Prognostic factors and treatment comparison in small cell neuroendocrine cervical carcinoma

Z.M. Yin, A.J. Yu, M.J. Wu, J.Q. Zhu, X. Zhang, J.H. Chen, S.H. Yuan, H. Yu

Department of Gynecologic Oncology, The Zhejiang Cancer Hospital, Hangzhou (China)

Summary

Objective: To determine the clinicopathologic factors associated with survival in small cell neuroendocrine cervical cancer (SCNEC) patients. *Materials and Methods:* The study was approved by the ethics committee of the hospital. The records of 64 SCNEC patients from 9,474 Chinese patients with cervical cancer at the Zhejiang Cancer Hospital were reviewed. Kaplan-Meier and Cox regression methods were used for analyses. *Results:* Of 64 patients, 47 had Stages I-IIA, 12 had Stages IIB-IVA, and five had Stage IV-B disease. A total of 81.25% underwent surgery, 89.1% received chemotherapy, 62.5% received radiation, 34.4% received neoadjuvant chemotherapy (NACT), and 34.4% received concurrent chemoradiation (CCRT). The median follow-up for surviving patients was 35.7 months (range: 0.5-160), and 29 (50%) of the 58 patients with Stages I-III had either disease recurrence or progression. The median time to first relapse was 10.5 months (range: 0-88.2). The five-year overall survival of patients in Stages I-IIA and IIB-IVB disease was 54.4% and 9.8%, respectively ($p = 0.001$). Women with early-stage (Stages IB-IIA) disease had median survival rates of 94 months compared with 21.4 months in the advanced-stage (Stages IIB-IVB) group. In univariate analysis, advanced-stage ($p = 0.001$), without radical surgery ($p = 0.002$) and deep stromal invasion (DSI) ($p = 0.000$) were considered poor prognostic factors. In a multivariable analysis, tumor size > four cm ($p = 0.048$), postoperative radiation ($p = 0.038$) for early-stage patients and the FIGO stage($p = 0.040$) of disease in the overall population remained as independent prognostic factor of survival. *Conclusion:* The FIGO stage was found to be an independent prognostic factor of SCNEC. In addition, tumor size > four cm and DSI was associated with poor survival. Postoperative radiation for early-stage patients may not improve survival. The role of primary and postoperative NACT or CCRT is unclear. Clinical trials are needed.

Key words: Neuroendocrine carcinoma; Prognosis; Small cell; Uterine cervix.

Introduction

Small cell neuroendocrine carcinoma of the uterine cervix (SCNEC) is a rare gynecologic malignancy that represents less than three percent of all cervical cancer [1-3]. The histology and biologic behaviors of the tumor are similar to that of small cell lung carcinoma (SCLC), which is highly aggressive. The tumor is characterized by a high incidence of early distant metastases, resulting in poorer prognosis than other subtypes of cervical cancer [3-5]. Due to its rarity studies exploring therapeutic efficacy in this setting generally require long enrolment period to obtain a sufficient number of cases. Therefore, to date most studies of neuroendocrine cervical cancer are comprised of a small series and case reports, making it difficult to draw conclusions on prognostic factors and optional treatment modalities.

Given the aggressive nature of neuroendocrine small cell cervical cancer, it is imperative to identify potential treatments that can improve the outcomes of these patients. As such, the authors carried out a retrospective review to determine the clinicopathologic factors associated with survival, patterns of relapse, and potential therapeutic modalities that may improve survival in neuroendocrine cervical cancer patients.

Revised manuscript accepted for publication July 23, 2013

Materials and Methods

The study was approved by the ethics committee of the hospital. Due to the retrospective nature of the study, informed consent was waived. A total of 70 patients with SCNEC were identified from 9,474 Chinese patients with cervical cancer through registry databases at the Zhejiang Cancer Hospital from January 1997 to December 2010. All histopathologic review was carried out by two independent pathologists from the Pathology committee of the Zhejiang Cancer Hospital. Six patients were excluded because follow-up data were incomplete. Thus, the study population consisted of 64 patients.

Of the 64 patients with available paraffin blocks who were diagnosed as having small cell carcinoma on the basis of hematoxylin and eosin (H&E) staining, all had positive staining for one or more neuroendocrine markers. All tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system for cervical cancer based on physical examination, chest X-ray, intravenous paleography, cystoscopy, sigmoidoscopy, and abdomino-pelvic computed tomography (CT) or magnetic resonance imaging (MRI) scan. When there were suspicious findings on chest X-ray or the presence of signs and symptoms upon physical examination, a CT scan of the chest and/or brain was carried out.

For primary treatment, 52 patients underwent radical hysterectomy (RH), 57 patients received chemotherapy, 22 patients had neoadjuvant chemotherapy (NACT), and 19 patients received concurrent chemoradiation (CCRT). Among patients who received adjuvant chemotherapy or NACT, 38 received etoposide together with cisplatin (EP), five received etoposide together with adriamycin and cisplatin (EAP), four received paclitaxel and cisplatin (TP), and two received bleomycin, vincristine, and cisplatin (BVP). In addition, cyclophosphamide, adriamycin, and vin-

cristine (CAV), ifosfamide, adriamycin, and cisplatin (IAP), paclitaxel and carboplatin (TC), ifosfamide and etoposide and (IE), and ifosfamide together with etoposide and cisplatin (IEP) was given in one patient. Radiation was delivered using external beam radiation therapy and intracavitary brachytherapy. External-beam therapy was delivered using anterior-posterior fields, box fields, or conformal radiotherapy and ten MV photons. Intracavitary treatment was delivered using Fletcher-suit after loading high-dose-rate applicators.

The clinical and pathological variables analyzed included patient age, tumor size, stage, lymph node involvement (LNI), depth of stromal invasion (DSI), lymph vascular space invasion (LSI) , and treatment modalities. The primary end point was any cancer-related death. All end points were calculated from the date of diagnosis 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 China National Statistical Office.

All statistical analyses were performed using SPSS v.19 software. Survival curves were estimated using the Kaplan-Meier method, and *p* values were generated using the log-rank test. Cox regression analysis was used for multivariate analysis of significant variables. All tests were two-tailed with p values < 0.05 considered significant. All end points were updated in May 2012.

Results

The median age of the 64 patients was 37.5 years (range: 25-85). The mean gravidity of the 64 patients was three times (range: 0-6). Of the 64 patients, 28 had Stage IB1, six had Stage IB2, seven had Stage IIA1, six had Stage IIA2, six had Stage IIB, one had Stage IIIA, four had Stage IIIB, one had Stage IVA, and four had Stage IVB disease. Vaginal bleeding at presentation was noted in 59.4% patients and 25% of patients had cervical bleeding. In addition, 10.9% of patients had vaginal drainage and 4.7% had other symptoms.

Of the 64 patients with FIGO Stages IB-IVB SCNEC, the estimated three- and five-year overall survival (OS) rates for all patients were 53.1% and 36.5%, respectively (Figure 1). Women with early-stage (Stages IB-IIA) disease had median survival rates of 94 months compared with 21.4 months in the advanced-stage (Stage IIB-IVB) group (Table 1). The five-year OS rates for all patients in Stages IB1-IIA and IIB-IVB diseases were 54.4% and 9.8%, respectively ($p = 0.001$; Figure 2).

The median survival was 35.7 months (range: 0.5-160) for all patients. The five-year survival for all patients who received a RH was 48.8% compared to 16.7% for those who did not undergo a RH ($p = 0.002$). Women who received a RH had median survival rates of 54.4 months compared with 16.5 months for those who did not undergo a RH (Table 1). In univariate contrast, age ($p = 0.666$), tumor size ($p = 0.558$), chemotherapy ($p = 0.712$), radiotherapy ($p = 0.455$), CCRT ($p = 0.242$), NACT ($p = 0.338$), and menopause ($p = 0.107$) were not found to be important prognostic factors. In a multivariate analysis, FIGO stage (HR, 2.83; 95%CI, 1.05-7.51; $p = 0.040$) remained as a significant independent prognostic factor for survival (Table 1).

For 47 patients in FIGO Stages IB-IIA, in univariate contrast, age ($p = 0.687$), menopause ($p = 0.510$), stage ($p = 0.532$), tumor size ($p = 0.714$), primary RH ($p = 0.132$), radiotherapy ($p = 0.082$), chemotherapy ($p = 0.631$), NACT ($p = 0.109$), and CCRT ($p = 0.778$) were not found to be important prognostic factors. Although not statistically significant, patients with Stages IB-IIA who received NACT tended to have a better prognosis, with a five-year survival of 76.9% compared to 46.7% for those who did not undergo NACT ($p = 0.109$). Contrary to the authors' experience, patients with Stages IB-IIA who received adjuvant radiation tended to show a worse prognosis compared to those who did not receive adjuvant radiation (five-year survival: 46.3% vs. 78%, respectively). To examine the variables identified as important in univariate analyses further, a multivariate analysis was performed. Tumor size > four cm ($p = 0.048$), postoperative radiation ($p = 0.038$) for early-stage patients as significant independent poor prognostic factors for survival in early-stage disease (Table 2).

For some of the patients who received a RH with surgical pathology, LNI, LSI, and DSI were assessed, and DSI (stromal invasion depth of cervix > 2/3) was found to be significantly associated with a worse prognosis compared to those patients without DSI (five-year survival rate: 22.4% vs. 82.5%, respectively $p < 0.001$. Although not statistically significant, LNI and LSI tended to adversely affect survival (Table 3).

Forty (62.5%) of the 64 patients exhibited recurrence or uncontrolled tumor. Twenty-nine (50%) of the 58 patients with Stages I-III had a relapse. The median time to first relapse was 10.5 months (range: 0-88.2). Among 40 patients, 35 patients succumbed to the disease, and four patients were alive with disease. No patient had brain metastasis as the sole site of first recurrence. Among 64 patients, seven (10.9%) patients developed brain metastases; however, seven (100%) patients had brain metastases concurrently or after lung metastases. Among 11 patients with lung metastases, seven (63.6%) patients developed brain metastases.

Among the 64 analyzed patients, 28 patients were in Stages IB1, with 12 and 16 patients with and without recurrence, respectively. Based on the clinical and pathological factors for these two groups of patients, the treatment modality was similar, but the number of DSI, LSI, and LNI occurrences was higher in the recurrence group (Table 4).

Discussion

Based on reports from different hospitals, SCNEC is a rare disease [6]. That is associated with a poor prognosis. The present results found that the estimated three- and five-year survival rates for all patients were 53.1% and 36.5%, respectively. The five-year OS rates of patients with Stages

Table 1. — Demographic and treatment factors with associated five-year OS (n = 64).

Variables			Median survival	Five-year OS		Multivariate	
		n	(mos)	%	Univariate *p*	HR (95%CI)	*p*
Age	≤ 40	36	54.5	46.2	0.666	-	-
	> 40	28	35.7	39.1		-	-
Menopause	Yes	15	27.8	27.5	0.107	1.25 (0.54-2.90)	0.597
	No	49	54.5	47		-	-
Stage	IB-IIA	47	94	54.4	0.001	2.83 (1.05-7.51)	0.040
	IIB-IV	17	21.4	9.8		-	-
Tumor size	≤ 4cm	45	39.7	47.9	0.558	-	-
	> 4cm	19	28.8	26.3		-	-
RH	Yes	52	54.4	48.8	0.002	0.78(0.25-2.43)	0.663
	No	12	16.5	16.7		-	-
RT	Yes	40	31.3	39.6	0.455	-	-
	No	24	54.5	39.5		-	-
CT	Yes	57	35.7	42.4	0.712	-	-
	No	7	35.8	42.9		-	-
NACT	Yes	22	54.5	43.2	0.338	0.60 (0.25-1.45)	0.258
	No	42	34.9	40.2		-	-
CCRT	Yes	19	39.7	52.6	0.242	1.09 (0.50-2.36)	0.829
	No	45	31.1	36		-	-

NACT: neoadjuvant chemotherapy; RT: radiation; CT: chemotherapy; NART: neoadjuvant radiation; CCRT: concurrent chemoradiation; RH: radical hysterectomy.

Table 2. — Demographic and treatment factors with associated five-year OS for IB1-IIA (n = 47).

Variables			Five-year OS		Multivariate	
		n	%	Univariate *p*	HR (95%CI)	*p*
Age	≤ 40	28	60.3	0.687	-	-
	> 40	19	46.6		-	-
Menopause	Yes	39	57.3	0.510	1.47 (0.43-5.04)	0.538
	No	8	38.1		-	-
Stage	IB1	28	62.7	0.532	-	-
	IB2-IIA	19	42.1		-	-
Tumor size	≤ 4cm	37	55.7	0.714	4.02 (1.01-15.93)	0.048
	> 4cm	10	50		-	-
RH	Yes	44	33.3	0.132	0.62 (0.14-2.71)	0.522
	No	3	55.8		-	-
RT	Yes	32	46.3	0.082	4.53 (1.09-18.84)	0.038
	No	15	78		-	-
CT	Yes	43	55.1	0.631	-	-
	No	4	50		-	-
NACT	Yes	13	76.9	0.109	0.30 (0.07-1.21)	0.091
	No	34	47.1		-	-
CCRT	Yes	18	55.6	0.778	-	-
	No	29	53.4		-	-

NACT: neoadjuvant chemotherapy; RT: radiation; CT: chemotherapy; NART: neoadjuvant radiation; CCRT: concurrent chemoradiation; RH: radical hysterectomy.

Table 3. — Pathologies characteristic and associated five-year PFS and OS for postoperative patients.

Variables			Five-year PFS		Five-year OS	
		n	%	Univariate *p*	%	Univariate *p*
LNI	Yes	13	33.8	0.177	35.9	0.391
	No	35	51.1		51.9	
LSI	Yes	25	27.8	0.052	34	0.328
	No	21	56.7		55.6	
DSI	Yes	26	13.9	0.000	22.4	0.000
	No	20	84.4		82.5	

LNI: lymph node involvement; LSI: lymphovascular space invasion; DSI: depth of stromal invasion.

Table 4. — The clinic and pathologic factor compare for recurrence and no recurrence patients of Stage I B1 (n =28).

Variables	Recurrence	No recurrence
Patients	12	16
Age (mean)	38.2 (30-57)	41.6 (27-83)
Treatment modality		
RH	12 (100%)	15 (93.8%)
CT	10 (83.3%)	12 (75%)
RT	12 (100%)	10 (62.5%)
CCRT	5 (41.7%)	7 (43.8%)
NACT	1 (8.3%)	4 (25%)
Period of CT (median)	3 (1-7)	4 (0-8)
DSI	9 (75%)	3 (18.8%)
LSI	8 (66.7%)	3 (18.8%)
LNI	1 (8.3%)	2 (12.5%)

NACT: neoadjuvant chemotherapy; RT: radiation; CT: chemotherapy; CCRT: concurrent chemoradiation. RH: radical hysterectomy; LNI: lymph node involvement; LSI: lymphovascular space invasion; DSI: depth of stromal invasion.

I-IIA and IIB-IVB disease were 54.4% and 9.8%, respectively, which were consistent with previous reports (40-50% and 8.0%, respectively) [7-8].

Because SCNEC occurs infrequently, it is difficult to perform a randomized controlled clinical trial to determine optimal therapy. The current study analyzed a large series of patients diagnosed with SCNEC from a single institution experience, which included an update of a previous reported series [9]. The objective was to identify the clinical and pathologic factors that are responsible for survival of women with this aggressive tumor.

Stage, large tumor size, DSI, lymph node metastases, smoking, and a pure histologic type have been found to be possible poor prognostic factors in the literature [3-5, 10-13]. The present data showed that the FIGO stage is independent prognostic factors for all patients. Consistent with other studies [4, 5,12], according to the present data, the recurrence or progression rate increases as the stage of development increased. For patients with Stages I, II and III-IV, the recurrence or progression rate was 44%(15/34), 68%(13/19), and 100%(10/10), respectively, indicating that the FIGO stage was an important prognostic factor for survival.

In early-stage disease, patients with small (< four cm) tumors were found to have better survival rates than those with large (> four cm) tumor in multivariate analysis (p = 0.048). Similarly, Chan *et al.* Showed that in early-stage disease patients with tumor < two cm had significant better survival rates than patients with > two cm lesions in univariate analysis [5, 13].

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 CCRT in other subtypes of cervical cancer [4, 5, 10, 11, 14]. In early-stage disease, patients who received adjuvant radiation, however, had a poorer prognosis than those who did not; the five-year estimated survival rate were 46.3% and 78%, respectively, in multivariate analysis (p = 0.038). In the current study, adjuvant radiation did not improve outcome and this finding is consistent with other studies that adjuvant radiation did not alter the course of pelvic recurrence [8, 13]. However the present authors found that 32 patients with Stages IB-IIA who received radiation had a mean of 1.437 risk factors (LNI, LSI, DSI, or large tumor size), but 15 patients who did not receive radiation had a mean of 0.733 risk factors. This suggests that the gynecologic oncologists at the present hospital tended to select patients with more risk factors for radiation therapy, similar to cervical cancer patients. This may partly explain why patients who had received radiation had a prognosis than patients who had not received radiation. However, the value of radiation in early-stage SCNEC patients will require further evaluation through addition clinical trials [9].

The authors also observed that DSI was a poor prognostic factor. The five-year survival rate for patients without DSI was 82.5% compared to 22.4% for patients with DSI (p < 0.001). These results were consistent with those of a previous a study [15]. Although not statistically significant, LNI and LSI tended to adversely affect survival. Due to the small number of patients in the study, it is difficult to gain independent prognostic factors from DSI, LNI, and LSI. However, when the authors compared the clinical and pathological factors of 28 IB1 patients with and without recurrence, the treatment modality was similar, but the number of DSI, LSI, and LNI occurrences was completely different. In the recurrence group, there were nine (75%) patients with DSI, eight (66.7%) patients with LSI, and one (8.3%) patient with LNI, whereas there were three (18.8%) patients with DSI, three (18.8%) patients with LSI, and two (12.5%) patients with LNI in the group without recurrence. These results indicated that patients with more risk factors (DSI, LSI, or LNI) had a higher rate of recurrence and shorter survival time.Therefore, these factors may be prognostic indicators for patients, and a sufficient number of chemotherapy courses is needed for those patients with these risk factors.

The current data also showed that RH (p = 0.002) is an important prognostic factor in all patients. RH may have been associated with better survival rates because most patients who had received the procedure were early-stage patients. However, for patients with Stages IB-IIA , RH did not provide an obvious survival advantage, which was consistent with other studies showing that radical surgery was not associated with prolonged survival relative to definitive radiation for patients with SCNEC [3, 16]. Nevertheless, most gynecological oncologists and patients in China still favor RH as the treatment choice.

Adjuvant chemotherapy tended to favor survival, although the effect did not attain statistical significance. Many authors have recommended adjuvant chemotherapy due to the aggressive behavior of this disease [10, 11]. A recent study of 188 patients showed that chemotherapy and chemoradiation were independent prognostic factors for improving survival [7]. It is possible that the small sample size of the present study was not sufficient for showing a benefit associated with chemotherapy in the treatment of this the aggressive cancer.

NACT has been recommended for patients with tumor size > four cm [5, 17], However, another previous study that found that patients who received NACT tended to have a worse median OS that those who did not receive NACT [8]. Whether NACT can improve the prognosis for cervical cancer patients remains a matter of debate. The current data did show that the overall five-year survival for patients with early-stage disease who received NACT was higher compared to those who did not receive NACT (univariate: 76.9% vs. 47.1%, respectively). In the current study, NACT was found to have a marginal significant in univariate analysis ($p = 0.109$) or in multivariate analysis ($p = 0.091$). With more patients NACT may prove to be an prognostic for survival. The authors hypothesized that different chemotherapies, chemotherapy interval times, and chemotherapy periods may result in different results. Most gynecologic oncologists choose NACT for patients with tumors > four cm, and the use of NACT for patients with early-stage tumors may provide them with the opportunity for radical surgery. The present data showed that for 13 early-stage patients who received NACT, four (30.7%) patients achieved a complete response (CR) after one to two cycles of NACT. These four patients achieved long-term survival without recurrence, with a mean survival time of 77.1 months (range: 33.9-160). Therefore, NACT may be an approach for assessing response to treatment.

CCRT is recommended for small cell carcinoma of the lung, but the benefit of CCRT for SCNEC is unclear. Some studies have shown that chemoradiation is associated with higher survival in SCNEC [7, 17], but other studies have found that chemoradiation does not improve survival compared to adjuvant chemotherapy alone for early-stage patients [8]. Therefore, the value of CCRT for early-stage SCNEC patients will require further assessment through additional clinical trials.

The authors recognize some of the limitations of this study. This was a retrospective analysis of a single institutional experience with a small number of patients. Nevertheless, they hope that their experience contributes to the foundation of knowledge regarding this rare and aggressive tumor. Their data indicate that patients with early-stage tumors, tumor size < four cm, and without DSI or less risk factors (DSI, LSI, or LNI) are associated with improved survival.

References

[1] Tsunoda S., Jobo T., Aria M., Imai M., Kanai T., Tamura T., *et al.*: "Small-cell carcinoma of the uterine cervix: a clinicopathologic study of 11 cases". *Int. J. Gynecol. Cancer*, 2005, *15*, 295.

[2] Chung H.H., Jang M.J., Jung K.W., Won Y.J., Shin H.R., Kim J.W., *et al.*: "Cervical cancer incidence and survival in Korea: 1993-2002". *Int. J. Gynecol. Cancer,* 2006, *16*, 1833.

[3] Crowder S., Tuller E.: "Small cell carcinoma of the female genital tract". *Semin. Oncol.*, 2007, *34*, 57.

[4] Viswanathan A.N., Deavers M.T., Jhing A., Ramirez P.T., Levenback C., Eifel P.J.: "Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence". *Gynecol. Oncol.*, 2004, *93*, 27.

[5] Chan J.K., Loizzi V., Burger R.A., Rutgers J., Monk B.J.: "Prognostic factors in neuroendocrine small cell cervical carcinoma: a multivariate analysis". *Cancer*, 2003, *97*, 568.

[6] Chen J., Macdonald O.K., Gaffney D.K.: "Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix". *Obstet. Gynecol.*, 2008, *111*, 1394.

[7] Cohen J.G., Kapp D.S., Shin J.Y., Urban R., Sherman A.E., Chen L.M., *et al.*: "Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients". *Am. J. Obstet. Gynecol.*, 2010; *203*, 347.e1. doi: 10.1016/j.ajog.2010.04.019. Epub 2010 Jul 1.

[8] Lee J.M., Lee K.B., Nam J.H., Ryu S.Y., Bae D.S., Park J.T., *et al.*: "Prognostic factors in FIGO stage IB–IIA small cell neuroendocrine carcinoma of the uterine cervix treated surgically: results of a multicenter retrospective Korean study". *Ann. Onc.*, 2008, *19*, 321.

[9] Lan-Fang L., Hai-Yan S., Zuo-Ming Y., Jian-Qing Z., Ya-Qing C.: "Small cell neuroendocrine carcinoma of the cervix: analysis of the prognosis and role of radiation therapy for 43 cases". *Eur. J. Gynaecol. Oncol.*, 2012, *33*, 68.

[10] Chang T.C., Lai C.H., Tseng C.J., Hsueh S., Huang K.G., Chou H.H.: "Prognostic factors in surgically treated small cell cervical carcinoma followed by adjuvant chemotherapy". *Cancer*, 1998, *83,* 712.

[11] Boruta D.M. 2nd., Schorge J.O., Duska L.A., Crum C.P., Castrillon D.H., Sheets E.E.: "Multimodality therapy in early-stage neuroendocrine carcinoma of the uterine cervix". *Gynecol. Oncol.*, 2001, *81*, 82.

[12] Straughn J.M. Jr., Richter H.E., Conner M.G., Meleth S., Barnes M.N.: "Predictors of outcome in small cell carcinoma of the cervix—a case series". *Gynecol. Oncol.*, 2001. *83*, 216.

[13] Sheets E.E., Berman M.L., Hrountas C.K., Liao S.Y., Disaia P.J.: "Surgically treated, early-stage neuroendocrine small-cell cervical carcinoma". *Obstet. Gynecol.*, 1988, *71*, 10.

[14] Wang K.L., Yang Y.C., Wang T.Y., Chen J.R., Chen T.C., Chen H.S., *et al.*: "Neuroendocrine carcinoma of the uterine cervix: A clinicopathologic retrospective study of 31 cases with prognostic implications". *J. Chemother.*, 2006, *18*, 209.

[15] Tian W.J., Zhang M.Q., Shui R.H.: "Prognostic factors and treatment comparison in early-stage small cell carcinoma of the uterine cervix". *Oncol. Lett.*, 2012, *3*, 125.

[16] Hoskins P.J., Swenerton K.D., Pike J.A., 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.

[17] Bermudez A., Vighi S., Garcia A., Sardi J.: "Neuroendocrine cervical carcinoma: a diagnostic and therapeutic challenge". *Gynecol. Oncol.*, 2001, *82*, 32.

Address reprint requests to:
H. YU, M.D.
Department of Gynecologic Oncology,
Zhejiang Cancer Hospital,
No 38, Guangji Road, Hangzhou 310022 (China)
e-mail: ayuhua@126.com