Original Article

J Gynecol Oncol Vol. 22, No. 1:39-43
DOI:10.3802/jgo.2011.22.1.39

pISSN 2005-0380
eISSN 2005-0399

Journal of Gynecologic Oncology
JGO

Pap smear screening for small cell carcinoma of the uterine cervix: a case series and review of the literature

Hyun Jong Park, Young Mi Choi, Chan Kyung Chung, San Hui Lee, Ga Won Yim, Sang Wun Kim, Eun Ji Nam, Young Tae Kim

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, Korea

Objective: Small cell carcinoma of the uterine cervix (SMCC) is extremely rare, and an aggressive disease that proliferates rapidly. It was often reported that the diagnostic accuracy of cytologic smears in diagnosing SMCC was low. This is a report of the Severance Hospital experience with the patients suffering from SMCC.

Methods: Twenty-seven patients with small cell carcinoma of the uterine cervix were diagnosed and treated at the Severance Hospital from November 1991 to January 2010. The data were analyzed retrospectively, based on the available charts and pathology reports. Various fields, such as chief complaints and symptoms present at first clinic visit, age, International Federation of Obstetrics and Gynecology (FIGO) clinical stage, treatment modality, the 5-year overall survival rate, and recurrence rate were investigated.

Results: Among the 27 patients diagnosed with small cell carcinoma of the uterine cervix, 18 of them (66.7%) presented with symptoms, including vaginal bleeding, at the first clinic visit, and the remaining 9 patients (33.3%) showed abnormal Pap smear screening in the process of their routine health check-up. The median age of the patients was 54 years (range, 24 to 77 years). FIGO stage IIB was the most common stage (11 of 27 patients). The 5-year overall survival rate of 21 patients, who could be followed up, was 57.2%. Six patients showed recurrence after remission, and the mean disease free interval of them was 9.2 months (range, 6 to 11 months). Abnormal Pap smear screening results of 9 patients was investigated, and the diagnostic accuracy of the cytologic findings was 22.2%.

Conclusion: Our study was consistent with the concept that Pap smear screening might not be helpful in early diagnosis of SMCC considering its low diagnostic accuracy. Further large-scale multicenter prospective studies are definitely needed in order to produce abundant information about optimal therapy and diagnosis.

Keywords: Small cell carcinoma, Uterine cervix, Low prevalence, Pap smear, Survival rate, Recurrence

INTRODUCTION

Small cell carcinoma of the uterine cervix (SMCC), which comprises about 2% to 5% of most cervical malignancies, tends to be progressive at an early stage, with metastasis to distant organs and lymph nodes, and is known to have a worse prognosis than squamous cell carcinoma or adenocarcinoma of the uterine cervix [1-3].

Due to the rarity of SMCC, previously reported studies were all conducted in a single institution with a limited number of patients with prognostic factors, such as tumor size and International Federation of Obstetrics and Gynecology (FIGO)

Received Aug. 29, 2010, Revised Nov. 14, 2010, Accepted Nov. 21, 2010

Correspondence to Young Tae Kim
Department of Obstetrics and Gynecology, Yonsei University College of Medicine, 250 Seongsanno, Seodaemun-gu, Seoul 120-752, Korea. Tel: 82-2-2228-2230, Fax: 82-2-313-8357, E-mail: ytkchoi@yuhs.ac

stage [4,5], which led to the conclusion that early detection of the disease is important.

The Pap test is a screening test initially introduced to clinical services by George N. Papanicolau in 1939. It has been proved that the test is effective to decreasing the frequency and recurrence rate of the invasive cervical cancer as well as the mortality rate due to the disease. The Pap test is also known to have contributed to prominently cordoning off the development of the invasive cervical cancer through detecting and treating the cervical intraepithelial neoplasia, the very prior stage of the disease [6].

However, in the case of SMCC, the earlier detection rate of SMCC was relatively low due to the rare prevalence of the disease, a growth pattern downward into the epithelium while maintaining a normal epithelium, and the relative tumor location at a high endocervical portion [7,8]. In these regards, it was often reported that, as a screening test, the Pap test for SMCC seemed to be destitute of its diagnostic values and effectiveness itself [9-11].

The aim of this study is to review the Severance Hospital experience in the patients suffering from the SMCC with a review of the literature.

MATERIALS AND METHODS

Twenty-seven patients with small cell carcinoma of the uterine cervix were diagnosed and treated at the Severance Hospital from November 1991 to January 2010. The clinical symptoms and chief complaints of the patients at their first clinic visit, age, FIGO clinical stage, and treatment modalities were investigated. The FIGO classification system was used for the determination of disease stages. The survival rate of patients was identified by means of correspondence and telephone.

Physical examination, including Pap smears, of patients was performed every 3 months after treatment. The abdominal and pelvic computed tomography and the magnetic resonance imaging were performed every 6 months, and the patients were carefully followed up. When recurrence was suspected, bone scan and other imaging studies were performed, and biopsy was used to confirm the recurrence, if necessary. If recurrent disease was confirmed, radiation therapy and combination chemotherapy followed. The data were analyzed retrospectively based on the available charts and obtained from pathology reports.

RESULTS

Twenty-seven patients with small cell carcinoma of the uterine cervix were diagnosed between November 1991 and January 2010. Among 27 patients, 18 of them (66.7%) showed symptoms, including vaginal bleeding, at their first clinic visit, and the remaining 9 patients (33.3%) showed abnormal Pap smear screening in the process of their routine health check-up, which were the chief complaints at the first clinic visit. It was reported that the median age of the patients were 54 years (range, 24 to 77 years). Eight of 27 patients were less than 45 years old. FIGO stage IIB was the most common stage (11 of 27 patients) followed by stage IB (9 of 27 patients). In terms of treatment modalities, there were 6 cases (23.1%) who received adjuvant radiation therapy or chemotherapy after radical hysterectomy. In 17 cases (65.4%), combination chemoradiation therapy was performed. Three patients (11.5%) received radical hysterectomy following neoadjuvant chemotherapy (Table 1).

The 5-year overall survival rate of 21 patients, who could be followed up, was 57.2%. During the follow-up after primary treatment, 16 cases (59.3%) were reported to be in complete remission status. Six patients showed recurrence after

Table 1. Clinical characteristics of the patients

Characteristics	Values
Total number of patients	27
Age (yr), median (range)	54 (24-77)
Age distribution (yr)	
<45	8 (29.6)
≥45	19 (70.4)
Stage	
IA	0 (0.0)
IB	9 (33.3)
IIA	1 (3.7)
IIB	11 (40.8)
III	4 (14.8)
IV	2 (7.4)
Reason for initial clinic visit	
Abnormal Pap smear screening	9 (33.3)
Symptoms such as vaginal bleeding	18 (66.7)
Treatment	
RH+adjuvant RTx or CTx	6 (23.1)
Chemoradiation Tx	17 (65.4)
Neoadjuvant CTx+RH+adjuvant Tx	3 (11.5)

Values are presented as number (%) unless otherwise indicated.
RH: radical hysterectomy, RTx: radiation therapy, CTx: chemotherapy, Tx: therapy.

DOI:10.3802/jgo.2011.22.1.39

remission. The mean disease-free interval was 9.2 months (range, 6 to 11 months) in the recurrent cases. Recurrence sites included the para-aortic lymph nodes (n=3), bone (n=3), lung (n=2), neck nodes (n=2), liver (n=1), and brain (n=1) (Table 2).

Of 9 patients who showed abnormal Pap smear screening results, 2 were diagnosed as squamous cell carcinoma, and 2 cases as small cell carcinoma on the initial cytologic diagnosis. In addition, 2 cases were diagnosed as atypical squamous cells of undetermined significance (ASCUS), and 3 cases as high-grade squamous intraepithelial lesions (HSIL), respectively.

Table 2. The 5 year overall survival rate and recurrence of the patients

The 5 year overall survival rate	57.2% (12/21)
Complete remission (CR)	16 (59.3)
Recurrence after CR	6 (37.5)
FIGO stage of recurrence cases	
Stage I	2 (33.3)
Stage II	2 (33.3)
Stage III	2 (33.3)
Interval to recurrence (mo), mean (range)	9.2 (6-11)
Sites of recurrence	
Para-aortic LN	1
Para-aortic LN+neck LN	1
Neck LN+bone	1
Lung+brain	1
Para-aortic LN+bone+right iliac LN	1
Liver+lung+bone	1

Values are presented as number (%) unless otherwise indicated.
FIGO: International Federation of Obstetrics and Gynecology, LN: lymph node.

At the final histologic diagnosis, only one case was identified as the mixture of small cell carcinoma and a squamous cell component, and 8 cases as small cell carcinoma of the uterine cervix. The diagnostic accuracy of the cytologic findings was 22.2% (Table 3). For 9 patients with abnormal Pap smear screening results, there were 5 cases (55.6%) of stage IB, 3 cases (33.3%) of stage IIB, and 1 case (11.1%) of stage III.

DISCUSSION

The rare prevalence of SMCC makes its diagnosis difficult and at the same time decreases the sensitivity of cytologic diagnosis. According to Kim et al. [9], the diagnostic accuracy of cytologic smears in diagnosing SMCC is low (approximately 38.5%). In addition, Wang et al. [10] reported that only 46% of the patients diagnosed with SMCC were diagnosed as having abnormal or malignant growths in cytologic smears, and Zhou et al. [11] reported that only 14% were diagnosed with abnormal or malignant growths. There was no patient diagnosed with SMCC in the cytology smears in both studies. In this study, only two of the nine patients with abnormal Pap smear results were diagnosed with SMCC, resulting in 22.2% in terms of diagnostic accuracy with the cytologic findings.

It is known that SMCC shows a histological finding and prognosis that are similar to those of small cell carcinoma of the lung. SMCC shows rapid progression and early metastasis commonly occurring in the lymph nodes or other organs, leading to a 60-82% lymph lumen invasion and a 40-60% pelvic lymph node metastasis at the time of diagnosis [12,13]. Sheets et al. [14] reported that when surgical treatment was conducted on patients with early-stage SMCC, nodal

Table 3. Clinical features and cytologic findings of the abnormal Pap smear results

Case	Initial cytologic Dx	Histologic Dx	Treatment	FIGO stage	Follow-up (mo)	Recurrence
1	SCC	SMCC	RH+adjuvant RTx	IB	NED (129)	Para-arotic LN
2	SMCC	SMCC	Chemoradiation Tx	IIB	NED (17)	
3	ASCUS	SMCC	Chemoradiation Tx	III	NED (50)	Para-arotic LN+neck LN
4	HSIL	SMCC	Chemoradiation Tx	IB	UK (140)	
5	ASCUS	SMCC	RH+adjuvant RTx	IB	NED (22)	
6	HSIL	SMCC	Chemoradiation Tx	IB	NED (218)	
7	SCC	SMCC	Chemoradiation Tx	IB	NED (91)	
8	HSIL	SMCC	Neoadjuvant CTx+ RH+adjuvant Tx	IIB	DoD (14)	Bone (spine)+neck LN
9	SMCC	SCC+SMCC component	Chemoradiation Tx	IIB	NED (79)	

Dx: diagnosis, FIGO: International Federation of Obstetrics and Gynecology, SCC: squamous cell carcinoma, SMCC: small cell carcinoma of the uterine cervix, RH: radical hysterectomy, RTx: radiation therapy, NED: live with no evidence of disease, LN: lymph node, Tx: therapy, ASCUS: atypical squamous cells of undetermined significance, HSIL: high-grade squamous intraepithelial lesion, UK: dead of unknown causes, CTx: chemotherapy, DoD: dead of disease.

metastasis was found in approximately 57% of the patients. In addition, Sevin et al. [3] reported that, unlike squamous-cell carcinoma or adenocarcinoma of the uterine cervix, SMCC shows a shallow depth of invasion and a small tumor size, yet is an aggressive neoplasm that has a higher incidence of lymphovascular space involvement and lymph node metastasis.

The outcome of SMCC is associated with the disease stage. Chan et al. [15] reported that, in the case of an early-stage disease, where the disease is limited within the radiation field, combined-modality therapy showed approximately 30% treatment success. On the other hand, in the case of an advanced-stage disease, the prognosis was too bad to find survivors over two years. Due to the rare prevalence of this disease, the number of study specimens seen at a single institution was relatively small, and prognostic factors, such as the tumor size, LN involvement, and FIGO stage, were identified [4,5]. In this study, FIGO stage IIB was the most common stage (11 of 27 patients), and the 5-year overall survival rate of 21 patients who could be followed up was reported to be 57.2%.

As the pathophysiology of SMCC is similar to that of small cell carcinoma of the lung (SCLC), SMCC treatment can also be deduced from the treatment of SCLC. It has been continually reported that, if an anticancer agent that is used for the treatment of general uterine cervical cancer is used, the survival rate of SMCC patients will be 33%; however, if an anticancer agent that is used for the treatment of SCLC is used, the survival rate will be 68%, showing a statistically significant difference. This suggests that the anticancer agent used for the treatment of SCLC can be used for the postoperative adjuvant chemotherapy regimen of SMCC [12]. In fact, other researchers reported that chemotherapy in combination with cisplatin and etoposide, and radiotherapy used for the treatment of SCLC, were applied to SMCC patients and successfully treated approximately 55% of the patients [16].

According to a large-scale multicenter retrospective study that was conducted involving 68 stage IB-IIA patients who underwent surgery, neoadjuvant chemotherapy results in the downsizing of a bulky mass into an appropriate size for surgery, but had no benefit in the overall survival rate. In addition, adjuvant chemoradiation therapy after surgery contributed less to the survival rate than adjuvant chemotherapy alone. Therefore, it was concluded that, for early-stage SMCC, primary radical surgery followed by adjuvant chemotherapy should be conducted as a preferable treatment modality [17].

Although this study suffered from limited case samples, it was consistent with the concept that Pap smear screening might not be helpful in early diagnosis of SMCC considering its low diagnostic accuracy. In the light of its low prevalence, a large-scale multicenter prospective study may be required to improve its diagnosis and treatment.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Miller B, Dockter M, el Torky M, Photopulos G. Small cell carcinoma of the cervix: a clinical and flow-cytometric study. Gynecol Oncol 1991;42:27-33.
2. Appetecchia M, Benevolo M, Mariani L. Neuroendocrine small-cell cervical carcinoma. Eur J Obstet Gynecol Reprod Biol 2001;96:128-31.
3. Sevin BU, Method MW, Nadji M, Lu Y, Averette HA. Efficacy of radical hysterectomy as treatment for patients with small cell carcinoma of the cervix. Cancer 1996;77:1489-93.
4. Chen J, Macdonald OK, Gaffney DK. Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix. Obstet Gynecol 2008;111:1394-402.
5. Zivanovic O, Leitao MM Jr, Park KJ, Zhao H, Diaz JP, Konner J, et al. Small cell neuroendocrine carcinoma of the cervix: analysis of outcome, recurrence pattern and the impact of platinum-based combination chemotherapy. Gynecol Oncol 2009;112:590-3.
6. Addis IB, Hatch KD, Berek JS. Intraepithelial disease of the cervix, vagina and vulva. In: Berek JS, editor. Berek & Novak's gynecology. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p.561-99.
7. Kim Y, Ha HJ, Kim JS, Chung JH, Koh JS, Park S, et al. Significance of cytologic smears in the diagnosis of small cell carcinoma of the uterine cervix. Acta Cytol 2002;46:637-44.
8. Albores-Saavedra J, Larraza O, Poucell S, Rodriguez Martinez HA. Carcinoid of the uterine cervix: additional observations on a new tumor entity. Cancer 1976;38:2328-42.
9. Kim MJ, Kim NR, Cho HY, Lee SP, Ha SY. Differential diagnostic features of small cell carcinoma in the uterine cervix. Diagn Cytopathol 2008;36:618-23.
10. Wang PH, Liu YC, Lai CR, Chao HT, Yuan CC, Yu KJ. Small cell carcinoma of the cervix: analysis of clinical and

 DOI:10.3802/jgo.2011.22.1.39

pathological findings. Eur J Gynaecol Oncol 1998;19:189-92.
11. Zhou C, Hayes MM, Clement PB, Thomson TA. Small cell carcinoma of the uterine cervix: cytologic findings in 13 cases. Cancer 1998;84:281-8.
12. Chang TC, Lai CH, Tseng CJ, Hsueh S, Huang KG, Chou HH. Prognostic factors in surgically treated small cell cervical carcinoma followed by adjuvant chemotherapy. Cancer 1998;83:712-8.
13. Sykes AJ, Shanks JH, Davidson SE. Small cell carcinoma of the uterine cervix: a clinicopathological review. Int J Oncol 1999;14:381-6.
14. Sheets EE, Berman ML, Hrountas CK, Liao SY, DiSaia PJ. Surgically treated, early-stage neuroendocrine small-cell cervical carcinoma. Obstet Gynecol 1988;71:10-4.
15. Chan JK, Loizzi V, Burger RA, Rutgers J, Monk BJ. Prognostic factors in neuroendocrine small cell cervical carcinoma: a multivariate analysis. Cancer 2003;97:568-74.
16. Hoskins PJ, Swenerton KD, Pike JA, Lim P, Aquino-Parsons C, Wong F, et al. Small-cell carcinoma of the cervix: fourteen years of experience at a single institution using a combined-modality regimen of involved-field irradiation and platinum- based combination chemotherapy. J Clin Oncol 2003;21:3495-501.
17. Lee JM, Lee KB, Nam JH, Ryu SY, Bae DS, Park JT, et al. Prognostic factors in FIGO stage IB-IIA small cell neuroendocrine carcinoma of the uterine cervix treated surgically: results of a multi-center retrospective Korean study. Ann Oncol 2008;19:321-6.