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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

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Background: To determine the clinical and pathologic prognostic factors in surgically treated patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB–IIA small cell neuroendocrine carcinoma of the uterine cervix (SCNEC).

Patients and methods: We retrospectively reviewed a total of 68 patients with FIGO stage IB–IIA SCNEC surgically treated from January 1997 to December 2003 in Korea.

Results: Of the 68 patients, 43 had FIGO stage IB1 SCNEC, 15 had stage IB2, and 10 had stage IIA. Seven were treated with radical surgery alone; 11 with neoadjuvant chemotherapy (NACT) followed by radical surgery; 24 with radical surgery followed by adjuvant chemotherapy; and 26 with radical surgery followed by adjuvant radiation or chemoradiation. After a median follow-up of 44 months (range, 6–113 months), the 2-year and 5-year survival rates for all patients were 64.6% and 46.6%, respectively. Univariate and multivariate analysis showed that FIGO stage was predictive of poor prognosis. Patients who received NACT showed poorer prognosis than those who did not receive NACT. Adjuvant chemoradiation did not improve survival compared with adjuvant chemotherapy alone.

Conclusions: FIGO stage may act as a surrogate for factors prognostic of survival. Primary radical surgery followed by adjuvant chemotherapy is the preferred treatment modality for patients with early stage SCNEC.

Key words: neuroendocrine carcinoma, prognosis, small cell, uterine cervix

introduction

Uterine cervical cancer is the most common malignant disease of female genital tract accounting for 9.1% of total malignances in Korean women in 2002 [1]. The overall age-standardized incidence rates (ASRs) were 19.0, 17.8, and 15.1 per 100 000 women during 1993–1995, 1996–1998, and 1999–2002, respectively. The ASR of small cell neuroendocrine carcinoma of the uterine cervix (SCNEC) was 0.1 per 100 000 women during 1993–2002 [2]. SCNEC is a rare tumor, accounting for <5% of all cervical cancers [3, 4]. These tumors are characterized by a high incidence of early nodal and distant metastases, resulting in poorer prognosis than other subtypes of cervical cancers [3–5]. Due to its rarity and the long time period required to enroll a sufficient number of patients, however, there is a paucity of information pertaining to prognostic factors associated with survival. Moreover, the optimal treatment strategies for this aggressive tumor have not yet been determined [3, 5], making it difficult to treat patients with SCNEC.

To improve treatment strategies, we therefore carried out a retrospective multicenter clinical trial to determine the clinical and pathologic prognostic factors responsible for survival in surgically treated the International Federation of Gynecology and Obstetrics (FIGO) stage IB–IIA patients with SCNEC.

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materials and methods

A total of 75 surgically treated patients with early stage SCNEC (stages IB–IIA) were identified from the tumor registry databases of 16 tertiary medical centers in Korea from January 1997 to December 2003. All histopathologic review was carried out by two pathologists (KRK and SYS) of Pathology Committee of Korean Gynecologic Oncology Group. Three patients were excluded because histopathologic review showed that they did not have small cell carcinoma in the reviewed slides and four were excluded because follow-up data were incomplete. Thus, the study population consisted of 68 patients. Institutional review board approval was obtained from each of the participating centers.

Histopathologic diagnosis was based on morphologic criteria and on immunohistochemical staining for neuron-specific enolase (DAKO, Glostrup, Denmark; 1:300), synaptophysin (DAKO; 1:50), chromogranin (DAKO; 1:100), and CD56 (Novocastra, Newcastle upon Tyne, UK; 1:100) [6–9]. The morphologic criteria revealed by hematoxylin–eosin staining included the presence of small cells with hyperchromatic nuclei and scanty cytoplasm, absent or inconspicuous nucleoli, and numerous mitotic figures and extensive necrosis, and all tumors had to be positive for at least one of the neuroendocrine markers. All tumors were staged according to the FIGO clinical staging system for cervical cancer, based on physical examination, chest X-ray, i.v. pyelography, cystoscopy, sigmoidoscopy, and abdomino-pelvic computed tomography scan (CT) or magnetic resonance imaging. When there were suspicious findings on chest X-ray, and/or sign and symptom on physical examination, CT of chest and/or brain was carried out. As primary treatment, all patients underwent type III hysterectomy and pelvic lymphadenectomy, with or without para-aortic lymphadenectomy.

Clinical and pathological variables analyzed included patient age, tumor size and stage, tumor homology, lymph node involvement, depth of stromal invasion, lymph vascular space invasion, parametrial extension, surgical margin, and treatment modalities. The primary end point was any cancer-related death. All end points were calculated from the date of radical hysterectomy to death, or censored at last follow-up. The date of death was obtained from the medical records, personal contact or the National Registry of Death Statistics of the Korea National Statistical Office.

Overall survival was evaluated using the Kaplan–Meier method and log-rank tests. The Cox proportional hazards model was used to estimate the independent factors prognostic for overall survival. The significance level for all analyses was 0.05. All analyses were carried out using SPSS 11 software (SPSS, Chicago, IL, USA). All end points were updated in July 2007.

results

Of the 68 patients, FIGO stage IB1 SCNEC was diagnosed in 43 (63.2%) patients, stage IB2 in 15 (22.1%), and stage IIA in 10 (14.7%). Forty-seven (69.1%) patients had a pure histologic type composed of SCNEC and 21 (30.9%) had a mixed histologic pattern associated with squamous cell carcinoma or adenocarcinoma in addition to the SCNEC component. Radical surgery alone was carried out in 7 (10.3%) patients; neoadjuvant chemotherapy (NACT) followed by radical surgery, with or without adjuvant radiation, in 11 (16.2%); radical surgery followed by adjuvant chemotherapy in 24 (35.3%); and radical surgery followed by adjuvant radiation or chemoradiation in 26 (38.2%) (Table 1). Several chemotherapeutic agents such as bleomycin (B), carboplatin (C), cisplatin (P), etoposide (E), 5-fluorouracil (F), ifosphamide (I), paclitaxel (T), or vinblastine (V) were used in various combinations. Among 11 patients who received NACT, five received EP, two received TP, and four received VPB. In 24 patients who received adjuvant chemotherapy, 13 received EIP or EP, three received VPB, four received TP or TIP, two received TC, and two received FP. In 24 patients who received adjuvant chemoradiation, EIP or EP was given in 11 patients, FP in four, TP or TIP in four, TC in two, VPB in two, and P alone in one.

Of the 68 patients with FIGO stage IB–IIA SCNEC, the estimated 2-year and 5-year survival rates for all patients were 64.6% and 46.6%, respectively (Figure 1).

Table 1. Patients characteristics at baseline

Variables		
Mean age (range)	45.8 (32–87)	
Mean gravidity (range)	4.1 (0–11)	
Mean parity (range)	2.5 (0–9)	
Stage (%)	IB1	43 (63.2)
	IB2	15 (22.1)
	IIA	10 (14.7)
Tumor homology (%)	Pure	47 (69.1)
	Mixed	21 (30.9)
Treatment modality (%)	Surgery only	7 (10.3)
	NACT + surgery ± RT	11 (16.2)
	Surgery + CTX	24 (35.3)
	Surgery + RT or CCRT	26 (38.2)

NACT, neoadjuvant chemotherapy; RT, radiation; CTX, chemotherapy; CCRT, concurrent chemoradiation.

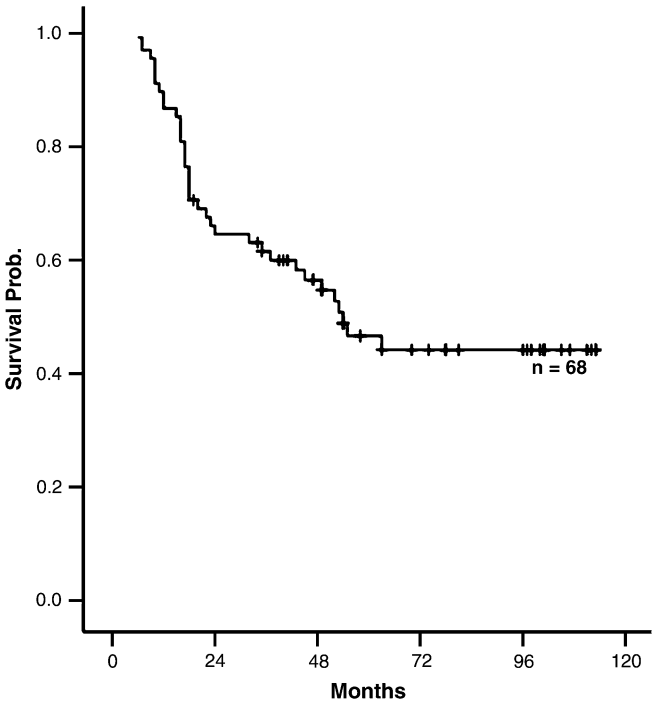

Figure 1. Overall survival in patients with International Federation of Gynecology and Obstetrics stage IB–IIA small cell neuroendocrine carcinoma of the uterine cervix.

We assessed various clinicopathologic variables to identify factors prognostic for survival. The median survival for all patients was 54 months (range, 6–113 months); the median survival in FIGO stage IB2–IIA and IB1 were 18 months (range, 6–105 months) and not reached (range, 10–113 months), respectively ($P = 0.02$) (Figure 2). In contrast, age ($P = 0.39$), tumor size ($P = 0.40$), depth of stromal invasion ($P = 0.35$), and lymph vascular space invasion ($P = 0.67$) were not prognostic for survival. Although not statistically significant, a pure histologic type, lymph node metastasis, parametrial extension, and positive surgical margin were tended to adversely affect survival. Patients with a pure histologic type had a 5-year survival rate of 42.1%, compared with 56.6% for patients with a mixed histologic type ($P = 0.24$); patients without lymph node metastases had a 5-year survival rate of 53.4%, compared with 34.9% for patients with lymph node metastases ($P = 0.10$); patients without parametrial extension had a 5-year survival rate of 51.0%, compared with 22.2% for patients with parametrial extension ($P = 0.12$); and patients without positive surgical margin had a 5-year survival rate of 48.6%, compared with 20.0% for patients with positive surgical margin ($P = 0.10$).

We also assessed whether multimodal therapy improved prognosis. Because of the limited numbers of patients, we divided the patients into three groups: those receiving NACT, those receiving adjuvant chemotherapy, and those receiving adjuvant radiation. Eleven patients received NACT; two of five patients with stage IB1 and all six patients with stage IB2–IIA tumors died of their disease within 2 years. Patients who received NACT showed poorer prognosis than those who did not receive NACT ($P = 0.02$). Adjuvant chemotherapy tended to favor survival, although the effect did not attain statistical significance. The 48 patients who received adjuvant chemotherapy had a 5-year survival rate of 48.9%, compared with 42.0% in those who did not receive chemotherapy [hazard ratio (HR), 0.83; 95% confidence interval (CI), 0.41–1.70; $P = 0.62$]. Contrary to our expectations, patients who received adjuvant radiation tended to show a poorer prognosis than those who did not receive radiation, with 5-year survival rates of 40.2% and 53.9%, respectively ($P = 0.09$). When we excluded women with tumors ≤2 cm, because of the relatively favorable prognosis associated with small tumor size, 29 patients who received adjuvant radiation had a 5-year survival rate of 37.2%, compared with 51.1% in 18 those who did not receive radiation ($P = 0.12$). We also compared survival rate in patients who received adjuvant chemotherapy with that in those who received adjuvant chemoradiation; these groups showed no significant differences in age, tumor size, stage, tumor homology, positive lymph node, depth of stromal invasion, lymph vascular space invasion, parametrial extension, and status of surgical margin (data not shown). The 5-year survival rates in patients who received adjuvant chemotherapy and chemoradiation were 52.5% and 45.5%, respectively ($P = 0.37$) (Figure 3).

A multivariate analysis was carried out to assess the variables with P values <0.10. FIGO stage of disease (HR, 2.16; 95% CI, 1.01–4.61; $P = 0.046$) remained as a significant independent prognostic factor for survival. Other factors, such as lymph node metastases, positive surgical margin, NACT, and adjuvant radiation, were not significant independent prognostic factors for survival (Table 2).

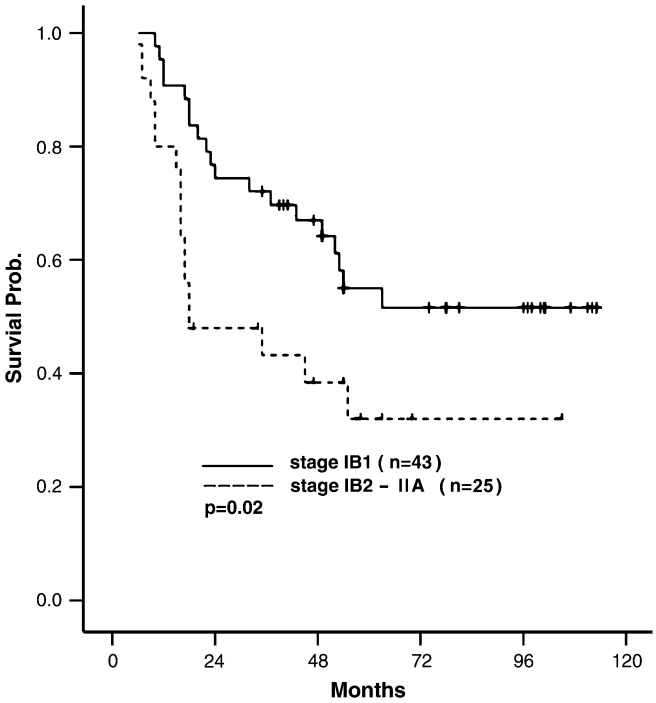

Figure 2. Overall survival based on International Federation of Gynecology and Obstetrics stage.

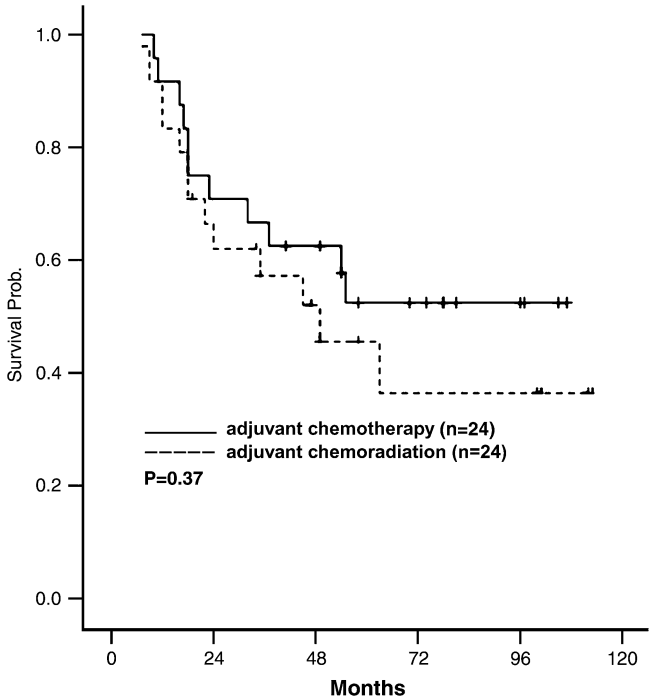

Figure 3. Overall survival based on modality of adjuvant treatment.

Table 2. Univariate and multivariate analysis of survival based on clinical and pathologic factors

Variables		Univariate		Multivariate	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age	≤46 (*n* = 45, 66%)	1.34 (0.68–2.65)	0.39	–	–
	>46 (*n* = 23, 34%)				
Tumor size	≤2 cm (*n* = 21, 31%)	1.39 (0.65–3.00)	0.40	–	–
	>2 cm (*n* = 47, 69%)				
Stage	IB1 (*n* = 43, 63%)	2.13 (1.09–4.15)	0.02	2.16 (1.01–4.61)	0.046
	IB2–IIA (*n* = 25, 37%)				
TH	Mixed (*n* = 21, 31%)	1.58 (0.74–3.36)	0.24	–	–
	Pure (*n* = 47, 69%)				
Positive LN	No (*n* = 43, 63%)	1.75 (0.89–3.42)	0.10	1.25 (0.54–2.90)	0.60
	Yes (*n* = 25, 37%)				
DSI	Inner 2/3 (*n* = 37, 54%)	1.37 (0.71–2.66)	0.35	–	–
	Outer 1/3 (*n* = 31, 46%)				
LVSI	No (*n* = 27, 40%)	1.16 (0.58–2.31)	0.67	–	–
	Yes (*n* = 41, 60%)				
PME	No (*n* = 59, 87%)	1.93 (0.84–4.42)	0.12	–	–
	Yes (*n* = 9, 13%)				
SMS	No (*n* = 63, 93%)	2.40 (0.84–6.83)	0.10	3.01 (0.88–10.24)	0.08
	Yes (*n* = 5, 7%)				
NACT	No (*n* = 57, 84%)	2.52 (1.14–5.59)	0.02	2.55 (1.00–6.51)	0.05
	Yes (*n* = 11, 16%)				
ACT	No (*n* = 20, 29%)	0.83 (0.41–1.70)	0.62	–	–
	Yes (*n* = 48, 71%)				
RT	No (*n* = 32, 47%)	1.81 (0.92–3.57)	0.09	1.50 (0.68–3.31)	0.32
	Yes (*n* = 36, 53%)				

HR, hazard ratio; CI, confidence interval; TH, tumor homology; LN, lymph node; DSI, depth of stromal invasion; LVSI, lymph vascular space invasion; PME, parametrial extension; SMS, surgical margin status; NACT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy; RT, radiation.

discussion

SCNEC is a rare and aggressive subtype of cervical cancer. We observed a 5-year survival rate for all patients with FIGO stages IB1 and IB2–IIA tumors of 46.6%, consistent with previous reports that, even for patients with early stage disease, overall survival ranges from 30% to 60% [3–5, 10]. Concurrent chemoradiation could be used to treat patients with advanced stage disease, despite their poor prognosis. However, the optimal treatment strategies for patients with early stage disease have not yet been determined [3, 5]. We therefore carried out a retrospective multicenter trial to identify the clinical and pathologic factors prognostic of survival, and to determine optimal treatment strategies for patients with early stage SCNEC.

Table 3 is a review of literature published until a recent date for SCNEC [3, 5, 10–17]. Large tumor size, lymph node metastases, smoking, stage, deep stromal invasion and a pure histologic type have been indicated as possible poor prognostic factors [3–5, 10, 12, 13, 18]. Consistent with other studies [3, 5, 13], we found that FIGO stage was an independent prognostic factor for survival. The 5-year survival rate for patients with stage IB1 tumors was 55.0%, whereas the rate for patients with stage IB2–IIA tumors was 32.0% ($P = 0.02$). Other variables, including a pure histologic type, lymph node metastasis, parametrial extension, and positive surgical margin were tended to adversely affect survival, but the differences were not statistically significant. Since these variables have been found to be significant prognostic factors in SCNEC, as well as in more common subtypes of cervical cancer [3, 5, 12, 19, 20], it is likely that the number of patients in our study was too small to determine statistical significance. Smoking has been shown to be a significant prognostic factor for survival of patients with SCNEC [3, 5]; however, we did not evaluate smoking in this study, both because it is extremely rare in Korean women, as well as being a culturally private concern. There is therefore a paucity of compliance on data resulting from the characteristics of such a retrospective study.

Although radical surgery is not associated with prolonged survival relative to definitive radiation for patients with SCNEC [4, 21], most gynecologic oncologists and patients in Korea favor radical surgery. During this study period, 81 patients were diagnosed with FIGO stage I–IIA SCNEC, of whom 75 underwent radical surgery as the main mode of treatment. Although favorable results have been reported for patients with SCNEC who received concurrent chemoradiation followed by several additional cycles of chemotherapy [3, 21], other studies have reported that radical surgery is an important component in the multimodal treatment of SCNEC [5, 18, 22]. NACT has been recommended for patients with tumor size >4 cm [5, 23]; however, we found that two of five patients with stage IB1 and all six patients with stage IB2–IIA tumors treated with NACT died of their

Table 3. Review of literature published for small cell neuroendocrine carcinoma of the uterine cervix

Reports authors (Y)	Number of cases	FIGO stage	Study period Main treatment	Prognostic factor	Survival outcome
Chang et al. [10]	23	IB–II	1984–1996 S + CT ± RT	CT regimen including VAC or EP ($P = 0.045$)	10 DOD (median F/U 14.6 M, range; 2.0–33.6 M) 13 alive (median F/U 69.2 M, range; 2.9–166 M)
Delaloge et al. [11]	10	IA–IV	1988–1997 S or RT ± CT	Not evaluated	Eight DOD (median survival 16.3 M, range; 8–29 M) Two alive (13 and 53 M)
Boruta et al. [12]	11	IB–IIA	1978–1998 S + CT	Meta-analysis of 34 patients: LN metastasis ($P < 0.01$) VAC ($P = 0.05$), EP ($P = 0.01$) CT	Overall median F/U 14 M, range; 4.5–118 M Eight DOD (median F/U 16 M, range; 4.5–30.8 M) Three alive (median F/U 12 M, range; 9–118 M)
Straughn et al. [13]	16	IB–IV	1978–1999 S and/or RT ± CT or CT alone	Stage of disease ($P = 0.035$) Chromogranin positivity ($P = 0.014$)	11 DOD (median survival 19 M, range; 6–54 M) Five alive
Conner et al. [14]	23	IB–IIB	Not mentioned S and/or RT ± CT	Not evaluated	15 DOD (F/U range; 6–43 M) Seven alive (F/U range; 12–273 M)
Weed et al. [15]	15	IA–IV	1977–1997 S and/or RT ± CT or CT alone	Not evaluated	Survival range: 11–44 M for stage IB–IIA 1–30 M for stage IIB–IV
Chan et al. [5]	34	IB–IV	1979–2001 S ± RT and/or CT or RT ± CT	Smoking ($P = 0.037$) in stage I–IIA Advanced stage ($P = 0.006$) in all stage	Median survival: 30.6 M for stage I–IIA 9.8 M for stage IIB–IV
Ishida et al. [16]	10	IA2–IIB	Not mentioned	Not evaluated	Median survival 2.5 Y
Viswanathan et al. [3]	21	IB–IIIB	1980–2000 S ± CT or RT ± CT	Stage of disease ($P = 0.01$)	5 Y survival rate 29%
Wang et al. [17]	25	IA–IVB	1991–2003 S ± CT ± RT or RT ± CT	No significant prognostic factor	Median survival 24 M, range; 1.5–143 M
Lee et al. (current study)	68	IB–IIA	1997–2003 S ± CT ± RT	Stage of disease ($P = 0.02$)	5 Y survival rate: 55.0% for stage IB1 32.0% for stage IB2–IIA

Y, year; S, surgery; CT, chemotherapy; RT, radiation; VAC, vincristine + doxorubicin + cyclophosphamide; EP, etoposide + cisplatin; DOD, died of disease; F/U, follow-up; M, months; LN, lymph node.

disease. These results indicate that, although NACT might be useful for enhancing the resectability of bulky tumors, it did not improve survival.

Although there are few clinical data supporting the use of adjuvant multimodality treatment in early stage SCNEC disease, most clinicians favor use of chemotherapy and/or radiation because of the strong evidence supporting concurrent chemoradiation in other subtypes of cervical cancer and the high incidence of distant metastases in patients with SCNEC [3, 5, 10, 12, 17, 24]. Patients who received adjuvant radiation, however, had a poorer prognosis than those who did not; even after excluding patients with small tumors (≤2 cm), adjuvant radiation did not improve outcome. This finding is consistent with other study that adjuvant radiation did not alter the course of pelvic recurrence [18]. In contrast, chemotherapy has been indicated because adjuvant chemotherapy, though associated with toxicity, resulted in better survival for patients primarily treated with surgery for SCNEC [5, 10, 18]. In the current study, adjuvant chemotherapy tended to favor survival, but the difference was not statistically significant. When adjuvant chemotherapy and chemoradiation were compared, the latter did not improve outcomes. Although adjuvant radiation may decrease pelvic recurrence, the lack of improvement in overall survival was likely due to the inability to prevent distant metastases. In addition, adjuvant radiation plus concurrent chemotherapy may increase toxicity, with subsequent treatment delays. Because of the limited number of patients in the present study, we could not detect a significant survival benefit in patients who

received adjuvant chemotherapy. Due to high incidence of early nodal and distant metastases in early stage SCNEC, it is likely that adjuvant chemotherapy would enhance survival relative to radiation.

The results of the present study indicate that FIGO stage may act as a surrogate for factors prognostic of survival. Moreover, our results indicate primary radical surgery followed by adjuvant chemotherapy is the preferred treatment modality for patients with early stage SCNEC disease. Although this study was retrospective in design, with a limited number of patients, it is one of the largest series reported to date. We hope that our experience contributes to the foundation of knowledge regarding this rare and aggressive tumor.

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references

1. Ministry of Health and Welfare. 2002 Annual Report of the Korea Central Cancer Registry (2002.1.–2002.12). Republic of Korea: Korea Central Cancer Registry, Ministry of Health and Welfare 2003.
2. Chung HH, Jang MJ, Jung KW et al. Cervical cancer incidence and survival in Korea: 1993–2002. Int J Gynecol Cancer 2006; 16: 1833–1838.
3. Viswanathan AN, Deavers MT, Jhingran A et al. Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence. Gynecol Oncol 2004; 93: 27–33.
4. Crowder S, Tuller E. Small cell carcinoma of the female genital tract. Semin Oncol 2007; 34: 57–63.
5. Chan JK, Loizzi V, Burger RA et al. Prognostic factors in neuroendocrine small cell cervical carcinoma: a multivariate analysis. Cancer 2003; 97: 568–574.
6. Albores-Saavedra J, Gersell D, Gilks CB et al. Terminology of endocrine tumors of the uterine cervix: results of a workshop sponsored by the college of American pathologists and the National Cancer Institute. Arch Pathol Lab Med 1997; 121: 34–39.
7. Gersell DJ, Mazoujian G, Mutch DG, Rudloff MA. Small-cell undifferentiated carcinoma of the cervix. A clinicopathologic, ultrastructural, and immunocytochemical study of 15 cases. Am J Surg Pathol 1988; 12: 684–698.
8. Tsunoda S, Jobo T, Arai M et al. Small-cell carcinoma of the uterine cervix: a clinicopathologic study of 11 cases. Int J Gynecol Cancer 2005; 15: 295–300.
9. McCluggage WG. Immunohistochemistry as a diagnostic aid in cervical pathology. Pathology 2007; 39: 97–111.
10. Chang TC, Lai CH, Tseng CJ et al. Prognostic factors in surgically treated small cell cervical carcinoma followed by adjuvant chemotherapy. Cancer 1998; 83: 712–718.
11. Delaloge S, Pautier P, Kerbrat P et al. Neuroendocrine small cell carcinoma of the uterine cervix: what disease? what treatment? report of ten cases and a review of the literature. Clin Oncol 2000; 12: 357–362.
12. Boruta DM II, Schorge JO, Duska LA et al. Multimodality therapy in early-stage neuroendocrine carcinoma of the uterine cervix. Gynecol Oncol 2001; 81: 82–87.
13. Straughn JM Jr, Richter HE, Conner MG et al. Predictors of outcome in small cell carcinoma of the cervix—a case series. Gynecol Oncol 2001; 83: 216–220.
14. Conner MG, Richter H, Moran CA et al. Small cell carcinoma of the cervix: a clinicopathologic and immunohistochemical study of 23 cases. Ann Diagn Pathol 2002; 6: 345–348.
15. Weed JC Jr, Graff AT, Shoup B, Tawfik O. Small cell undifferentiated (neuroendocrine) carcinoma of the uterine cervix. J Am Coll Surg 2003; 197: 44–51.
16. Ishida GM, Kato N, Hayasaka T et al. Small cell neuroendocrine carcinomas of the uterine cervix: a histological, immunohistochemical, and molecular genetic study. Int J Gynecol Pathol 2004; 23: 366–372.
17. Wang KL, Yang YC, Wang TY et al. Neuroendocrine carcinoma of the uterine cervix: a clinicopathologic retrospective study of 31 cases with prognostic implications. J Chemother 2006; 18: 209–216.
18. Sheets EE, Berman ML, Hrountas CK et al. Surgically treated, early-stage neuroendocrine small-cell cervical carcinoma. Obstet Gynecol 1988; 71: 10–14.
19. Lee JM, Lee KB, Park CY. Prognostic factors predicting survival in patients with FIGO stage IB cervical cancer treated surgically. Int J Gynaecol Obstet 2006; 94: 143–144.
20. Fuller AF Jr, Elliott N, Kosloff C et al. Determinants of increased risk for recurrence in patients undergoing radical hysterectomy for stage IB and IIA carcinoma of the cervix. Gynecol Oncol 1989; 33: 34–39.
21. Hoskins PJ, Swenerton KD, Pike JA 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: 3495–3501.
22. Sevin BU, Method MW, Nadji M et al. Efficacy of radical hysterectomy as treatment for patients with small cell carcinoma of the cervix. Cancer 1996; 77: 1489–1493.
23. Bermudez A, Vighi S, Garcia A, Sardi J. Neuroendocrine cervical carcinoma: a diagnostic and therapeutic challenge. Gynecol Oncol 2001; 82: 32–39.
24. Lewandowski GS, Copeland LJ. A potential role for intensive chemotherapy in the treatment of small cell neuroendocrine tumors of the cervix. Gynecol Oncol 1993; 48: 127–131.