

Case Report

Definitive radiation therapy for an elderly Japanese patient with advanced clear cell adenocarcinoma of the uterine cervix: a rare case report and review of the literature

Naoya Ishibashi¹, Toshiya Maebayashi¹, Takuya Aizawa¹, Masakuni Sakaguchi¹, Takahiro Nakajima², Yoshiaki Kusumi³

Departments of ¹Radiology, ²Obstetrics and Gynecology, ³Pathology and Microbiology, School of Medicine, Nihon University, Itabashi-ku, Tokyo 173-8610, Japan

Received December 22, 2016; Accepted June 5, 2017; Epub July 15, 2017; Published July 30, 2017

Abstract: Cervical clear cell adenocarcinoma is rare in Japanese patients, and such patients are generally older than those from other countries. We herein describe a case involving radiation therapy for cervical clear cell adenocarcinoma in the most elderly patient reported to date. An 84-year-old Japanese woman presented with lower abdominal pain. Magnetic resonance imaging and colposcopy revealed hematometra and a mass in the uterine cervix. Examination of a biopsy specimen showed invasive growth of cancer cells with glycogen-positive clear cytoplasm. Immunohistochemical examination revealed expression of hepatocyte nuclear factor 1- β in the nucleus, resulting in a diagnosis of clear cell adenocarcinoma. Radiation therapy comprised external irradiation and high-dose-rate remote afterloading brachytherapy. Upon treatment completion, multiple pulmonary metastases and peritoneal dissemination were observed, but the primary tumor exhibited a complete response 1 month after radiation therapy. We conclude that pelvic radiation therapy and brachytherapy can be safely administered to elderly Japanese patients with cervical clear cell adenocarcinoma.

Keywords: Clear cell adenocarcinoma, definitive, elderly patient, radiation therapy, uterine cervix

Introduction

Cervical clear cell adenocarcinoma (CCAC) is very rare and constitutes 4% of all adenocarcinomas of the uterine cervix [1]. In the United States and the Netherlands, studies have suggested a link between cervical CCAC and exposure to diethylstilbestrol (DES), a synthetic estrogen prescribed to prevent miscarriage [2]. In Japan, DES has never been available and cervical CCAC is rare. In a study that reviewed 32 cases of cervical CCAC in Japanese patients, the mean age of the patients was 50.8 ± 19.6 years, which is relatively higher than in other countries [3]. For this reason, definitive radiation therapy is often chosen over surgery in Japan. We herein report a case involving definitive radiation therapy with brachytherapy for treatment of cervical CCAC in an 84-year-old Japanese patient. This patient is the oldest

reported to date among studies of definitive radiation therapy for cervical CCAC.

Case report

An 84-year-old Japanese woman presented with lower abdominal bloating and pain. Computed tomography (CT) revealed hematometra, and magnetic resonance imaging (MRI) showed a mass in the uterine cervix. Colposcopy revealed an elevated mass in the uterine cervix, from which tissue samples were collected for biopsy. Histological examination showed proliferation of neoplastic epithelial cells with clear cytoplasm and marked nuclear atypia. The cytoplasm contained Periodic acid-Schiff (PAS)-positive material. After diastase digestion, the PAS staining became negative and the presence of glycogen was confirmed (**Figure 1A, 1B**). Furthermore, immunohistochemical

Radiation therapy for cervical CCAC

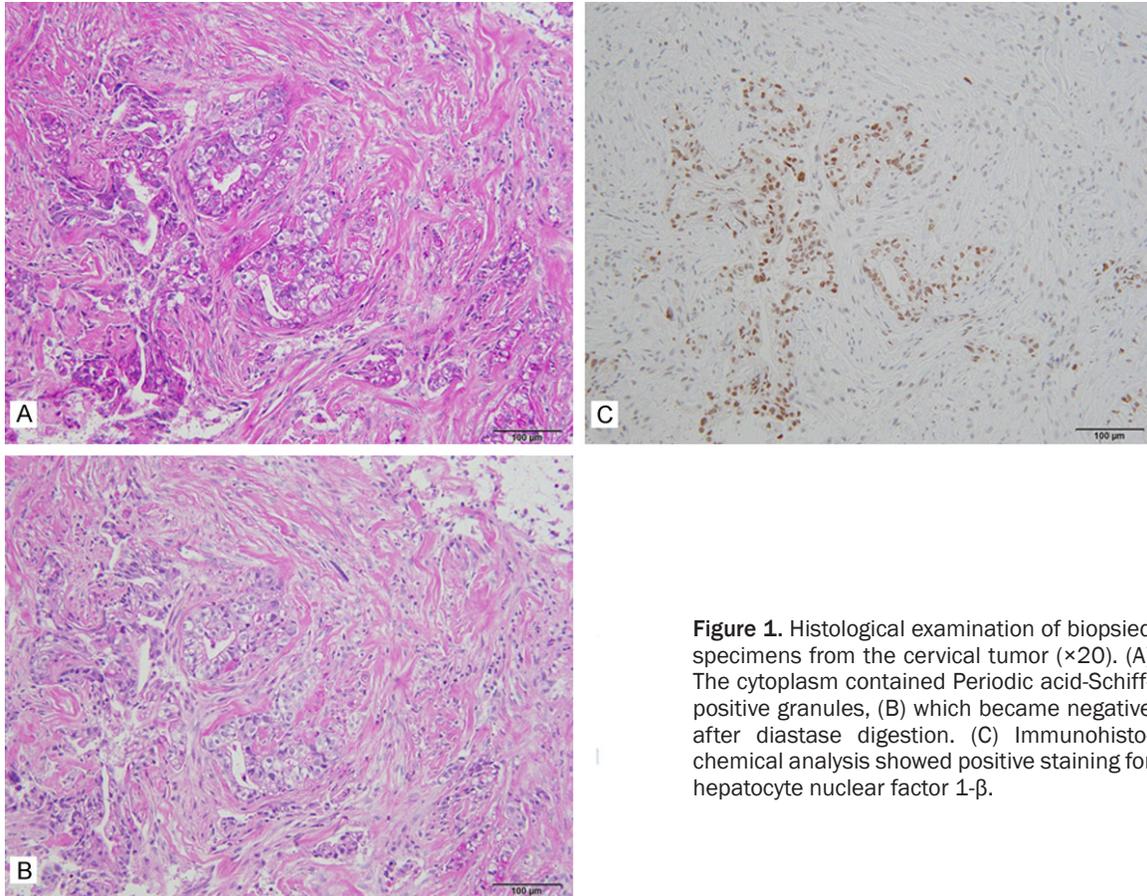


Figure 1. Histological examination of biopsied specimens from the cervical tumor ($\times 20$). (A) The cytoplasm contained Periodic acid-Schiff-positive granules, (B) which became negative after diastase digestion. (C) Immunohistochemical analysis showed positive staining for hepatocyte nuclear factor 1- β .

analysis showed positive staining for hepatocyte nuclear factor 1- β (HNF-1 β) (**Figure 1C**). Based on the above findings, the patient was diagnosed with cervical CCAC. The cells were estrogen receptor-negative, and the patient had not been prenatally exposed to DES. The cervical tumor extended to the pelvic wall and was classified as stage IIIB according to the International Federation of Gynecology and Obstetrics staging system. Despite her advanced age, the patient's Eastern Cooperative Oncology Group performance status score was good at 1; therefore, we decided to pursue definitive treatment and selected chemoradiotherapy because of multiple pelvic lymph node metastases. The radiation therapy was administered to the whole pelvic region encompassing the pelvic lymph node metastases and comprised external irradiation at a dose of 21.6 Gy (1.8 Gy/fraction), high-dose-rate remote afterloading brachytherapy at 24 Gy (6 Gy to point A, 1 fraction/week), and external irradiation with a central shield at 23.4 Gy (1.8 Gy/fraction). Concurrent chemotherapy was administered

with weekly cisplatin at 40 mg/m²; however, after one cycle of treatment, the patient developed hyponatremia caused by the syndrome of inappropriate antidiuretic hormone secretion, necessitating discontinuation of chemotherapy. Grade 1 dermatitis was the only side effect of the radiation therapy. Immediately after completion of the radiation therapy, multiple pulmonary metastases and peritoneal dissemination were noted. MRI performed after completion of the radiation therapy showed that the primary tumor in the cervix had decreased in size, and a cervical biopsy showed no malignant cells. The primary tumor was rated as showing a complete response according to the Response Evaluation Criteria in Solid Tumors, version 1.1. The patient was being followed up under strict monitoring at the time of this writing.

Discussion

CCAC is a histologically rare cervical cancer. The disease is even rarer in Japan, where DES has never been available. According to previ-

Radiation therapy for cervical CCAC

Table 1. Definitive radiation therapy and outcomes in patients with cervical CCAC

| Report | Number of cases | Age (years) | FIGO stage (n) | Radiation Therapy | Chemotherapy (schedule) | Outcome |
|------------------------|-----------------|-------------------|-------------------------|--|---|---|
| Kaminski et al. [8] | 4 | 30-67 median 60.5 | IB (1), IIA (2) IIB (1) | IB case GTV 72 Gy other cases not mentioned | None | IB case DOD, 108 months after RT IIA case NED, 12 months after RT IIA case Lost IIB case Alive, 84 months after RT |
| Ding et al. [9] | 1 | 19 | IB2 (1) | Pelvis 45 Gy Brachytherapy 15 Gy | None | NED, 24 months after RT |
| Chan et al. [10] | 1 | 14 | IIIA (1) | whole pelvis 40 Gy and with central shield 14 Gy brachytherapy 24 Gy | Carboplatin + paclitaxel Carboplatin + gemcitabine (after RT) | NED, 12 months after chemotherapy |
| Thomas et al. [11] | 8 | NA | III (6), IV (2) | NA | 5 received platinum based (concurrent) | 2-year OS for stage III 50% 2-year OS for stage IV 0% |
| Ansari et al. [12] | 1 | 14 | IIIA (1) | GTV and LN meta 45 Gy Brachytherapy 34 Gy | Cisplatin (concurrent) | NED, 24 months after RT |
| Taga et al. [13] | 1 | 69 | IIIB (1) | Whole pelvis 50 Gy | None | Radical hysterectomy with lymphadenectomy NED, 28 months after surgery |
| Ferrandina et al. [14] | 1 | 39 | IB2 (1) | Whole pelvis 40 Gy GTV 50 Gy | Cisplatin + 5-fluorouracil (concurrent) | Radical hysterectomy with lymphadenectomy NED, 18 months after diagnosis |
| Our case | 1 | 84 | IIIB (1) | Whole pelvis 45 Gy Brachytherapy 24 Gy | Cisplatin (concurrent) | |

Abbreviations: CCAC = clear cell adenocarcinoma; NA = not available; GTV = gross tumor volume; LN = lymph node; RT = radiation therapy; DOD = died of disease; NED = no evidence of disease; OS = overall survival.

ously published Japanese statistics in 2000, only 2 of 621 (0.3%) cases of cervical cancer were diagnosed as CCAC [4]. The cervical cancer in the present case contained glycogen and was positive for HNF-1 β , which led to the diagnosis of CCAC. HNF-1 β is a transcription factor expressed in association with glycogen accumulation and has recently been identified as an excellent marker for clear cell carcinoma of the endometrium [5]. Cervical CCAC is often detected at an early stage, and curative surgery with pelvic lymphadenectomy is usually selected as the primary treatment in such cases [6]. However, few reports have described the treatment of advanced-stage cervical CCAC, and an optimal treatment strategy has yet to be established. Even in the latest treatment guidelines (National Comprehensive Cancer Network guidelines for cervical cancer 2016), no distinctions in treatment plans are made among different histological types, such as squamous cell carcinoma and adenocarcinoma [7]. For stage IIB tumors with pelvic lymph node-positive adenopathy, as in the present case, the recommended treatment plan involves pelvic radiation therapy, concurrent cisplatin-containing chemotherapy, and brachytherapy. We selected chemoradiotherapy in accordance with the guidelines. Past studies have provided detailed information on the treatments and clinical courses of 17 patients with cervical CCAC treated with definitive radiation therapy; among those 17 patients, only 11 had advanced-stage cervical CCAC classified as stage III or IV [8-14]. The patient in our study is the 12th case and the oldest reported to date among studies of definitive radiation therapy for cervical CCAC. A summary of these previous cases and ours is shown in **Table 1**. The total radiation doses used in the past varied, ranging from 45 to 72 Gy in definitive radiation therapy and from 15 to 34 Gy in brachytherapy. Most of the concurrent chemotherapy was platinum-based. Only a few studies have focused on treatment outcomes in cervical CCAC, and the differences from those in squamous cell carcinoma remain unclear. In a study of 34 cases of cervical CCAC, stage I or IIA had better 3-year overall survival than stage III or stage IV (91% vs. 22%, respectively), while the 2-year overall survival for stage III was 50% and that for stage IV was 0% [11]. Among five patients who died of stage III or IV cervical CCAC, three had distant metastases, which the authors stated should

be treated with a combination of radiation therapy and chemotherapy. However, cervical CCAC treatment outcomes reported in other countries include cases of juvenile onset resulting from DES exposure; therefore, their findings may not be applicable to elderly-onset cervical CCAC in Japan. There is also a report that *in vitro* CCAC of the ovary is highly radiosensitive [15], giving rise to the possibility that CCAC may respond to radiation therapy better than other histological types. In our case, the primary cervical tumor had maintained its reduced size at the time of this writing, 1 month after the completion of radiation therapy.

In conclusion, we were able to administer pelvic radiation therapy and brachytherapy, the standard treatment for other types of advanced-stage cervical cancer, in a safe and effective manner in an elderly Japanese patient with advanced-stage cervical CCAC. Because many cases of cervical CCAC in Japan are elderly-onset, definitive radiation therapy may be selected more frequently in the future.

Acknowledgements

Informed consent was obtained from the patient for publication of this report.

Disclosure of conflict of interest

None.

Address correspondence to: Naoya Ishibashi, Department of Radiology, School of Medicine, Nihon University, 30-1 Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan. Tel: +81 339728111; Fax: +81 339582454; E-mail: ishibashi.naoya@nihon-u.ac.jp

References

- [1] Noller KL, Decker DG, Dockerty MB, Lanier AP, Smith RA, Symmonds RE. Mesonephric (clear cell) carcinoma of the vagina and cervix. A retrospective analysis. *Obstet Gynecol* 1974; 43: 640-644.
- [2] Horwitz RI, Viscoli CM, Merino M, Brennan TA, Flannery JT, Robboy SJ. Clear cell adenocarcinoma of the vagina and cervix: incidence, undetected disease, and diethylstilbestrol. *J Clin Epidemiol* 1988; 41: 593-597.
- [3] Seki H, Takada T, Sodemoto T, Hoshino H, Saitoh K, Uekusa T. A young woman with clear cell adenocarcinoma of the uterine cervix. *Int J Clin Oncol* 2003; 8: 399-404.

Radiation therapy for cervical CCAC

- [4] Kase H, Kodama S, Kurabayashi T, Tanaka K, Nagai E, Yamada K. Clear cell carcinoma of the uterine cervix. A report of two cases. *J Jpn Soc Clin Cytol* 2000; 39: 527-530.
- [5] Yamamoto S, Tsuda H, Aida S, Shimazaki H, Tamai S, Matsubara O. Immunohistochemical detection of hepatocyte nuclear factor 1beta in ovarian and endometrial clear-cell adenocarcinomas and nonneoplastic endometrium. *Hum Pathol* 2007; 38: 1074-1080.
- [6] Hasegawa K, Nagao S, Yasuda M, Millan D, Viswanathan AN, Glasspool RM, Devouassoux-Shisheboran M, Covens A, Lorusso D, Kurzedler C, Kim JW, Gladielf L, Bryce J, Friedlander M, Fujiwara K. Gynecologic Cancer InterGroup (GCIg) consensus review for clear cell carcinoma of the uterine corpus and cervix. *Int J Gynecol Cancer* 2014; 24: S90-95.
- [7] Koh WJ, Greer BE, Abu-Rustum NR, Apte SM, Campos SM, Cho KR, Chu C, Cohn D, Crispens MA, Dorigo O, Eifel PJ, Fisher CM, Frederick P, Gaffney DK, Han E, Huh WK, Lurain JR 3rd, Mutch D, Fader AN, Remmenga SW, Reynolds RK, Teng N, Tillmanns T, Valea FA, Yashar CM, McMillian NR, Scavone JL. Cervical cancer, version 2.2015. *J Natl Compr Canc Netw* 2015; 13: 395-404; quiz 04.
- [8] Kaminski PF, Maier RC. Clear cell adenocarcinoma of the cervix unrelated to diethylstilbestrol exposure. *Obstet Gynecol* 1983; 62: 720-727.
- [9] Ding DC, Chang FW, Yu MH. Huge clear cell carcinoma of the cervix in teenager not associated with diethylstilbestrol: a brief case report. *Eur J Obstet Gynecol Reprod Biol* 2004; 117: 115-116.
- [10] Chan KK, Ip P, Kwong P, Tam KF, Ngan HY. A combination of chemoradiation and chemotherapy for treatment of advanced clear cell adenocarcinoma of the cervix. *Int J Gynecol Cancer* 2008; 18: 559-563.
- [11] Thomas MB, Wright JD, Leiser AL, Chi DS, Mutch DG, Podratz KC, Dowdy SC. Clear cell carcinoma of the cervix: a multi-institutional review in the post-DES era. *Gynecol Oncol* 2008; 109: 335-339.
- [12] Ansari DO, Horowitz IR, Katzenstein HM, Durham MM, Esiashvili N. Successful treatment of an adolescent with locally advanced cervicovaginal clear cell adenocarcinoma using definitive chemotherapy and radiotherapy. *J Pediatr Hematol Oncol* 2012; 34: e174-176.
- [13] Taga S, Haraga J, Sawada M, Nagai A, Yamamoto D, Hayase R. Two cases of clear cell adenocarcinoma of the cervix. *Mod Trends Obstet Gynecol* 2013; 62: 95-100.
- [14] Ferrandina G, Lucidi A, De Ninno M, Carbone A, Chiantera V, Morganti AG, Macchia G. Successful treatment of a young patient with locally advanced clear cell adenocarcinoma of the uterine cervix undergoing chemoradiation followed by radical surgery. *Gynecol Obstet Invest* 2014; 77: 64-67.
- [15] Saga Y, Suzuki M, Machida S, Ohwada M, Sato I. Establishment of a new cell line (TAYA) of clear cell adenocarcinoma of the ovary and its radiosensitivity. *Oncology* 2002; 62: 180-184.