We aimed to analyze the clinical outcome of patients with small cell carcinoma (SmCC) of uterine cervix.

We retrospectively reviewed the clinical courses of patients with SmCC of uterine cervix referred to Taipei Veterans General Hospital between 1993 and 2001. Demographic and clinical data were presented and analyzed. Survival analysis was performed by using the Kaplan-Meier method. The statistical significance was determined by the log-rank test.

SmCC represented 0.38% of malignancies of uterine cervix in this institution. Nine patients with SmCC of uterine cervix were included in this study. The median age at diagnosis was 45 years (range, 32-77 years). Vaginal bleeding was the most common symptom presented in all our patients. The median duration of the symptoms before diagnosis was 3 months (range, 1-6 months). Three patients were stage IB, two IIA, one IIB, two IIIB, and one IVB by FIGO staging at diagnosis. Five patients underwent radical surgery and adjuvant chemotherapy; two, radical surgery, adjuvant chemotherapy and radiotherapy; one, chemotherapy and radiotherapy; and one, chemotherapy only. With a median follow-up of 28 months, three patients died of this disease, five patients remained alive without disease and the remaining one patient died of a non-cancer related cause. The median overall survival (OS) was not reached and the estimated 5-year survival rate was 66.67%. The median OS was significantly longer in patients with early stage disease (P = 0.02). There was no significant difference in median OS between pre-menopausal and menopausal patients (P = 0.466).

In summary, SmCC of uterine cervix is a relatively rare but aggressive neoplasm with high potential of metastases. Patients with early stage disease had better prognosis. Combined-modality treatment is necessary to achieve the optimal outcome.

Key words: Radiotherapy; Small cell carcinoma; Uterine neoplasm

Carcinoma of uterine cervix was the most common malignancy of the female genital tract in Taiwan. The mortality rate was decreasing due to successful screening techniques and established optimal treatment [1, 2]. In contrast, small cell carcinoma (SmCC) of uterine cervix, which was first described in 1957, was an uncommon gynecological cancer comprising less than 3% of all cervical cancers [3]. It was a histological entity that was frequently compared with small cell carcinoma of lung. Morphologically, it was composed of neoplastic cells that were typically arranged in clusters, sheets, or trabeculae separated by a delicate fibrovascular stroma. The cells were small, approximately 1.5 to 2.5 times the size of a small resting lymphocyte. They had scant cytoplasm, finely granular nuclear chromatin, indistinct nucleoli and evidence of neuroendocrine differentiation [4, 5]. It was considered to confer a poor prognosis because of their propensity to metastasize early to regional lymph nodes and distant...
sites [6]. The optimal management for SmCC of uterine cervix remained undetermined due to the rarity of this disease. Data regarding the effectiveness of various therapies mostly derived from small retrospective series. In this article, we presented the clinical findings and evaluated the treatment outcome of nine patients with SmCC of uterine cervix.

MATERIALS AND METHODS

Based on Cancer Registry of Taipei Veterans General Hospital, patients with histologically proven SmCC of uterine cervix from January 1993 to December 2001 were selected. The medical records were retrospectively reviewed in detail. The following data for each patient were reported, including age, tobacco history, symptoms, duration of symptoms, types of treatment and outcome.

Demographic and clinical data were described with medians. Survival was measured from the time of diagnosis to the date of death or the latest follow-up. Survival analysis was performed according to the Kaplan-Meier method. The statistical significance was determined by the log-rank test.

RESULTS

Ten patients with the diagnosis of SmCC of uterine cervix were identified between 1993 and 2001, representing 0.38% of uterine cervical malignancies seen in this institution during the same period. After one patient without complete data was excluded, nine patients with SmCC of uterine cervix were included in this retrospective study. Patients’ characteristics and clinical manifestations were summarized in Table 1. The median age at diagnosis was 45 years (range, 32-77 years). Vaginal bleeding was the predominant symptom and present in all our patients. The median duration of the symptoms before diagnosis was 3 months (range, 1-6 months). Three patients were stage IB, two IIA, one IIB, two IIIB, and one IVB by FIGO staging at diagnosis.

Regarding the management, various combinations were used. Five patients (No1, 2, 3, 4 and 5) underwent radical surgery (3 radical hysterectomy <RH>, bilateral pelvic lymph node dissection <BPLND> and bilateral salpingo-oophorectomy <BSO>, 1 RH and BPLND, 1 laparoscopically assisted vaginal hysterectomy) and adjuvant chemotherapy. Two of them (40%) kept a recurrence-free status for 16 and 80 months, respectively. Another patient (20%) had local recurrence at 14 months. She was later successfully treated with concurrent chemo-radiotherapy and then remained alive without disease at 47 months. The remaining two women (40%) suffered and died of distant relapse (1 brain

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Stage</th>
<th>Symptoms</th>
<th>Duration (Months)</th>
<th>Treatment (Primary//Salvage)</th>
<th>Survival (Months)</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>Ila</td>
<td>Vaginal bleeding</td>
<td>1</td>
<td>RS, EPx1, VIPx5</td>
<td>16</td>
<td>AWD</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>IIb</td>
<td>Vaginal bleeding</td>
<td>0.5</td>
<td>RS, EPx6</td>
<td>80</td>
<td>AWD</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>Ib</td>
<td>Vaginal bleeding</td>
<td>1</td>
<td>RS, EPx3 // CCRT 50 Gy/ 25 Fx (for local recurrence)</td>
<td>47</td>
<td>AWD</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>IIb</td>
<td>Vaginal bleeding</td>
<td>5</td>
<td>RS, POBx6 // XRT (for brain metastasis)</td>
<td>11</td>
<td>DOD; Brain, liver metastases</td>
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<tr>
<td>5</td>
<td>45</td>
<td>Ib</td>
<td>Vaginal bleeding</td>
<td>6</td>
<td>RS, EPx6 // XRT (for brain metastasis)</td>
<td>120</td>
<td>DOD; Brain metastasis</td>
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<tr>
<td>6</td>
<td>32</td>
<td>Ib</td>
<td>Vaginal bleeding</td>
<td>3</td>
<td>RS, IPx6, XRT 54 Gy/ 30 Fx</td>
<td>28</td>
<td>AWD</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>Ila</td>
<td>Vaginal bleeding</td>
<td>3</td>
<td>RS, VPx6, XRT 46.8 Gy/ 26 Fx, IVRT 21 Gy/ 3 Fx</td>
<td>109</td>
<td>AWD</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
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<td>Vaginal bleeding</td>
<td>6</td>
<td>EPx3, XRT 60 Gy/ 30 Fx, ICRT 30 Gy/ 6 Fx</td>
<td>3</td>
<td>DOOD</td>
</tr>
<tr>
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<td>Vaginal bleeding</td>
<td>3</td>
<td>Carboplatin1</td>
<td>1</td>
<td>DOD; SCF metastasis</td>
</tr>
</tbody>
</table>

Abbreviations: RS, radical surgery; XRT, radiotherapy; EP, etoposide + cisplatin; VIP, vincristine + ifosfamide + cisplatin; IP, ifosfamide + cisplatin; POB, cisplatin + vincristine + bleomycin; VPC, vincristine + cisplatin + cyclophosphamide; ICRT, intra-cavitary radiotherapy; IVRT, intra-vaginal radiotherapy; Gy, Gray; Fx, fraction; AWD, alive without disease; DOD, die of disease; DOOD, die of other disease; SCF, supraclavicular fossa
Small cell carcinoma of uterine cervix

With a median follow-up period of 28 months, three patients had distant failure and died of this disease, five patients remained alive and free of disease, and the remaining one died of a non-cancer related cause. The median overall survival (OS) was not reached. The 5-year overall survival rate was 66.67%. Patients with early disease (stage I and IIa) had longer median OS than patients with advanced disease (stage IIb, III and IV) (P=0.02, Fig 1). There was no significant difference in median OS between pre-menopausal and menopausal patients (P=0.466, Fig 2).

**DISCUSSION**

SmCC was a common pulmonary neoplasm, representing about 20-25% of all bronchogenic carcinoma [7]. But it was also described in the uterine cervix, esophagus, stomach, pancreas, small intestine, urinary bladder and salivary gland. Extrapulmonary SmCC was associated with smoking and shown to confer a poor prognosis [8, 9]. In comparison with SmCC of other extrapulmonary sites, SmCC of uterine cervix had some distinct characteristics. SmCC of uterine cervix was less associated with smoking and reported to have a better clinical course than their counterparts of other extrapulmonary origins [8, 9, 10]. In our study, only one patient (11%) had a history of use of tobacco. No definite correlation between smoking and SmCC of uterine cervix could be confirmed. In addition, the current review showed five patients were still in disease-free state with a median follow-up of 28 months. A 5-year overall survival rate of 66.7% was achieved. Our result confirmed the relatively favorable prognosis of SmCC of uterine cervix.

Due to the rarity of SmCC of uterine cervix, it was difficult to perform controlled clinical trials to determine the optimal therapy. A variety of options had been utilized in the management of this disease. Patients with stage I SmCC of the cervix had been managed successfully by radical hysterectomy, but local therapy alone was almost never curative if the regional lymph nodes were involved [4, 6, 8, 11]. In the previous series from Sheets et al and Sevin et al, about 60% patients treated with radical hysterectomy and pelvic irradiation relapsed locally. Sykes et al reported 11 patients who were treated (7 had irradiation, 2 underwent surgery, and 2 received both modalities); seven of the patients relapsed, all of whom had a component of pelvic failure. Thus, some authors concluded that postoperative radiotherapy did not alter the course of the disease [9, 12, 13, 14].
In our series, we used platinum-based chemotherapy in addition to local therapy (5 surgery, 2 surgery and adjuvant radiotherapy, 1 radiotherapy) in patients with locoregional disease. The surgery and radiotherapy given were similar to those routinely used in the squamous cell carcinoma of uterine cervix. Pelvic recurrence occurred in only one patient (12.5%). This was a lower rate than the rates in the above three series. The major difference between our regimen and those in the above studies was the use of chemotherapy. Our result supported that chemotherapy had an important role in the local control.

SmCC of uterine cervix tended to metastasize early [10, 11, 14] that distal disease was a common cause of failure, especially when local therapy alone was used. Chemotherapy was emphasized and routinely incorporated into the treatment [15]. Of our nine patients, three (33%) eventually had distant disease during their course despite systemic chemotherapy administered. Brain was the most common site of distal relapse (2 of 3 patients with distant metastases) in our series in which prophylactic cranial irradiation was not performed. While cranial irradiation was proved to improve overall survival and cranial control in small cell lung cancer [16], its role remained undetermined in SmCC of uterine cervix or other extra-pulmonary sites. It might be tested in the future trials of extrapolmonary SmCC.

As in the small cell lung cancer, a concurrent combination of platinum-based chemotherapy and radiation therapy was used in SmCC of uterine cervix. In a series of thirty-three patients with SmCC of uterine cervix [17], the radiotherapy was 40 Gy in 25 daily fractions to the pelvis and para-aortic lymph nodes. This regimen was followed by two intracavitary insertions if the cervix was present and technically amenable to brachytherapy, or an external-beam pelvic boost of 15 Gy in 7 daily fractions if the cervix was not suitable for brachytherapy, or the regimen was followed by an external-beam pelvic boost of 10 Gy in 5 daily fractions if a hysterectomy had been performed. Chemotherapy was given before, during and after the radiotherapy. The 3-year overall survival rate was 60%. Distant failure (28%) was the most common cause of failure, with local failure occurring in 13% of patients. They concluded that the combination of chemotherapy and radiation was an effective and reasonable alternative to surgery in patients with SmCC of uterine cervix [17, 18].

Radiological stage and age were proved to be positive predictive factors for overall survival [17]. In our review, it showed that the survival was affected by the disease stage, but not menopausal status. A 5-year survival rate of 66.7% was achieved with local therapy (surgery and/or radiotherapy) and subsequent chemotherapy. The sequential treatment strategy might be an option for patients who could not tolerate the concurrent treatment mode. In addition, one of our patients undergoing radical surgery plus chemotherapy had local recurrence at 14 months. She was later successfully managed with concurrent chemo-radiotherapy. From this case, we recommended that aggressive salvage treatment was worthwhile and could be curative in patients with local recurrence.

Our study retrospectively reviewed nine patients who were accrued in an 8-year period. The observations must be viewed in light of the small numbers and short follow-up time. In summary, SmCC of uterine cervix represented a unique entity in gynecologic cancer. Patients with early stage disease had significantly better prognosis. Long-term survival can be achieved with a combined-modality treatment consisting of local therapy (surgery and/or radiotherapy) and chemotherapy. The optimal treatment needs to be determined.

REFERENCES
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子宮頸小細胞癌: 單一機構之經驗

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奇美醫院 放射腫瘤科 3

為了了解子宮頸小細胞癌的治療效果，我們回顧台北榮民總醫院從一九九三年至二○○一年間的子宮頸小細胞癌病例，分析病患各項人口學特徵及臨床相關資料，以Kaplan-Meier method計算病患存活狀況，以log-rank test來確認統計上的顯著差異。

子宮頸小細胞癌占該醫院同時期子宮頸惡性腫瘤的0.38%。本研究共含括九位病人，他們的年齡中位數為45歲（32-77歲），陰道出血為所有病患的主要表現病徵，診斷前病徵持續時間為3個月（1-6個月）。在9位病患的臨床期別中，3位ⅠB、2位ⅠIA、1位ⅠIB、2位ⅢB及1位ⅣB。關於治療方面，5位病患接受根除性手術及化學治療，2位接受根除性手術，化學治療及放射治療，1位接受化學治療及放射治療，1位接受化學治療。在追蹤28個月後，5位病患無病存活，3位因小細胞癌死亡，1位因非腫瘤疾病死亡；病患的中位存活時間仍未達到，五年存活率為66.67%。早期疾病的病患存活期較晚期者長，但隨經靜及停經後病患的存活狀況則沒有顯著差異。總之，子宮頸小細胞癌是一種少見的高度惡性腫瘤，容易轉移；早期疾病的病患較好的預後，必須使用多科整合的治療方可達到最佳效果。

關鍵詞: 放射治療: 小細胞癌: 子宮腫瘤