Small cell neuroendocrine carcinoma of the cervix: analysis of the prognosis and role of radiation therapy for 43 cases

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Summary

Objective: To explore the outcomes and pattern of recurrence in patients with small cell neuroendocrine carcinoma of the cervix (SCNEC), and to determine the effects of adjuvant radiation therapy on survival in patients with early-stage disease. *Methods:* A retrospective analysis of 43 patients with SCNEC was carried out at Zhejiang Provincial Tumor Hospital between January 1985 and August 2007. All pathological specimens were examined and definitively diagnosed by two independent pathologists.The radiotherapeutic efficacy and prognosis of SCNEC were explored. Patient survival status was analyzed with the Kaplan-Meier method and survival rate was compared with the log-rank test; $p < 0.05$ was considered statistically significant. *Results:* Of 43 patients, 32 were early-stage and 11 were advance-stage. The median age was 45 years (range 25-85 years). There were 21 cases of metastasis or progression occurring in the lungs, retroperitoneal lymph node and brain within two years. In early-stage patients, distant metastasis or progression occurred in 13 cases within two years. The estimated 5-year survival rate for the entire group was 29%. Median overall survival for patients with early-stage disease was 89.6 months and 34.4 months for patients with advance-stage disease ($p = 0.001$). The 3-year survival for early-stage patients who received postoperative adjuvant chemotherapy was 57.1% compared with 56.4% for those who underwent adjuvant chemoradiotherapy, and their median survival periods were 84.7 and 89.1 months, respectively ($p = 0.671$). *Conclusion:* We confirmed the unfavorable prognosis related to early nodal and hematogenous metastasis in SCNEC, resulting in a relatively poor prognosis; clinical staging was an important prognostic factor. Chemoradiotherapy may be provided for advance-stage patients. For early-stage patients, the efficacy and site of postoperative adjuvant radiotherapy need further evaluation.

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

Introduction

Small cell neuroendocrine carcinoma arising from the uterine cervix is an uncommon malignancy comprising less than 3% of all cervical malignancies [1, 2]. It is known to be highly malignant and is associated with the lowest rate of survival of the cervical cancers due to the tumor's propensity for distant spread. The time interval of a definitive diagnosis to recurrence is less than 35 months and median survival period is around 14.19 months. Five-year survival rates vary from 14%-30% [3, 4]. Long-term survival can be achieved only in patients with limited stage disease. Due to the rarity of this disease, it has been difficult to conduct prospective trials. Clear treatment recommendations for SCNEC have not been defined. How to treat SCNEC patients more effectively and improve their survival rates have become a great challenge for gynecological oncologists. Currently there is a heated debate on the effect and mode of radiation for SCNEC. For SCNEC patients beyond clinical Sage IIA, the survival period never surpassed 30 months in the literature reports [5-7]. Among the SCNEC patients admitted and treated at our hospital, two Stage IIb patients who underwent radiotherapy survived for 112 and 114 months, respectively.

We performed a retrospective review to explore the outcomes and pattern of recurrence in 43 patients with SCNEC. The objectives were to compare the effects of adjuvant chemoradiotherapy versus adjuvant chemotherapy on the survival rate in patients with early-stage disease and to explore the role of radiation of SCNEC so as to provide rationale for the therapy of SCNEC.

Materials

Clinical data

During the period January 1985 to August 2007, a total of 43 cases of SCNEC at first diagnosis were admitted and treated at our hospital. All were definitively diagnosed by two pathologists after a second examination of specimen slides. All cases received gynecological examinations, chest films and such imaging studies of the abdomen and pelvis as computed tomography (CT) and magnetic resonance imaging (MRI). Staging was in strict accordance with the FIGO International Federation of Gynecology and Obstetrics criteria for cervical carcinoma. The early stages were IB-IIA and advanced stages were IIB-IV. The radical surgical approach was extensive hysterectomy plus pelvic lymph node dissection with or without paraaortic lymph node dissection. The radical radiation was extra-pelvic plus intracavitary radiotherapy; the cumulative dose of Point A was 73-77 GY, postoperative adjuvant radiotherapy external whole pelvic radiotherapy at a dose of 45 Gy/25 sessions (1.8 Gy per session, 5 sessions per weeks). In case of common iliac lymph node or abdominal aortic lymphatic metastases, abdominal paraaortic radiotherapy was provided at a dose of 40 Gy. Most patients received the chemotherapeutic protocol of EP (etoposide & cisplatin). The adjuvant chemotherapeutic protocol was cisplatin 60 mg/m^2 + VP16 100 mg (dl-5), and concurrent chemotherapy was one course of chemotherapy within 24 hours of the initiation of radiotherapy,

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Fig. 1

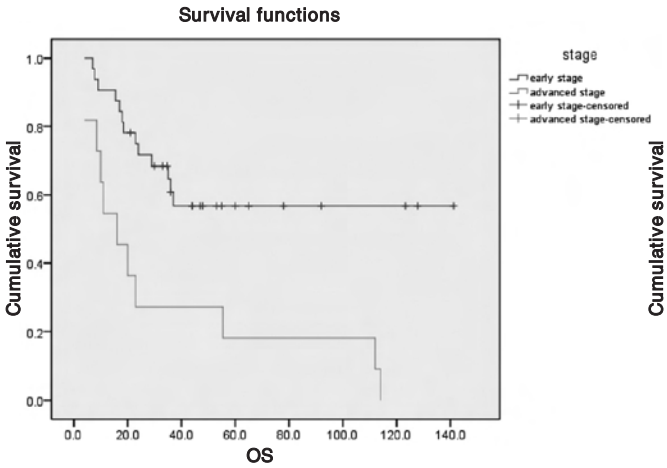

Figure 1. — Overall survival according to stage of SCNEC.

Fig. 2

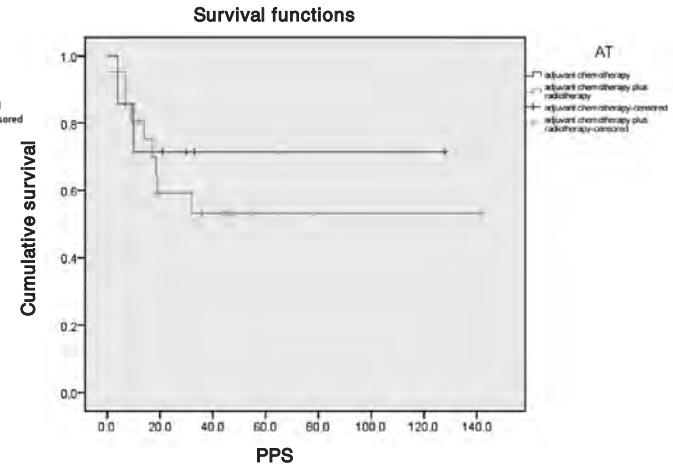

Figure 2. — Progression-free survival based on modality of adjuvant treatment in early-stage patients.

cisplatin 30 mg/m^2 +VP16 50 mg (dl-5), repeated for 3-4 weeks. Since 2007, two patients received the TP protocol of chemotherapy, i.e. taxol 175 mg/m^2 + cisplatin 60 mg/m^2. All patients received an average of four courses (range: 2-6).

Follow-up

The follow-up period began from the first day of definite diagnosis until August 10, 2010. Follow-up rate was 100%, and the median follow-up period was 36 months (5-141.2. months).

Statistical methods

The SPSS 15.0 statistical package was used. Clinical data are described with values of percentages or medians. Total survival time was counted from the definitive diagnosis until the final follow-up or death, and the progression-free survival time was calculated from the definitive diagnosis until initial recurrence or progression. Survival status was analyzed by the Kaplan-Meier method, and the log-rank test was used to compare the survival rate; $p < 0.05$ was considered as having statistical significance.

Results

General data: There were a total of 43 patients with a (median age of 45 years old - range: 25-85). Fifteen had Stage IB1, six Stage IB2, 11 Stage IIA, two Stage IIB, one Stage IIIA, three Stage IIIB and five Stage IV. Thirty-two patients were in early-stage (Stage IIA or below). Thirty-four patients had a pure histological type composed of SCNEC, five patients had a mixed histological pattern associated with squamous cell carcinnoma and four patients had a mixed histological pattern associated with adenocarcinoma in addition to the SCNEC component.

Therapeutic protocols: A total of 34 patients underwent operations. Except for one Stage IVb patient undergoing palliative cytoreductive operation, the others received a radical hysterectomy. There were 26 cases of radiotherapy: radical radiotherapy (n = 4); simple radiotherapy (n = 1); concurrent chemoradiotherapy (n = 3); adjuvant pelvic radiotherapy and/or adjuvant aortic radiotherapy (n = 22). None of the patients received prophylactic abdominal paraaortic or whole brain radiotherapy. Thirty-nine patients underwent chemotherapy: neoadjuvant chemotherapy (n = 10), simple palliative chemotherapy (n = 5) and adjuvant chemotherapy (n = 30); of those 30 patients treated with adjuvant chemotherapy, there were six patients treated with neoadjuvant chemotherapy as well as double counting against those ten patients with pure neoadjuvant chemotherapy.

Twenty-eight early-stage patients received comprehensive therapy: postoperative adjuvant chemotherapy (n = 8) and postoperative adjuvant chemoradiotherapy (n = 20). Demographic characteristics of the patients and therapeutic protocols are shown in Table 1.

Time and location of metastasis or recurrence: At the final follow-up, 23 patients had either metastasis or progression. Among them, the metastatic locations for two cases remained undefined. One case had a local pelvic recurrence without receiving adjuvant radiotherapy. The remaining 20 cases had distant metastasis. The metastatic sites were in descending order lungs, retroperitoneal lymph node, breast and brain (in Table 2). There were four cases of brain metastasis; among them, three cases had concurrent lung metastasis and one case bony and systemic metastasis. Thirteen (41%) early-stage patients had distant metastasis or progression within two years, and one Stage IIA patient had metastasis to the lung at 31.2 months after diagosis (Table 3).

Survival rate: The follow-up period was up to August 2010. Twenty-two patients had already died. The median survival time was 37 months. The 3-year OS (overall survival) rates for 32 early-stage patients and 11 advance-stage patients were 56.7% and 27.3%, respectively. The median survival periods were 89.6 and 34 months, respectively ($p = 0.001$) (Figure 1). Among 11 advance-staged patients, the median survival period was 16 months. Nine cases died within two years. After radiotherapy, two Stage IIB patients survived for 112 and 114 months, respectively, and one had still survived at the

Table 1. — *Characteristics of patients with SCNEC*.

Variable	
Mean age (range)	45 (25-85)
FIGO stage (N)	
IB1	15
IB2	6
IIA	11
IIB	3
IIIB	3
IV	5
Tumor size (%)	
≤ 4 cm	34
> 4 cm	9
Tumor homology (%)	
Pure	34
Mixed	9
Primary treatment modality (n)	
Surgery only	1
Radiation only	1
Chemotherapy only	5
Multimodality therapy	36
Adjuvant therapy for early-stage patients	
Chemoradiation	20
Radiation	0
Chemotherapy	8
Neoadjuvant chemotherapy	10

Table 2. — *Outcome and patterns of recurrence or matastasis in a 2-year period*.

Variable	n	%
Recurrence rate		
Early stage	13	41
Advanced stage	8	63
Sites of recurrence		
Lung	10	
Lymph node	7	
Brain	4	
Chest	1	
Bone	2	
Live	1	
Pelvis	1	
Unknown sites	2	

Table 3. — *Rate and site of first recurrence in patients with early-stage disease*.

N	32
Local, only	0
Distant, only	11 (34%)
Local and distant	1 (3%)
Unknown sites	2 (6%)
Total number	14 (43%)

time of last follow-up. The early-stage patients received either postoperative adjuvant chemotherapy (n = 8) or postoperative adjuvant chemoradiotherapy (n = 20). The 3-year OS rates of the two patient groups were 57.1% and 56.4%, respectively. The median survival periods were 84.7 and 89.1 months, respectively ($p = 0.671$) (Figure 2). The median progression-free survival (PFS) period was 93.3 and 81.9 months, respectively ($p = 0.569$).

Discussion

Prognosis of SCNEC

Small cell carcinoma of the cervix is a rare gynecological malignancy. The natural history of this disease differs from the more commonly seen squamous cell or adenocarcinoma. It is noted for its very aggressive behavior and has the poorest prognosis of the various cervical carcinomas, even after multimodal therapy. In our cohort of 43 patients, the 3- and 5-year OS rates were 45% and 29%, respectively. The median survival period was 45 months. The 3-year OS rates of early- and late-stage patients were 56.7% and 27.3%, respectively. The difference had statistical significance. In some previous retrospective reports, the 3-year survival rate of SCNEC was around 30% and the 5-year OS rate around 20-25 [8, 9]. The 5-year OS rates of early to middle, and late patients were 36.7% and 0-8.9%, respectively [10]. It was reported in the literature that patients with diseases beyond Stage IB1 had a survival period of over 30 months [5]. Clinical and imaging staging are important prognostic factors [8-11]. The prognosis of this disease is limited due to tumor propensity for distant hematogenous metastases. Even in early stage, 40% to 60% of patients experience lymph node metastasis and hematogenous metastasis within one year of diagnosis [8, 12, 13]. In our cohort, 23 patients had metastasis or progression at the last follow-up, and the rate of definitive distant metastasis was 87%. The metastatic sites were in descending order lungs, retroperitoneal lymph nodes and breast. Four brain metastasis patients had concurrently lung and other distant metastases. No single patient had brain metastasis alone. Even for the early-stage patients, the rate of distant metastasis or progression within two years was as high as 41%. Only one Stage IIA case had lung metastasis at 31 months after diagnosis. As recently reported by Lee *et al*. [13] the median PFS of SCNEC was merely 16.9 months. The rate of recurrence or distant metastasis for early patients was up to 67%, and it was obviously higher than 6% for cervical squamous cell carcinoma at the same stage [12]. As demonstrated by the analytic results of Kasamatsu *et al*., the recurrence rate of early SCNEC patients was up to 70%, and 80% occurred outside the pelvic cavity [14]. As reported by Zinvanovic *et al*., the 3-year PFS of SCNEC was only 22% and the median progression period nine months [8].

Therapeutic approach for SCNEC

Because of the rarity of the disease the Gynecologic Oncology Group attempted to study small cell cervical carcinoma (protocol 66) between 1982 and 1986, but failed to recruit sufficient numbers of patients. To date, most studies on neuroendocrine cervical carcinoma are comprised of only small series and case reports; no large-scale multicenter study has been conducted on the disease, and the optimal initial therapeutic approach has not been clarified. It is generally established that the etoposide/platinum (cisplatin) (EP) chemotherapeutic protocol and comprehensive therapy could reduce distant metasta-

sis and improve the prognosis [6, 8, 15]. As reported by Huang *et al*. [16] the 3-year survival rate of SCNEC on comprehensive therapy reached 45% [16]. Although some authors had doubts of the surgical efficacy for SCNEC patients [14], surgeons and patients at most medical institutions have choosen operations as one of the important therapeutics for early-stage patients [6, 17, 18]. In the present study, there were 32 early-stage patients. Among them, 29 opted for surgery, as did another five Stage IIB patients; small cell lung cancer (SCLC) is sensitive to radiotherapy thus it is one of the important therapeutics for SCLC. Although the biological behaviors of SCNEC and SCLC are quite similar, the radiotherapeutic efficacy and mode of SCNEC have remained a major focus of debate and clinicians are actively exploring answers.

Role of radical radiation therapy in the treatment of early SCNEC

The possible role of radical radiation therapy in the treatment of early SCNEC is unknown. Chemoradiotherapy has been widely applied for localized and diffuse stages of SCLC. Surgery is reserved only for Stage IA patients with a tumor size less than 2 cm, containing drug-resistant non-small cell components or the resection of residual foci insensitive to radiotherapy [19-21]. Currently there has been no literature report of any efficacy study on radical radiation therapy in patients with early-stage SCNEC. In our cohort, one Stage IB1 patient who underwent simple radiotherapy who was in advanced age survived for 92 months. It is expected that more treatment centers of gynecological tumors will cooperate and conduct comparative studies of early SCNEC operations versus radiotherapy so as to search for more optimized and effective therapy for early SCNEC.

There is a heated debate on the postoperative adjuvant radiotherapy. Although SCNEC has a frequent occurrence of early lymphatic and distant metastasis, many scholars hold the opinion that most SCNEC patients have a local pelvic recurrence prior to the onset of distant metastasis. Thus it has been recommended that early-stage SCNEC patients receive pelvic adjuvant radiotherapy to boost the local control rate [5, 10]. The team of Hoskins [12] reported that 31 SCNEC patients received adjuvant radiotherapy and chemotherapy and achieved a 3-year tumor-free survival rate of 57%. There was a pelvic recurrence in four cases (13%), and two recurrent cases occurred beyond the pelvic radiotherapy field although they underwent routine abdominal paraaortic radiotherapy. In the authors' opinion, it was impossible for the operation to achieve such a high local control rate. Adjuvant radiotherapy could markedly reduce local and retroperitoneal lymph node metastasis [12]. However, some reports have stated that postoperative radiotherapy was harmful. In 2007, Lee *et al*. [9] reported that the 5-year survival rates of early SCNEC patients accepting and declining adjuvant radiotherapy were 40.2% and 53.9%, respectively. We surmised that postoperative adjuvant radiotherapy boosted the toxic and unpleasant effect, delayed the initiation of chemotherapy and lowered the survival rate [9]. A comparison of efficacy was conducted between the regimens of postoperative adjuvant chemoradiotherapy and adjuvant chemotherapy in early-stage patients. In our research it was found that the 3-year OS rates were 57.1% and 56.4%, respectively, in two patient groups, and the median survival periods were 84.70 and 89.126 months, respectively. Apparently the result showed that the overall survival period of postoperative adjuvant chemoradiotherapy was shortened. At the same time, we considered such a fact that most patients opting for adjuvant chemoradiotherapy had one or more high postoperative pathological risk factors while those on adjuvant chemotherapy often had no high-risk factors. Among eight patients, undergoing postoperative adjuvant chemotherapy except for one infiltrative case of the outer membrane, infiltrations involved superficial interstitial and even mucous layers in the other seven cases. Among 20 cases undergoing postoperative adjuvant chemoradiotherapy, infiltration of the superficial interstitium occurred in only two cases after neoadjuvant chemotherapy while the other 18 cases had one or more high-risk factors. As reported by Kasamatsu *et al*. [14] the recurrence rate was as high as 70% in the postoperative SCNEC patients with such high-risk pathological factors as infiltration of deep interstitium, tumor embolus within the lymphovascular space and lymphatic metastasis. Yet for the patients with a depth of interstitial infiltration less than 6 mm, there was no tumor recurrence [14]. The definitive efficacy of adjuvant chemoradiotherapy in early-stage SCNEC patients needs to be analyzed by studies of a larger sample size. In the present study, among 20 patients on adjuvant chemoradiotherapy, no single case had pelvic metastasis and eight patients underwent adjuvant chemotherapy. One case had pelvic metastasis. Considering the fact that small cell carcinoma was sensitive to radiotherapy, we recommended the SCNEC patients with high postoperative risk factors receive adjuvant chemoradiotherapy to boost the local control rate.

Effect of radiation for advanced stage

The chemoradiotherapeutic efficacies of advance-stage SCNEC patients are currently well established. It was reported that post-chemoradiotherapeutic OS rates showed no marked differences between medium and advance-stage SCNEC and cervical squamous cell carcinoma. The median survival period was around seven months for late-stage SCNEC. For SCNEC patients beyond the clinical stage of IIA, a survival period of over 30 months has never been reported in the literature [5-7]. In our cohort, two Stage IIB patients received chemoradiotherapy and survived for 112 and 114 months, respectively, and one of them had an onset of abdominal paraaortic lymph node metastasis at 20 months after pelvic chemoradiotherapy. Then there was a long-term survival after abdominal aortic radiotherapy. The pathological tissues of these two patients were definitively diagnosed after numerous re-examinations and eliminations of mis-

diagnoses with the combination of electron microscope and immunohistochemistry by two pathologists. Thus an aggressive regimen of chemoradiotherapy could achieve a relatively long-term survival in medium and late-stage SCNEC patients with localized disease foci.

Prophylactic brain and paraaortic radiotherapy for SCNEC

SCNEC and SCLC share many similar pathological and biological behaviors. Often there is an early onset of lymphatic and distant metastasis resulting in the failure of therapy. Currently all SCLC patients of localized and diffuse stages undergo prophylactic hilar and mediastinal lymph node radiotherapy in spite of the status of lymphatic metastasis [20]. It has remained unclear whether or not SCNEC should receive prophylactic abdominal paraaortic radiotherapy similarly as SCLC, and the number of the relevant literature reports is still quite limited. Hoskins *et al*. once reported the routine use of abdominal paraaortic radiotherapy for SCNEC, but the case numbers were too few to analyze the efficacy [12]. Considering both the unpleasant effects and indefinite efficacy of radiotherapy, we only selected abdominal paraaortic radiotherapy for the patients with common iliac lymph node or abdominal aortic lymphatic metastasis. The brain metastatic rate of localized SCLC was around 20%-30% while that of diffuse SCLC was around 40%. It was because prophylactic whole brain radiotherapy boosted the 3-year survival rate by 5.4%. Thus prophylactic whole brain radiotherapy became a routine procedure [22-24]. However, its efficacy for SCNEC has been debated. According to the literature reports, the brain metastatic rate of SCNEC was markedly lower than that of SCLC, and the patients with established brain metastasis often had concurrent lung metastasis [5, 25]. None of the patients had solely brain metastasis, and the SCNEC patients required no prophylactic whole brain radiotherapy [5, 25]. It was also reported in the literature that the rate of brain metastasis of early SCNEC patients was up to 25%. Thus prophylactic whole brain radiotherapy was recommended [26]. In our cohort, all four patients with brain metastasis had onset of lung and other distant metastases. Thus none of them received prophylactic whole brain radiotherapy.

Conclusion and limitation of this study

As compared with cervical squamous and adenocarcinomas at the same stages, SCNEC frequently has the clinical feature of an early occurrence of lymphatic and distant metastasis, and the recurrence and survival periods of the patients become markedly shortened with a poor prognosis. All patients in our study came from the same hospital. Their clinical data and follow-up information were complete. The treatment principles and methods of early and late-stage patients were basically the same: the former group was dominated by surgery and complimented with chemoradiotherapy or chemotherapy while chemoradiotherapy remained the major therapy for the latter group. The surgical approaches, radiotherapeutic regimens and doses were roughly the same. The predominant chemotherapeutic protocol was EP. The limitation was that there were too few cases to evaluate the efficacy of adjuvant radiotherapy in early-stage SCNEC patients so as to reach any definitive conclusion on whether or not there is a need for prophylactic abdominal paraaortic and whole brain radiotherapy. Furthermore there is still no efficacious comparison of surgery versus radical chemotherapy in early-stage patients. With the constantly improved proficiency of pathological diagnosis at our hospital, around eight to ten cases of SCNEC are newly diagnosed each year. In recent years a rising trend has been demonstrated. With the cooperation of other large tumor treatment centers, more prospective studies with a larger sample size need to be conducted to explore the optimal therapy for SCNEC so as to improve the prognosis of SCNEC patients.

References

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

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

[3] Tsunoda S., Jobo T., Arai 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.

[4] McCusker M.E., Coté T.R., Clegg L.X., Tavassoli F.J.: "Endocrine tumors of the uterine cervix: incidence, demographics, and survival with comparison to squamous cell carcinoma". *Gynecol. Oncol.,* 2003, *88*, 333.

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

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

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

[8] Zivanovic O., Leitao M.M., Park K.J., Zhao H., Diaz J.P., 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.

[9] 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 multi-center retrospective Korean study". Ann. Oncol., 2008, *19,* 321.

[10] Cohen J., 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,* 347e1.

[11] Yang D.H., Kim J.K., Kim K.W., Bae S.J.: "MRI of small cell Carcinoma of the uterine cervix with pathologic correlation". *J. AJR*, 2004, *182,* 1255.

[12] Hoskins P.J., Swenerton K.D., Pike J.A., Lim P., Parsons C.A., Wong F., Lee N.: "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.

[13] Lee S.W., Nam J.H., Kim D.Y., Kim J.H., Kim K.R., Kim Y.M., Kim Y.T.: "Unfavorable prognosis of small cell neuroendocrine carcinoma of the uterine cervix: a retrospective matched case-control study". *Int. J. Gynecol. Cancer,* 2010, *20*, 411.

[14] Kasamatsu T., Sasajima Y., Onda T., Sawada M., Kato T., Tanikawa M.: "Surgical treatment for neuroendocrine carcinoma of the uterine cervix". *Int. Fed. Gynecol. Obstet.,* 2007, *99*, 225.
[15] Kapp D.S., Cohen J., Shin J.Y., Urban R., Sherman A.E., Chen L.M. et al.: "The prognostic factors responsible for survival of women with neuroendocrine small-cell cervical carcinoma-A study of 188 women". J. Am. Soc. Clin. Oncol., 2007, *25* (18S), 5539.
[16] Huang C.Y., Chen Y.L., Chu T.C., Cheng W.F., Hsieh C.Y., Lin M.C.: "Prognostic factors in women with early-stage small cell carcinoma of the uterine cervix". *Oncol. Res.,* 2009, *18*, 279.
[17] Bermúdez A., Vighi S., García A.: "Neuroendocrine cervical carcinoma: a diagnostic and therapeutic challenge". *Gynecol. Oncol.,* 2001, *82,* 32.
[18] Sevin B.U., Method M.W., Nadji M., Lu Y., Averette H.A.: "Efficacy of radical hysterectomy as treatment for patients with small cell carcinoma of the cervix". *J. Cancer,* 1996, *77,* 1489.
[19] Pijls-Johannesma M., Ruysscher De, Vansteenkiste J., Kester A., Rutten I., Lambin P: "Timing of chest radiotherapy in patients with limited stage small cell lung cancer: a systematic review and meta-analysis of randomised controlled trials". *Cancer Treat. Rev.,* 2007, *33*, 461.
[20] van Loon J., Offermann C., Bosmans G., Wanders R., Dekker A., Borger J.: "18FDG-PET based radiation planning of mediastinal lymph nodes in limited disease small cell lung cancer changes radiotherapy fields: a planning study". *Radiother. Oncol.,* 2008, *87,* 49.
[21] Simon G.R., Turrisi A.: "Management of small cell lung cancer:ACCP evidence-based clinical practice guidelines (2nd edition)". *Chest,* 2007, *132*, 324S.
[22] Vines E.F., Le Pechoux C., Arriagada R.: "Prophylactic cranial irradiation for patients with small cell lung cancer in complete remission". *N. Engl. J. Med*., 2003, *341*, 476.
[23] Slotman B., Faivre-Finn C., Kramer G., Rankin E., Snee M., Hatton M. *et al*.: "Prophylactic cranial irradiation in extensive small cell lung cancer". *N. Engl. J. Med.,* 2007, *357*, 664.
[24] Brennan S.M., Gregory D.L., Stillie A., Herschtal A., Manus M.M., Ball D.L.: "Should extrapulmonary small cell cancer be managed like small cell lung cancer". *Cancer*, 2010, *116*, 888.
[25] 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.
[26] Weed J.C. Jr., Graff A.T., Shoup B., Tawfik O.: "Small cell undifferentitiated (neuroendocrine) carcinoma of the uterine cervix". *J. Am. Coll. Surg.,* 2003, *197,* 44.

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