina and cervix [4,10]. Herbst reviewed 705 patients with clear cell adenocarcinoma of the cervix and vagina born between 1948 and 1999, identified through the US Registry for Research on Hormonal Transplacental Carcinogenesis. This series included both vaginal and cervical adenocarcinoma, in DES-exposed and unexposed patients [4]. Hanselaar et al. reviewed 88 patients identified through the central Netherlands Registry with vaginal and cervical clear cell carcinoma born after 1947 and followed until 1993 [10]. In this retrospective review we describe 3 major gynecologic cancer center's experience in treating CCCC spanning 23 years (1982–2004). In contrast to the Herbst and Hanselaar et al. series, the majority of our cases occurred in the post-DES era, many received chemo-radiation, and vaginal clear cell carcinomas are excluded from analysis. The surgical outcomes are specifically examined in an attempt to identify risk factors for recurrence in early stage CCCC. We sought to assess the role of surgery with LND, and determine which patients would potentially benefit from adjuvant therapy.

It is noteworthy that CCCC is no longer a disease affecting teens and young adults; median age was 53 years. This finding is consistent with the description of Hanselaar et al. of a bimodal age distribution at a mean of 26 years and 71 years [10,11]. The early peak contained all DES-exposed patients. In our series 3 patients (9%) were younger than 30 years at diagnosis and a history of confirmed in utero DES exposure was elicited in only 2 (6%).

Our data suggest that several clinical characteristics associated with CCCC differ from squamous cell carcinoma of the cervix including advanced age, lack of smoking history, and

a lower frequency of abnormal cervical cytology. As previously stated by other authors, this may be a reflection of etiological differences between various histological subtypes of cervical cancer [12,13]. Goto et al. reported a synchronous case of cervical squamous cell cancer and CCCC in which HPV was detected in the squamous component, but not in the clear cell component of the tumor [14]. The potential absence of a precursor lesion, as well as reports that many non-DES-exposed CCCC are endophytic lesions, may account for a lower rate of abnormal pap smears [5].

However, aside from demographics and risk factors, there are more similarities between CCCC and squamous cell carcinoma of the cervix than differences. Clear cell histology by itself does not appear to portend a poor prognosis. In our series all stage I or IIA CCCC were amenable to surgical resection and displayed excellent overall survival (91%). Other studies have reported similar survival for early CCCC [4,5,10]. Although tumor size >4 cm was not an adverse risk factor in this series, this was likely to be a reflection of small sample size. Hanselaar et al. reported tumor size >4 cm as an important negative prognostic factor, similar to patients with squamous cancers [10,11]. Furthermore, nodal status appears to be a strong predictor of OS and PFS (Fig. 2). In our series 25% of patients had positive lymph nodes with a corresponding reduction in both PFS (31% vs. 92%, $p<0.001$) and OS (80% vs. 100%, $p=0.02$). Herbst reported a 17% node positivity rate in stage I CCCC [4]. Reich et al. noted that 47% of 15 patients with stages IB–IIB non-DES-exposed CCCC who underwent radical hysterectomy and PLND had nodal metastases. He noted a 27% recurrence rate, all of which were in lymph node positive patients [5]. A similar, but slightly lower rate of lymphatic involvement (10–21%) associated with compromised survival has been reported in patients with stages IB–II squamous cell carcinoma of the cervix [15–18]. As has been observed in patients with squamous cell carcinoma of the cervix, patients CCCC and positive lymph nodes are at higher risk of recurrence and would appear to benefit from chemo-radiation.

Of the 18 node negative patients there was only one recurrence, although this occurred at 47 months and may have been a new primary vaginal cancer. Our data do not support the use of radiation in node negative patients to improve PFS or OS. However, given the small sample size, particularly for patients with stage IB lesions, we recommend that adjuvant radiation be administered to high risk, node negative patients in a similar way it is given in patients with high risk stage I squamous cell carcinoma (parametrial involvement, positive surgical margins, >4 cm tumor diameter, lymph vascular space involvement, or >2/3 invasion through cervical stroma) [7,19].

We note a high incidence of metastatic involvement of PALN (20%) in patients who underwent PALND. However this is based on a small sample ($n=15$) and these patients may have been selected for PALND due to a high suspicion for lymphatic spread. All patients with positive PALN had metastatic involvement of PLN. Therefore, we recommend PALND in all patients noted to have positive PLN to help define the extent of the radiation field. Similarly, in a study of patients with cervical squamous cell carcinoma, Benedetti-Panici et al. noted that all patients with PALN involvement had positive PLN [16]. Sakuragi noted PLN involvement as an independent risk factor for PA involvement and has suggested removal of PALN if PLN are positive for tumor involvement [18].

Prolonged follow-up is important in CCCC patients. In our series median time to recurrence was 12 months, similar to Reich et al. [5]. However we noted 2 VR at 31 and 47 months. We also noted a secondary recurrence 61 M from the primary VR treated with total exenteration (92 M from initial surgery). Herbst reported 8 recurrences in stages I and II CCCC that occurred 8 or more years from initial therapy [4]. Jones et al. describe an abdominal recurrence in a CCCC patient 4.5 years after primary surgery [20].

Patients with advanced CCCC have a poor survival similar to that reported for advanced stages of other cervical cancer histologies [21]. In our series all 8 patients were treated with radiation therapy and 5 died of disease. Radiotherapy appears to be effective in local control, as only 2 of the 8 (25%) patients showed progression of pelvic disease. However, these patients are obviously at high risk of DR and may benefit from systemic CT considering that 3 of the 5 patients who died of disease had DR, and 1 had progression of distant disease.

The retrospective nature of this study, the small numbers of patients, and the fact that the pathological review was conducted at 3 different institutions are sources of bias. Despite the above limitations our investigation provides insight into the management of CCCC in the post-DES era. The prognosis of patients with stages I and IIA CCCC treated surgically and noted to be free of lymphatic dissemination is excellent irrespective of the use of adjuvant therapy. This series provides little information on the optimal treatment of patients with high-risk early stage disease. Traditional risk factors (positive lymph nodes, positive surgical margins, parametrial involvement, tumor diameter >4 cm, lymph vascular space involvement, and >1/3 cervical stromal involvement) as indications for chemoradiation should be applied to patients with early stage CCCC, but the clear cell carcinoma histology by itself does not appear to portend poor survival. It should be recognized that the rate of lymphatic involvement appears to be slightly higher for patients with CCCC; however, our data suggest that patients with low risk early stage CCCC may be managed with radical surgery alone, without the need for adjuvant chemotherapy or radiation. Advanced stage CCCC should be treated with a combination of RT and CT. In contrast to squamous cell carcinoma of the cervix, data from small series suggest that CCCC does not appear to be associated with HPV infection [13]. Thus, the HPV vaccine would not be expected to impact the prevalence of CCCC. Despite the discontinuation of DES in pregnancy, CCCC may represent a small, yet growing proportion of cervical cancer cases as the HPV vaccine becomes incorporated into health care delivery.

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Fig. 1. Kaplan Meier plot of overall survival (OS) in stages I and IIA vs. stages III and IV CCCC. 3-year OS for early stage ($n=26$) vs. advanced stage ($n=8$) CCCC was 91% vs. 22%, $p<0.001$.

Fig. 2.

Kaplan Meier plot of progression free survival (PFS) for stages I–IIA CCCC with or without nodal involvement. 5-year PFS for patients with ($n=6$) and without ($n=18$) nodal involvement was 31% vs. 92% ($p<0.001$).

Table 1

Characteristics of recurrences in stage I CCCC

Stage	Tumor diameter	LND	LN metastases	RT	CT	Recurrence
IA	No residual tumor	Yes	No	No	No	VR vs. new vaginal primary at 47 M treated with RT AWD
IB	1.7 cm	Yes	Yes	Yes	Cisplatin+Taxol+Adriamycin	DR at 7 M
IB	4.5 cm	Yes	Yes	Yes	Cisplatin	DOD at 20 M
IB	5.8 cm	Yes	Yes	Yes	No	DR at 12 M
IB	No residual tumor	No	Not assessed	Pre-operative	Cisplatin+5-FU	NED at 84 M
						VR at 31 M treated with total exent
						DOD at 92 M of DR
						VR at 11 M
						DOD 32 M

LND = lymphadenectomy, LN = lymph node, RT = radiation therapy, CT = chemotherapy, M = months, VR = vaginal recurrence, DR = distant recurrence, AWD = alive with disease, DOD = dead of disease, NED = no evidence of disease.