Asian Oncology Research Journal

2(1): 102-109, 2019; Article no.AORJ.53399

Uncommon Histological Variants of Cervical Cancer – A Single Center Experience

Swati Mittal[1*], Joydeep Ghosh[2] and Anik Ghosh[1]

[1]Department of Gynaecological Oncology, Tata Medical Center, Kolkata, India.
[2]Department of Medical Oncology, Tata Medical Center, Kolkata, India.

Authors' contributions

This work was carried out in collaboration among all authors. Authors SM and AG designed the study, wrote the protocol and wrote the first draft of the manuscript. Author JG performed the statistical analysis of the study. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Nina Tuncel, Department of Physics and Radiation Oncology, Akdeniz University, Turkey.
Reviewers:
(1) Abdul Kader Mohiuddin, Bangladesh.
(2) S. J. Carlan, Orlando Health Orlando Regional Medical Center, USA.
(3) Simona Gabriela Bungau, University of Oradea, Romania.
Complete Peer review History: http://www.sdiarticle4.com/review-history/53399

Original Research Article

Received 11 October 2019
Accepted 19 December 2019
Published 27 December 2019

ABSTRACT

Aim: To study the clinical and demographic characteristics of cancers of uterine cervix with histology other than SCC and AC at a tertiary referral hospital in eastern India.
Study Design: Retrospective study.
Place and Duration of Study: Tata Medical Center, Kolkata, India from May 2011 to July 2018.
Methodology: A retrospective review of cases of cervical cancer was done using prospectively collected data from electronic medical records from May 2011 to July 2018. Clinical and demographic characteristics of the cases were noted.
Results: A total of 644 cases of cervical cancer were treated in the study period. 14 cases of uncommon histological types were recorded (NECC – 6, Clear Cell Carcinoma – 1, Mucinous Adenocarcinoma – 3, Serous Carcinoma – 1, Melanoma – 1, Carcinosarcoma – 1 and Adenoma Malignum – 1). The median recurrence free survival for non-metastatic disease population was 24 months and the median 3 year overall survival for non-metastatic disease population 54%.
Conclusion: The prognosis of the uncommon histological types remains poor. However, further prospective studies are required to study the natural history, treatment and prognosis of these tumors.

**Corresponding author: E-mail: swati0611@gmail.com;*

Keywords: Cervical cancer; uncommon histology; Neuroendocrine Carcinoma of Cervix (NECC); Squamous Cell Carcinoma (SCC); Adenocarcinoma (AC).

1. INTRODUCTION

According to the World Health Organization, uterine cervix cancer was the fourth most common malignancy in women, and seventh most common overall, with 528,000 new incident cases reported in 2012 [1]. An estimated 266,000 women died around the world in 2012 from cervical cancer, accounting for almost 8% of all female cancer deaths [1]. Nearly 9 out of every 10 women with cancer of uterine cervix died in underdeveloped regions of the world [1]. In India cervical cancer is the second most common cancer among women [2]. The main risk factor for cervical cancer is infection with Human papilloma virus (HPV) types 16, 18, 31, 33, 35, 42, 55, 58. HPV types 16 and 18 are the cause of 70% of cervical cancer worldwide while 31 and 45 are the cause of another 10% [3]. Squamous cell carcinoma (SCC) accounts for about three quarters of all cases of cervical cancer worldwide [4].

Neuroendocrine carcinomas of the cervix (NECC) are rare tumors and account for 2–5% of cervical malignancies [5-8]. They include small cell, large cell, carcinoid and atypical carcinoid histologic types. Small cell and large cell tumors are poorly differentiated with a high mitotic rate, necrosis, frequent lymphovascular space invasion and an aggressive clinical course. Under light and electron microscopy, the characteristics of the tumor are indistinguishable from oat cell carcinoma of the lung. Carcinoid and atypical carcinoid tumors are well differentiated, are thought to be derived from neural crest cells, and are extremely rare [5]. Atypical carcinoid tumors display significant nuclear atypia and are poorly studied. Like other cervical cancers, NECC appear to be associated with human papillomavirus (HPV). Despite the association, it is unknown whether HPV vaccination is protective against the development of NECC.

NECCs are characterized by early spread beyond the cervix and a poor prognosis [9]. Five-year survival rates for NECC are reported at 0–30% [9,10]. These tumors also have a higher risk of lymph node involvement and distant metastases, often to the liver, lung, brain, bone, and bone marrow [11]. Survival for both early and late stage tumors is inferior to that of squamous cell carcinomas. The differential in survival is greatest for women with early-stage tumors.

Treatment of early stage disease includes radical surgery for tumors <4cm, often in combination with adjuvant chemotherapy [9]. Advanced stage disease is treated with combination chemotherapy and radiation [9]. The chemotherapy regimens most commonly utilized include Cisplatin and Etoposide (EP) or Vincristine, Doxorubicin, and Cyclophosphamide (VAC).

Clear cell adenocarcinoma of the cervix has been found to be associated with in utero exposure to diethylstilbestrol and related non-steroidal estrogens before the eighteenth week of pregnancy [12]. These cancers primarily affect adolescents and young women. The incidence among DES-exposed women is 1 in 1,000 [13]. A multi-institutional review of 34 cases in the post-DES era reported a median age of 53 years [14]. PFS for node-negative patients was 92% versus 31% for node-positive ($p < 0.001$). Treatment for clear cell carcinoma should be similar to that for other adenocarcinomas with comparable prognosis [14,15].

Mucinous Adenocarcinoma cervix has several variants, including endocervical, intestinal, signet ring cell, minimal deviation, and villoglandular variants. HPV DNA has been detected in more than 90% of cases [16]. Signet ring cell carcinomas and colloid carcinomas are extremely rare and must be distinguished from metastatic tumors from the gastrointestinal tract. Mucinous Adenocarcinoma, minimal deviation variant represents only about 1.3% of cervical adenocarcinomas and is not associated with HPV infection [17].

Papillary serous carcinoma of the uterine cervix has a bimodal age distribution, occurring in patients younger than 40 years and older than 65 years [18]. It is not associated with HPV DNA [17]. These tumors can behave aggressively with supra-diaphragmatic metastases and a rapidly fatal course when diagnosed at an advanced stage, but the outcome for patients with stage I tumors is similar to that of patients with cervical adenocarcinomas of the usual type [18,19].

Melanoma of the cervix is a rare cervical tumor, and hence a metastatic lesion must be excluded.

It originates from melanocytes that are present in the urogenital epithelium in about 3% of women [20]. They occur in seventh and eighth decades of life, and are mostly diagnosed in FIGO stage I and II. Recommended treatment is usually radical hysterectomy with or without pelvic lymphadenectomy. Adjuvant radiation may improve local control if the surgical margins are close. The 5-year survival rate is poor, less than 40% for stage I disease and 14% for stage II [21].

Malignant Mixed Mullerian Tumor of cervix (Carcinosarcoma) is a rare and aggressive sarcoma with a poor prognosis. It is associated with HPV DNA.22 A SEER databases review found the 5 year survival rate of FIGO IB sarcoma to be 67% compared to 80% for squamous carcinoma [22].

Adenoma Malignum is a very highly differentiated tumor and represents about 1% of adenocarcinomas of cervix, which occurs mainly in the fifth and sixth decades [17,23]. It has been found to be associated with Peutz-Jegher syndrome and sex cord tumors with annular tubules of ovary [24]. The prognosis for early stage tumors appears good [25,26,27]. However, for more advanced stage, lymph node metastases are common and overall prognosis is poor [25,28].

The present study aims to study the clinical and demographic characteristics of cancers of uterine cervix with histology other than SCC and AC at a tertiary referral hospital in eastern India.

2. MATERIALS AND METHODS

The present study was conducted to study the clinical and demographic characteristics of cancers of uterine cervix with histology other than SCC and AC at a tertiary referral hospital in eastern India. A retrospective review of cases of cervical cancers was done using prospectively collected data from electronic medical records from May 2011 to July 2018. Data regarding age at diagnosis, presenting complaints, stage, treatment modality, recurrence (if any) was noted in this observational study. Kaplan Meier curves were used for doing the survival analysis.

3. RESULTS AND DISCUSSION

3.1 Results

A total of 644 cases of cervical cancer were treated at the institution in the study period. Squamous Cell Carcinoma accounted for the majority of the cases followed by Adenocarcinoma (usual type). The other histological types included Neuroendocrine Carcinoma (6 cases), Clear Cell Carcinoma (1 case), Mucinous Adenocarcinoma (3 cases), Serous Carcinoma (1 case), Melanoma (1 case), Carcinosarcoma (1 case) and Adenoma Malignum (1 case).

Among these 14 cases of uncommon histological variants, the age range was 38-65 years and median age was 48 years. The most common presentation was postmenopausal bleeding followed by abnormal uterine bleeding and vaginal discharge. 6 patients had early stage disease (FIGO IA – IIA), 6 had locally advanced cancer (FIGO IIB – IVA) and 2 had metastatic disease (FIGO IVB) at presentation.

Upfront surgery was done in 6 cases, concurrent chemo-radiation given to 3 patients, systemic chemotherapy to 2 patients, while 3 patients received systemic chemotherapy followed by external beam radiation (Table 1).

The median follow up of these patients was 28 months (IQR; Q1: 10.5, Q3: 39). At the time of analysis, 2 patients were undergoing primary treatment, 1 was undergoing treatment for recurrence and 1 had completed primary treatment in March 2018. 6 patients had recurrence diagnosed in the study period. The median recurrence free survival for the non-metastatic disease population (Fig. 1) was 24 months. 5 patients had died at the time of analysis. The median 3 year overall survival (OS) and the projected 6 year OS of the non-metastatic disease population (Fig. 2) was 54%. The recurrence free and overall survival of various histological subtypes has been showed in Table 2.

3.2 Discussion

The present study was conducted to study the clinical and demographic characteristics of uncommon varieties of cervical cancer. Because of the paucity of cases, prognostic variables could not be ascertained. Among the patients with localized disease, the median recurrence free survival was 24 months and the 3 year overall survival was 54%.

Margolis et al did a population based analysis to examine the natural history, treatment patterns and outcomes of women with NECC compared

to Squamous Cell Carcinoma and Adenocarcinoma of the cervix [9]. They found that patients with NECC were younger and diagnosed with metastatic disease at presentation compared to women with Squamous Cell Carcinoma. Patients with early stage NECC were more likely to receive adjuvant chemotherapy and radiation after surgery in view

Table 1. Demographic characteristics

S No.	Age at diagnosis (Years)	Histology	Stage at primary presentation	Treatment modality: 1. Surgery; 2. CTRT; 3. Systemic Chemotherapy; 4. Chemotherapy followed by EBRT
1.	44	Neuroendocrine Carcinoma	IIB	4
2.	47	Neuroendocrine Carcinoma	IB2	1
3.	48	Neuroendocrine Carcinoma	IB1	1
4.	58	Neuroendocrine Carcinoma	IB1	1
5.	62	Neuroendocrine Carcinoma	IB2	4
6.	65	Neuroendocrine Carcinoma	IVB	3
7.	56	Clear Cell Carcinoma	IIB	2
8.	38	Mucinous Adenocarcinoma	IIIB	2
9.	47	Mucinous Adenocarcinoma	IVB	3
10.	61	Mucinous Adenocarcinoma	IB1	1
11.	54	Serous Carcinoma	IVA	4
12.	54	Melanoma	IIB	1
13.	41	Carcinosarcoma	IB2	1
14.	45	Adenoma Malignum	IVA	2

CTRT: concurrent chemo-radiation; EBRT: external beam radiation therapy

Table 2. Outcome of patients

Histology	Recurrence free survival (months)	Overall survival (months)
Neuroendocrine Carcinoma	a. 13 b. NA c. 16 d. 03 e. NA f. NA	a. 45 b. NA c. NA d. NA e. NA f. NA
Clear Cell Carcinoma	15	32
Mucinous Adenocarcinoma	a. NA b. NA c. NA	a. NA b. 13 c. NA
Serous Carcinoma	NA	NA
Melanoma	3	6
Carcinosarcoma	4	36
Adenoma Malignum	NA	NA

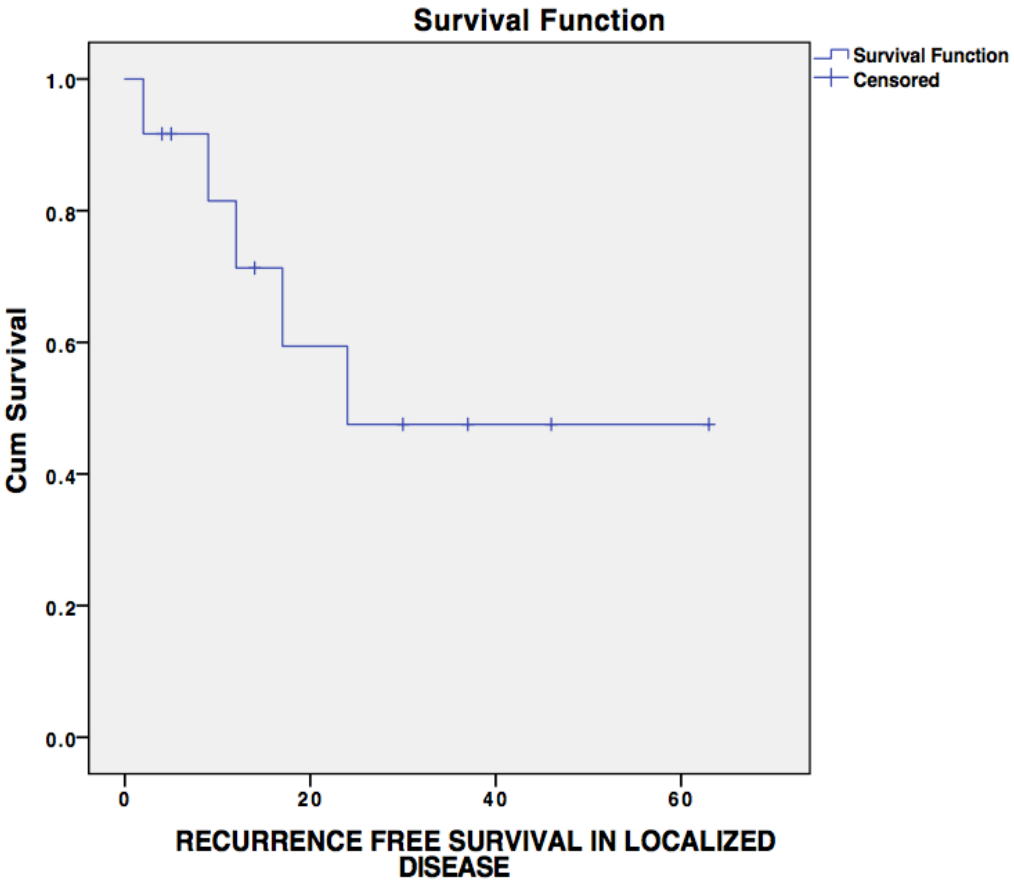

Fig. 1. Recurrence free survival in localized disease

of higher risk of distant failure and the risk of death was higher for patients with NECC compared to Squamous Cell Carcinoma for all stages of disease [9]. Even though NECC appears to be associated with human papilloma virus (HPV), it is unknown whether HPV vaccination is protective against its development [9,29].

Chen et al did a retrospective review of patients with FIGO stage IA-IIB small cell carcinoma cervix treated in Taiwan from 1987 to 2009 and found a lower incidence of failure in patients who received primary radiation than those treated by primary surgery (6% vs 27%; p = 0.009). Also, primary radiation therapy with aggressive chemotherapy was associated with better survival than surgery [30].

Cohen et al did an analysis of 188 patients with small cell cancer cervix to study the clinic-pathological factors associated with survival. 55.3% underwent surgery, 16.0% received chemo-radiation, 12.8% radiation, and 3.2% got chemotherapy alone. The 5-year disease-specific survival in stage I-IIA, IIB-IVA, and IVB disease was 36.8%, 9.8%, and 0%, respectively (*p* .001). Adjuvant chemotherapy or chemo-radiation was associated with improved survival in patients with stages IIB-IVA disease compared with those who did not receive chemotherapy (17.8% vs 6.0%; *p* = .04). On multivariable analysis, early-stage disease and use of chemotherapy or chemo-radiation were independent prognostic factors for improved survival [31].

Papillary Serous Carcinoma, Melanoma and Carcinosarcoma of uterine cervix have a poor prognosis, with survival rates inferior to Squamous Cell Carcinoma [18,19,21,22]. Adenoma Malignum is a highly differentiated tumor associated with Peutz-Jegher syndrome and sex cord stromal tumor of ovary with annular tubules [24]. The prognosis for early stage is good, while advanced stages present with lymph node metastases and have a poor prognosis [25-28].

Many current recommendations in treatment of NECC are extrapolated from data on small cell lung cancer, so emerging targeted therapies

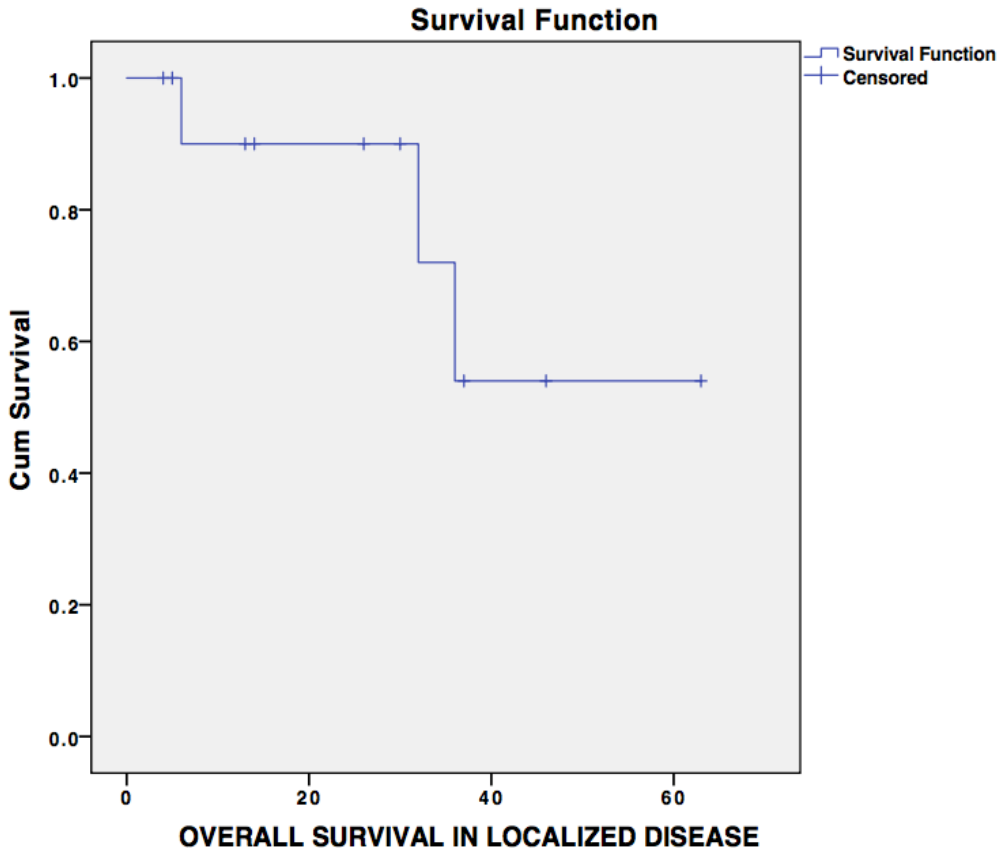

Fig. 2. Overall survival in localized disease

(including angiogenesis inhibitors, mTOR inhibitors, and PARP inhibitors) for the same could be explored. Improvements in 3 month PFS have been shown in small cell lung cancer with the addition of aflibercept, a VEGF inhibitor in combination with topotecan for recurrent disease. Though not studied for NECC, bevacizumab represents a reasonable option for women with NECC [9]. Small cell lung cancers have high expression of PARP1. PARP inhibitors are currently being explored in clinical trials. The tyrosine kinase inhibitor sunitinib has also been shown to increase PFS in small cell lung cancer in a phase II randomized trial [9]. Given the rarity of NECC, trials of targeted therapy specifically designed for women with neuroendocrine cervical tumors are unlikely.

Given the overall poor prognosis, even in those with early-stage disease, further studies are warranted to develop novel therapies with systemic regimens for this aggressive cancer. For instance, there are ongoing trials evaluating targeted agents such as gefitinib, bevacizumab, temsirolimus, sorafenib, and thalidomide in small cell lung cancer [31].

4. CONCLUSION

The prognosis of the uncommon histological types remains poor. Further studies to prospectively document the natural history, treatment and outcomes of women with these uncommon histological varieties of cervical cancer are needed.

5. RECOMMENDATIONS

Novel treatment approaches including use of inhibitors of vascular endothelial growth factor (VEGF) and VEGFR, mTOR, and COX2 should be explored [32].

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard, written ethical approval has been collected and preserved by

the author(s). IRB WAIVER NO.: EC/WV/TMC/ 011/19.

ACKNOWLEDGEMENTS

Author would like to thank his patients, support staff and the research team for their support.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015; 136(5).
2. Armstrong EP. Prophylaxis of cervical cancer and related cervical disease: A review of the cost- effectiveness of vaccination against oncogenic HPV types. J Managed Care Pharmacy. 2010;16(3): 217-30.
3. Dillman. Edited by Oldham RK, Robert O. Principles of cancer biotherapy. 5th ed. Dordrecht: Springer. 2009:149.
4. Vizcaino AP, Moreno V, Bosch FX, MUNoz N, Barros- Dios XM, Borras et al. International trends in incidence of cervical cancer: II. Squamous- cell carcinoma. Int J Cancer. 2000;86(3):429-35.
5. Albores-Saavedra J, Larraza O, Poucell S, Rodriguez Martinez HA. Carcinoid of the uterine cervix: additional observations on a new tumor entity. Cancer. 1976;38:2328–2342. [PubMed: 63316]
6. Scully RE, Aguirre P, DeLellis RA. Argyrophilia, serotonin and peptide hormones in the female genital tract and its tumors. International journal of gynecological pathology: Official journal of the International Society of Gynecological Pathologists. 1984;3:51–70. [PubMed: 6145674]
7. Miller B, Dockter M, Torky M, Photopulos G, et al. Small cell carcinoma of the cervix: A clinical and flow-cytometric study. Gynecologic oncology. 1991;42:27–33. [PubMed: 1655594]
8. van Nagell JR Jr, Donaldson ES, Parker JC, van Dyke AH, Wood EG. The prognostic significance of pelvic lymph node morphology in carcinoma of the uterine cervix. Cancer. 1977; 39:2624–2632. [PubMed: 872061]
9. Margolis B, Tergas AI, Chen L, Hou JY, Burke WM, Hu JC, Ananth CV, Neugut AI, Hershman DL, Wright JD. Natural history and outcome of neuroendocrine carcinoma of the cervix. Gynecologic oncology. 2016; 141(2):247-54.
10. Chan JK, Loizzi V, Burger RA, Rutgers J, Monk BJ. Prognostic factors in neuroendocrine small cell cervical carcinoma: A multivariate analysis. Cancer. 2003;97:568–574. [PubMed: 12548598]
11. Ota T, Kitano T, Miyai K, et al. Small cell carcinoma of the uterine cervix metastasizing to the bone marrow: A case report. J Obstet Gynaecol Res. 2008;34: 692–695.
12. Herbst AL, Kurman RJ, Scully RE, et al. Clear cell adenocarci- noma of the genital tract in young females. N Engl J Med. 1972;287:1259–1264.
13. Herbst AL. Behavior of estrogen-associated female genital tract cancer and its relation to neoplasia following intrauterine exposure to diethylstilbestrol (DES). Gynecol Oncol. 2000;76: 147–156.
14. Thomas MB, Wright JD, Leiser AL, et al. Clear cell carcinoma of the cervix: A multi-institutional review in the post-DES era. Gynecol Oncol. 2008;109:335–339.
15. Reich O, Tamussino K, Lauhousen M, et al. Clear cell carcinoma of the uterine cervix: Pathology and prognosis in surgically treated stage IB–IIB disease in women not exposed to in utero diethylstil-bestrol. Gynecol Oncol. 2000;76:331–335.
16. Pirog EC, Kleter B, Olgac S, et al. Prevalence of human papillomavirus DNA in different his- tological subtypes of cervical adenocarcinoma. Am J Pathol. 2000;157:1055–1062.
17. Hart WR. Special types of adenocarcinoma of the uterine cervix. Int J Gynecol Pathol. 2002;21: 327–346.
18. Zhou C, Gilks CB, Hayes M, et al. Papillary serous carcinoma of the uterine cervix: A clinicopathologic study of 17 cases. Am J Surg Path. 1998;22:113–120.
19. Togami S, Kasamatsu T, Sasajima Y, et al. Serous adenocarcinoma of the uterine cervix: A clinicopathological study of 12 cases and a review of the literature. Gynecol Obstet Invest. 2012;73:26–31.

20. Piura B. Management of primary melanoma of the female urogeni- tal tract. Lancet Oncol. 2008;9:973–981.
21. Mordel N, Mor-Yosef S, Ben-Baruch N, et al. Malignant mela- noma of the uterine cervix: Case report and review of the literature. Gynecol Oncol. 1989;32:375–380.
22. Bansal S, Lewin SN, Burke WM, et al. Sarcoma of the cervix: Natural history and outcomes. Gynecol Oncol. 2010;118:134–138.
23. Silverberg SG, Hurt WG. Minimal deviation adenocarcinoma ("*Adenoma malignum*") of the cervix: A reappraisal. Am J Obstet Gynecol. 1975;121:971–975.
24. McGowan L, Young RH, Scully RE. Peutz-Jeghers syndrome with "*Adenoma malignum*" of the cervix: A report of two cases. Gynecol Oncol. 1980;10:125–133.
25. Li G, Jang W, Gui SXUC. Minimal deviation adenocarcinoma of the uterine cervix. Int J Gynecol Obstet. 2010;110:89–92.
26. Hirai Y, Takeshima N, Haga A, et al. A clinicocytopathologic study of adenoma malignum of the cervix. Gynecol Oncol. 1998;70:219–223.
27. Lim KT, Lee IH, Kim TJ, et al. Adenoma malignum of the uter- ine cervix: Clinicopathologic analysis of 18 cases. Kaohsiung J Med Sci. 2012;28:161–164.
28. Gilks CB, Young RH, Aguirre P, et al. Adenoma malignum (mini- mal deviation adenocarcinoma) of the uterine cervix: A clinicopatho- logical and immunohistochemical analysis of 26 cases. Am J Surg Pathol. 1989;13:717–729.
29. Siriaunkgul S, Utaipat U, Settakorn J, Sukpan K, Srisomboon J, Khunamornpong S. HPV genotyping in neuroendocrine carcinoma of the uterine cervix in northern Thailand. Int J Gynaecol Obstet. 2011;115:175–179. [PubMed: 21872245]
30. Chen TC, Huang HJ, Wang TY, Yang LY, Chen CH, Cheng YM, Liou WH, Hsu ST, Wen KC, Ou YC, Hung YC. Primary surgery versus primary radiation therapy for FIGO stages I–II small cell carcinoma of the uterine cervix: A retrospective Taiwanese Gynecologic Oncology Group study. Gynecologic Oncology. 2015;137 (3):468-73.
31. Cohen JG, Kapp DS, Shin JY, Urban R, Sherman AE, Chen LM, Osann K, Chan JK. Small cell carcinoma of the cervix: Treatment and survival outcomes of 188 patients. American journal of obstetrics and gynecology. 2010;203(4):347-e1.
32. Cohen JG, Chan JK, Kapp DS. The management of small-cell carcinomas of the gynecologic tract. Current Opinion in Oncology. 2012;24(5):572-9.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/53399