Prognostic factors and treatment comparison in early-stage small cell carcinoma of the uterine cervix

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Abstract. Small cell carcinoma of the uterine cervix (SCCUC) is rare and its biologic behavior is aggressive. To analyze prognostic factors and determine optimal therapy in patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB1-IIA SCCUC, we retrospectively reviewed 96 patients (14 patients treated in our center and 82 patients identified by a search on PubMed) treated with radical surgery (SU), surgery plus adjuvant chemotherapy (SU+Chemo), or surgery plus adjuvant chemotherapy and radiotherapy (SU+Chemo+RT) between 1990 and 2010. Of the 96 patients, 11 patients were treated with SU, 33 with SU+Chemo, and 52 with SU+Chemo+RT. The 5-year survival rate for the 96 patients was 45%. A total of 6% (2/32) of patients had local recurrence, 75% (24/32) had distant metastases, and 19% (6/32) had both. The 5-year survival rate in stage IB1 and IB2-IIA disease was 58 and 34%, respectively (P=0.049). For patients with and without lymph node metastases (LNM), survival was 33 and 60%, respectively (P=0.045). Patients with inner 1/3 stromal invasion had a better survival than those with deep stromal invasion (DSI) (100 vs. 34%, P=0.003). Survival was not significantly different in patients treated with the above three modalities, albeit treatment selection was related to LNM (P=0.000) and DSI (P=0.027). Thus, FIGO stage, LNM and DSI are significant predictors of survival. Adjuvant therapy after SU has not improved survival compared with surgery alone. Thus, newer multimodality therapy should be evaluated.

Introduction

Small cell carcinoma of the uterine cervix (SCCUC) is a rare gynecologic malignancy and constitutes less than 5% of all invasive cervical carcinomas (1-4). The histology and biologic behavior of SCCUC are similar to that of small cell lung carcinoma (SCLC), which is highly aggressive. Due to the high incidence of lymph vascular space involvement (LVSI), lymph node metastases (LNM), and distant metastases, the prognosis of SCCUC is poorer than that of other histological types of cervical carcinoma (5,6). The 5-year survival rates for SCCUC range from 31.6 to 46.6% for early-stage disease and from 0 to 14% for advanced stage disease (1,2,7).

Previous studies showed that patients with SCCUC treated with a modality similar to the standard treatment for squamous cell carcinoma of the cervix have a poor prognosis (7-9). It is thus imperative to identify prognostic factors and optimal treatment strategies to improve treatment outcome. Due to the rarity of SCCUC, it is difficult to obtain comprehensive evidence-based information regarding prognostic factors and optimal treatment modalities. Therefore, a retrospective study of treatment experience is valuable to enhance our understanding of SCCUC.

Thus, we pooled our cases with all of the reported relevant cases in the literature and conducted a retrospective study to obtain more information pertaining to treatment outcome and prognostic factors in International Federation of Gynecology and Obstetrics (FIGO) stage IB1-IIA patients with SCCUC.

Patients and methods

Patients. We searched the computerized hospital database of patients treated for carcinoma of the uterine cervix between 1995 and 2008 at the Fudan University Shanghai Cancer Center, China, to identify patients whose tumors were diagnosed as SCCUC. Only patients who received radical surgery, with or without adjuvant treatment for FIGO stage IB1-IIA SCCUC at our hospital were included in this study. As primary treatment, patients underwent radical hysterectomy and pelvic lymphadenectomy, with or without para-aortic lymphadenectomy. Adjuvant treatment included chemotherapy or chemotherapy plus pelvic or extended-field radiotherapy. The follow-up data were updated on June 30, 2010.

Patient selection criteria and treatment modalities. Histologic sections were reviewed with criteria for the diagnosis of SCCUC (10). In brief, the criteria included the presence of small cells with scant cytoplasm, hyperchromatic nuclei with indistinct nucleoli and nuclear molding, and numerous

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mitoses and extensive necrosis. In addition, SCCUC had to be positive for at least one of the neuro-endocrine markers.

To obtain a sufficient number of cases of this rare disease for analysis, we also retrieved the relevant cases reported in the English literature since 1990 through a search on PubMed. Clinical and pathological variables included age, tumor size, FIGO stage, tumor homology, lymph node status, depth of stromal invasion, LVSI, types of chemotherapy and treatment modalities. Adjuvant chemotherapy was divided into two categories: similar or not similar to that of SCLC. The former category included VAC (vincristine, adriamycin, and cyclophosphamide) and PE (platinum and etoposide). The latter category included the single or multiple administration of mitomycin, ifosfamide, cyclophosphamide, paclitaxel and platinum.

Statistical analysis. The primary endpoints were any cancer-related death and overall survival (OS), calculated from the date of diagnosis to death, or censored at the last follow-up. Statistical analysis of the pooled data from the combined patients was performed. OS was estimated using the Kaplan-Meier method and log-rank test. $P<0.05$ was considered to be statistically significant. The statistical software package SPSS 13.0 (SPSS Inc. Chicago, IL, USA) was used for all data analyses.

Results

Among the 5,127 patients with cervical carcinoma who were treated at our hospital between 1995 and 2008, 24 patients presented SCCUC, representing 0.5% of the total. There were 9 patients with stage IB1 SCCUC, 2 stage IB2, 7 stage IIA, 4 stage IIB, and 2 stage IVB by FIGO staging. Only 14 patients with stage IB1-IIA SCCUC met our criteria and were included in this study. Characteristics of these patients are shown in Table I. Median age at diagnosis was 40 years (range 30-51). Median tumor size was 3.0 cm (range 2.0-8.0). The positive staining for synaptophysin, chromogranin, and neuron-specific enolase (NSE) was 85.7% (12/14), 78.6% (11/14), and 92.9% (13/14), respectively. Based on the preoperative histologic examination, 11 patients (79%) were accurately diagnosed as SCCUC and the remaining 3 patients were misdiagnosed as moderately differentiated squamous cell carcinoma, poorly differentiated carcinoma and poorly differentiated squamous cell carcinoma prior to surgery. A total of 12 patients were pure SCCUC while 2 had focal squamous cell carcinoma (n=1) or adenosquamous cell carcinoma (n=1). Postoperative adjuvant chemotherapy was administered to 1 patient, and the remaining 13 patients received postoperative chemotherapy and RT.

The median survival of the 14 patients was 45.8 months. During a median follow-up of 25.4 months (range 6.8-46.4), 7 patients remained alive without disease, while 7 patients succumbed to the disease. The 7 patients with recurrent disease received postoperative chemotherapy and RT. Of the 7 patients, no patient was found to have local recurrence alone, 5 (36%) had distant metastases, and 2 (14%) had both at the time of recurrence. The median time of recurrence was 14.2 months (range 4.6-30.4). Of the 7 patients with recurrent disease, 5 (71%) had relapse within 24 months after diagnosis.

Table I. Characteristics and survivorship of 14 patients at the Shanghai Cancer Center.

Characteristics	Survivorship, no. (survived/total)
Median age, years (range)	40 (30-51)
Median tumor size, cm (range)	3.0 (2.0-8.0)
FIGO stage	
IB1	5/8
IB2	0
IIA	2/6
Histology, (No. of patients)	
Pure	5/12
Mixed	2/2
DSI, (≥2/3 stromal invasion)	
Yes	3/10
No	4/4
LVSI	
Yes	3/8
No	4/6
LNM	
Yes	5/11
No	2/3
Treatment modalities	
SU+Chemo	1/1
SU+Chemo+RT	6/13
Chemotherapy regimen	
Cs	6/10
Cns	1/4

SCCUC, small cell carcinoma of the uterine cervix; FIGO, International Federation of Gynecology and Obstetrics; DSI, deep stromal invasion; LVSI, lymph vascular space invasion; LNM, lymph node metastases; SU, radical surgery; Chemo, chemotherapy; RT, radiotherapy; Cs, chemotherapy similar to that for small cell lung carcinoma (PE/VAC); Cns, chemotherapy not similar to that for small cell lung carcinoma.

A total of 82 early-stage SCCUC patients who had undergone SU with or without adjuvant therapy were identified by a search on PubMed (3,4,9,11-30). The total number of patients for analysis was 96. Median age was 40 years (range 20-67), and the median survival was 39.0 months (95% CI, 14.5-63.5). The estimated 2- and 5-year survival rates were 62 and 45%, respectively (Fig. 1). For the 96 patients, the independent variables of stage IB1, absence of LNM and inner 1/3 stromal invasion were found to have a significant, favorable impact on survival (Table II, Figs. 2-4). We observed that patients who received chemotherapy similar to that of SCLC appeared to have more survival benefits than patients who received other types of chemotherapy regimen. However, statistical significance

Table II. Analysis of prognostic factors in 96 early-stage SCCUC patients.

Characteristics	Survivorship, no. (survived/total) (%)		P-value[a]
Age (years)			
≤40 vs. >40	27/55 (49)	24/41 (59)	0.199
FIGO stage			
IB1 vs. IB2-IIA	29/47 (62)	9/20 (45)	0.049
Tumor size (cm)			
≤4 vs. >4	29/50 (58)	9/16 (56)	0.343
Histology			
Pure vs. Mixed	31/53 (58)	11/19 (58)	0.880
LVSI			
No vs. Yes	13/20 (65)	17/36 (47)	0.308
LNM			
No vs. Yes	26/41 (63)	13/30 (43)	0.045
DSI (≥2/3 stromal invasion)			
No vs. Yes	11/11 (100)	7/17 (41)	0.003
Chemotherapy regimen			
Cs vs. Cns	34/55 (62)	2/10 (20)	0.079
Treatment modalities			
SU vs. SU+Chemo	7/11 (64)	19/33 (58)	0.440
SU vs. SU+Chemo+RT	7/11 (64)	25/52 (48)	0.250
SU+Chemo vs. SU+Chemo+RT	19/33 (58)	25/52 (48)	0.573

SCCUC, small cell carcinoma of the uterine cervix; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymph vascular space involvement; LNM, lymph node metastases; DSI, deep stromal invasion; SU, radical surgery; Chemo, chemotherapy; RT, radiotherapy; Cs, chemotherapy similar to that for small cell lung carcinoma (PE/VAC); Cns, chemotherapy not similar to that for small cell lung carcinoma. [a]Assessed by the log-rank test of survival equality.

was not achieved (P=0.079). Treatment modalities were also not related to survival. Treatment selection was related to LNM and DSI (Table III). Following stratification according to these variables, we did not find any relationship between treatment and survival (data not shown). With a median follow-up of 24.5 months (range 9-209), 49 patients exhibited recurrence. Among them, 45 patients succumbed to the disease, and 4 patients were alive with disease. Detailed relapse data were available in 32 patients (Table IV). Of these 32 patients, 2 (6%) presented local, 24 (75%) distant, and 6 (19%) presented both local and distant recurrence.

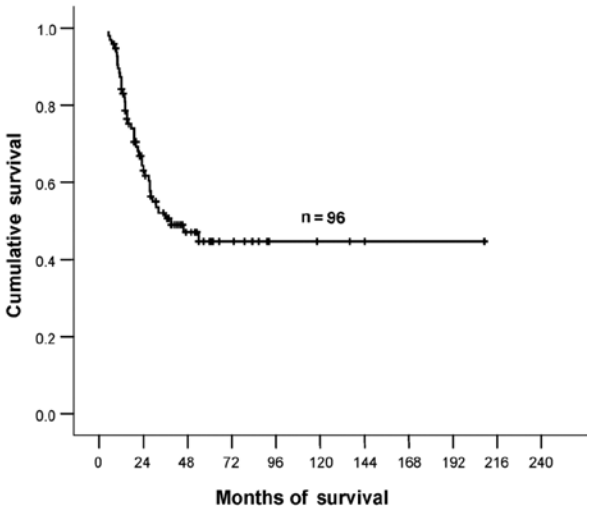

Figure 1. Overall survival in patients with FIGO stage small cell carcinoma of the uterine cervix.

Discussion

SCCUC is a rare and aggressive subtype of cervical carcinoma. Our results revealed that the 5-year survival rate for patients with FIGO IB1-IIA SCCUC was 45%, consistent with a previous report of 46.6% (2). FIGO stage, lymph node status, and depth of stromal invasion were significant predictors of survival. Although 85 of 96 patients in the current study had received chemotherapy, distant metastasis was found to be the main recurrent pattern. Thus, SCCUC remains a therapeutic challenge for clinicians.

Clinicopathological characteristics, such as large tumor size, LNM, advanced stage, DSI, number of positive lymph nodes, and pure small cell histology have been suggested as possible poor prognostic factors (1,3,8,9,31). As for early-stage SCCUC, only four studies exist concerning the analysis of prognostic features (2,23,31,32). FIGO stage (IB1 vs. IB2-IIA) (2,32) and lymph node status (23,31,32) are significant indicators for survival. In addition, postoperative VAC or PE is a favorable regimen for improving survival

Table III. The treatment relationship between LNM and DSI.

	LNM		DSI	
Treatment modality	No	Yes	No	Yes
SU	8	0	3	0
SU+Chemo	20	5	3	2
SU+Chemo+RT	13	25	5	15
P-value	0.000		0.027	

LNM, lymph node metastases; DSI, deep stromal invasion; SU, surgery; Chemo, chemotherapy; RT, radiotherapy.

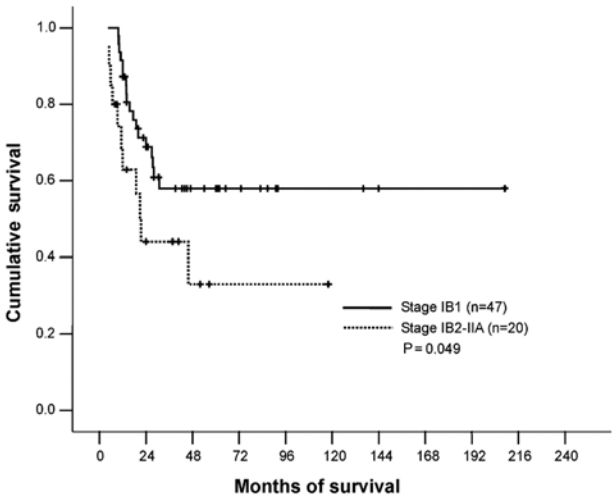

Figure 2. Overall survival for patients based on FIGO stage.

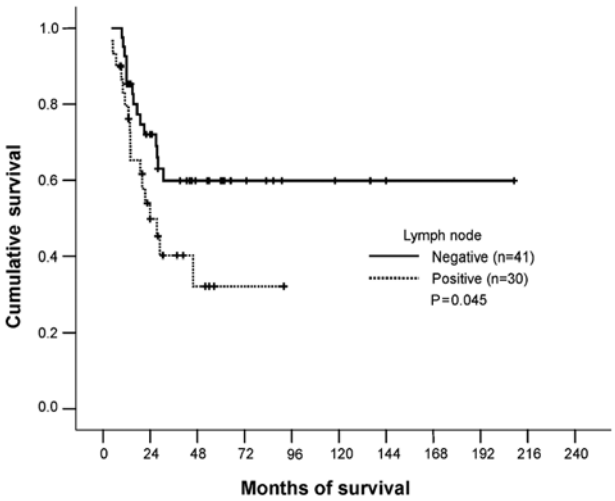

Figure 3. Overall survival for patients based on lymph node status.

(23,31). We observed a favorable survival for patients who received VAC or PE, but the difference was not statistically significant (P=0.079). This finding may be due to the small number of patients who received other chemotherapy regimens (Table II). In our current study, the 5-year survival rate for stages IB1 and IB2-IIA patients were 58 and 34%, respectively (P=0.049); for patients with and without LNM, the rates were 33 and 60%, respectively (P=0.045). These findings are consistent with those of previous reports (2,31). We also observed that DSI was a poor prognostic factor. The 5-year survival rate for patients with outer 2/3 stromal invasion was 34%, while it was 100% for patients with inner 1/3 stromal invasion (P=0.003).

However, determining the optimal treatment for early-stage SCCUC remains a challenge. While the majority of early-stage cervical carcinomas can be successfully managed with SU, this conventional local treatment has yet to be revealed to be successful in SCCUC. In the study by Sevin *et al* (9), where surgery with or without adjuvant radiation was used for early-stage SCCUC, the 5-year disease-free survival was 36.4%. Sheets *et al* (8) reported 14 patients with early-stage SCCUC, all treated with surgery; in addition, 7 patients with positive nodes or other high-risk features were also given adjuvant radiation. During follow-up, 12 patients had died of disease and the 2 survivors had recurrent disease. There are, however, some cases successfully treated with surgery alone. Boruta *et al* (23) described 3 early-stage patients who were treated with surgery alone and were noted to have no evidence of recurrent disease 56, 86 and 98 months after treatment. The 3 patients had negative surgical margins and no evidence of metastatic disease to their lymph nodes. In our current study, there were 11 patients treated with surgery alone. With a median follow up of 60 months, 7 patients survived without disease. Among them, 6 patients presented stage IB1 disease with tumor size ranging from 0.8 to 3.0 cm; LNM was negative for all 6 patients, and the remaining 1 stage IB patient had no detailed pathologic information. Based on these retrospective reviews, we believe that SU alone should be limited to patients with stage IB1 disease, small tumors and favorable features, otherwise multimodality treatment should be considered.

For early-stage SCCUC, most clinicians favor the use of SU with adjuvant multimodality treatment due to its poor prognosis. Recent studies, including the current one, have revealed the high incidence of distant metastases even in early-stage patients (3,31-33), indicating the need for systemic chemotherapy. Since the natural history of SCCUC is akin to that of SCLC, Pazdur *et al* (34) first recommended in 1981 that the chemotherapy regimen used for SCCUC patients be similar to that of SCLC. Zivanovic *et al* (33) reported that in patients with early-stage disease the addition of systemic platinum and etoposide-based chemotherapy appears to have

Table IV. Recurrence patterns of 32 patients with SCCUC.

Recurrence patterns	No. of patients (%)
Local	2 (6)
Local + distant	6 (19)
Distant	24 (75)
Multiple sites	12 (37.5)
Single site	12 (37.5)
Distant sites	
Liver	15
Bone	12
Lung	11
Para-aortic nodes	7
Brain	6
Breast	2
Pancreas	2
Inguinal nodes	2
Mediastinal nodes	2
Supraclavicular nodes	2
Kidney	1
Pleural	1
Vertebrae	1

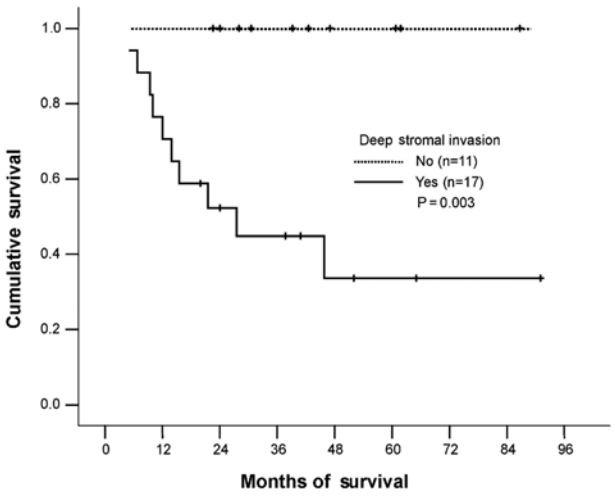

Figure 4. Overall survival for patients based on depth of stromal invasion.

a protective effect on the development of distant metastases. Of the 5 early-stage patients without chemotherapy as part of their initial treatment, all developed distant metastases within 2 years of diagnosis. This finding is in contrast to 6 patients who were treated with adjuvant platinum and etoposide-based combination therapy. In that group only 1 patient developed systemic disease (P=0.015). Two meta-analyses reported by Chang *et al* (31) (40 patients) and Boruta *et al* (23) (34 patients) revealed that for early-stage patients, the postoperative adjuvant chemotherapy using a VAC or PE regimen offered a more favorable survival than other chemotherapeutic regimens. In the current study, adjuvant VAC or PE chemotherapy tended to favor survival, but the difference was not statistically significant (P=0.079). Similarly, other studies were also unable to prove any statistically significant benefit to using adjuvant chemotherapy (1,3). Despite the propensity for early distant metastases, localized control should be emphasized. Viswanathan *et al* (3) reported 2 patients who exhibited recurrence following surgery and adjuvant chemotherapy; their first site of recurrence was in the pelvis. Neither patient received adjuvant RT. However, Sheets *et al* (8) proposed that these tumors may be radioresistant as 5 of 7 patients treated with surgery and adjuvant RT experienced pelvic failures. Sevin *et al* (9) reported similar results. Of the 5 patients receiving postoperative pelvic radiation who succumbed to their disease, 4 patients exhibited pelvic recurrences and 3 had distant metastases. However, the authors argued that radiation may be beneficial since, in their study, 2 patients with LNM and LVSI who received postoperative adjuvant radiation were cured, whereas the remaining 2 patients, who did not receive postoperative radiation, developed pelvic recurrences.

The above discussion indicates that it is impossible to provide an optimal treatment protocol due to the different results and the limited number of patients. To the best of our knowledge, no studies exist that have compared SU alone with SU plus adjuvant treatment in early-stage SCCUC. In the present study, patients with early-stage SCCUC who were treated with SU alone, or SU plus adjuvant chemotherapy (SU+Chemo), or SU plus adjuvant chemotherapy and RT (SU+Chemo+RT) were examined. The number of patients in the three groups was 11, 33 and 52, respectively. We observed that there were no differences in survival in the three groups, indicating that the current multimodality treatment did not improve survival compared with surgery alone for women with early-stage SCCUC. Given this, further studies are required to develop novel therapies for this aggressive cancer. For instance, SCCUC is a human papillomavirus (HPV)-associated neoplasm. Thus, it remains to be determined whether this approach has any survival benefit. In addition, there are ongoing trials evaluating targeted agents such as gefitinib, sorafenib, bevacizumab, and thalidomide in SCLC (35). These findings may stimulate the search for, and design of, clinical trials to test targeted therapies for the treatment of SCCUC.

The present study has certain limitations. This is a retrospective analysis and some clinicopathologic information, especially the depth of stromal invasion, was lacking. There is also a paucity of information for some reports regarding postoperative multimodality treatment including sequence, frequency and type of chemotherapeutic agents, which prevent us from making a more detailed analysis. Although it is one of the largest series reported thus far, given these limitations, these findings should be regarded as being preliminary to a large-scale study.

In conclusion, our results indicate that FIGO stage, LNM, and DSI are prognostic factors. Additionally, SU alone should be limited to patients with stage IB1 disease, small tumors and favorable characteristics. Since the current multimodality treatment is not associated with improved survival for patients with early-stage SCCUC, newer combined therapeutic protocols and newer effective multi-agent chemotherapy should be evaluated.

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