ONCOLOGY

Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients

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OBJECTIVE: To determine the clinicopathologic factors associated with survival in neuroendocrine small cell cervical cancer patients.

STUDY DESIGN: Patients were identified from a review of literature with an additional 52 patients from four hospitals. Kaplan-Meier and Cox regression methods were used for analyses.

RESULTS: Of 188 patients, 135 had stages I-IIA, 45 stages IIB-IVA, and 8 stage IVB disease. A total of 55.3% underwent surgery, 16.0% had chemoradiation, 12.8% radiation, and 3.2% chemotherapy alone. The 5-year disease-specific survival in stage I-IIA, IIB-IVA, and IVB disease was 36.8%, 9.8%, and 0%, respectively ($P < .001$). Adjuvant chemotherapy or chemoradiation was associated with improved survival in patients with stages IIB-IVA disease compared with those who did not receive chemotherapy (17.8% vs 6.0%; $P = .04$). On multivariable analysis, early-stage disease and use of chemotherapy or chemoradiation were independent prognostic factors for improved survival.

CONCLUSION: Use of adjuvant chemotherapy or chemoradiation was associated with higher survival in small cell cervical cancer patients.

Key words: cervix uteri, neuroendocrine, prognosis, small cell, treatment outcome

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Neuroendocrine small cell cervical carcinoma is an aggressive, but rare form of cervical cancer with an incidence of less than 3% of all cervical cancers.[1-3] Earlier reports have shown that the majority of patients present with advanced stage disease, have lymph node metastasis, and are at a high risk for recurrence and disease progression.[4] In a retrospective study of 21 patients with small cell cervical cancer, the 2- and 5-year survival rates were only 43% and 29%, respectively. In fact, of the patients with greater than IB1 disease, there were no survivors beyond 30 months.[5] Compared with patients with squamous cell carcinomas, women with small cell tumors have 1.84 times greater risk of death.[4] Women with small cell cervical cancer have a worse prognosis than other histologic cell types. Of those with stage IB1 disease, the 10-year survival was 55% in small cell compared with 76% and 88% in adenocarcinoma and squamous cell patients, respectively.[5] To date, most studies on neuroendocrine cervical carcinoma are comprised of only small series and case reports, making it difficult to draw conclusions on overall management. 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, we performed an analysis of 188 women comprised of patients from our own institutions and abstracted on a case by case basis from series in the English literature, to determine the prognostic factors and potential therapeutic modalities that may improve survival in neuroendocrine cervical cancer patients.

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Materials and Methods

Fifty-two patients with neuroendocrine small cell cervical carcinoma who received diagnoses from 1979-2005 were identified from tumor registry databases at 4 hospitals (University of California-San Francisco, Stanford University, University of California-Irvine Medical Center, and Long Beach Memorial Medical Center). After institutional review board approval from these institutions, data were collected from hospital charts, office records, and tumor registry files. The remaining 136 patients were collected from case-series reported in the literature. A literature search was performed in Pubmed using "small cell carcinoma," and "neuroendocrine and cervix," and "oat cell carcinoma and cervix." These papers were then analyzed for those which provided individual patient data on demographics, clinicopathologic characteristics, treatment, and outcome information and 44 papers met these criteria. Every attempt was made to include only patients meeting the criteria for high-grade small cell carcinomas of the cervix as characterized by the work-

TABLE 1
Demographic and treatment factors with associated 5-year DSS

Variables	n (%)	5-year DSS	*P* value
Age at diagnosis, y			.78
≤40	92 (48.9)	30.1%	
>40	96 (51.1)	28.6%	
Race			.44
White	42 (61.8)	28.7%	
Hispanic	3 (4.4)	33.3%	
Black	4 (5.9)	50.0%	
Others	19 (27.9)	0.0%	
Stage			< .001
I-IIA	135 (71.8)	36.8%	
IIB-IV	53 (28.2)	8.9%	
Radical hysterectomy			< .001
Yes	89 (52.4)	38.2%	
No	81 (47.6)	23.8%	
Chemotherapy			
Stage I-IV disease			.56
Chemotherapy	81 (43.1)	38.1%	
No chemotherapy	85 (45.2)	30.3%	
Stage I-IIA disease			.91
Chemotherapy	57 (46.7)	47.3%	
No chemotherapy	65 (53.3)	38.7%	
Stage IIB-IVA disease			.043[a]
Chemotherapy	17 (37.8)	17.8%	
No chemotherapy	20 (44.4)	12.0%	

DSS, disease-specific survival.

[a] Three-year survival listed, unable to calculate 5-y DSS due to death of all patients in at least 1 group by 60 mo.

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shop sponsored by the College of American Pathologists and the National Cancer Institute.[6] Cases that were clearly carcinoid tumors or large cell neuroendocrine tumors of the cervix were excluded. Of the cases, 50% were confirmed with either immunohistochemical staining or electron microscopy. Of the other cases, 89% came from large academic institutions with expert gynecologic pathologists. By reviewing the individual patient demographic and tumor characteristics, an attempt was made to exclude cases that may have been included in 2 or more publications. The individual patient data were abstracted from the text and tables in the publications and not extrapolated from the figures. Statistical analysis was performed using NCSS 2001.[7] Kaplan-Meier life table analyses were used to analyze the significant clinical and pathologic risk factors for survival. Independent prognostic factors predictive of survival were analyzed with Cox regression methods. All tests were 2-tailed with *P* values < .05 considered significant.

RESULTS

Of 188 patients, 135 had stage I-IIA, 45 had IIB-IVA, and 8 had stage IVB disease.[8-46] The median age was 42 years (range, 20–87 years). Demographic characteristics of the patients are shown in Table 1. Vaginal bleeding at presentation was noted in 21.8% of patients and 8% had pain and pressure. Of 115 patients with tumor size documented, 80.0% had tumor ≥2 cm in size. Other clinicopathologic characteristics are shown in Table 2.

For primary treatment, 55.3% underwent surgery, 16.0% had chemoradiation, 12.8% radiation, 3.2% chemotherapy alone, and 12.8% had other or no treatment. Of patients with stage I-IIA disease, 68.1% underwent surgery, 8.9% had radiation therapy, 8.9% underwent chemoradiation, 1.5% had chemotherapy only, and 12.6% had other or no treatment. Of those with stage IIB-IVA disease, 26.7% had surgery, 35.6% underwent chemoradiation, 24.4% had radiation therapy, 6.7% underwent chemotherapy alone, and 6.6% had other or no treatment. Of those with stage IVB disease, 25% underwent chemoradiation, 12.5% had surgery, 12.5% were treated with chemotherapy, 12.5% received radiation alone, and 37.5% had unknown treatment. Of all women who had surgery, 84.6% underwent a radical and 11.5% had a simple hysterectomy. Pelvic lymph node dissections were performed in 54% of patients and 36.2% had a paraaortic lymph node dissection. Of these patients, 49.5% had lymph node metastasis. Of those with information on lymphovascular space invasion (LVI), 69.4% had LVI; 71.2% of patients with stage I-IIA disease had tumors with LVI. Of the 81 patients who received chemotherapy, 51.9% had cisplatin combined with etoposide, 25.9% had other cisplatin combinations, and 7.4% had cisplatin alone, and 14.8% had other chemotherapy. Of those patients with known recurrence information, 10 patients had local recurrence, 61 had distant recurrence, and 5 patients had both local and distant recurrence.

The overall 5-year disease survival for patients with stage I-IIA and IIB-IV was 36.8%, and 8.9%, respectively ($P < .001$) (Figure 1). Chemotherapy (as primary, adjuvant, or with concurrent radiation) was associated with improved survival in stage IIB-IVA disease compared with those who did not receive chemotherapy (3-year survival: 17.8% vs 12.0%; $P = .043$) (Figure 2). However, in the 135 pa-

tients with stage I-IIA disease, those who had any chemotherapy vs no chemotherapy had 5-year survivals of 47.3% and 38.7%, respectively ($P = .908$). Those who had radiation therapy vs no radiation had a 5-year survival of 26.9% vs 36.4%, respectively ($P = .115$). Patients with tumors <2 cm had a 5-year survival of 67.4% vs 34.4% in those with larger tumors ($P = .057$). The 5-year survival for stage I-IIA patients who received a radical hysterectomy was 38.2% compared with 23.8% for those who did not undergo radical hysterectomy ($P < .001$) (Figure 3). In multivariate analysis, early-stage disease (I-IIA), use of any chemotherapy, and radical hysterectomy were independent prognostic factors for improved survival (Table 3).

TABLE 2
Pathologic characteristics and associated 5-year DDS

Variables	n (%)	5-year DSS	*P* value
Tumor size			.06
<2 cm	23 (20.0)	67.4%	
≥2 cm	92 (80.0)	34.4%	
Tumor histology			.014
Pure	82 (73.2)	14.3%	
Mixed	30 (26.8)	30.9%	
Lymphovascular space invasion			.26
Yes	50 (26.6)	40.7%	
No	22 (11.7)	52.0%	
Lymph node involvement[a]			
Pelvic lymphadenectomy			.12
No	37 (34.6)	55.7%	
Yes	70 (65.4)	32.8%	
Pelvic lymph node involvement			
No	44 (65.7)	31.7%	.20
Yes	23 (34.3)	27.8%	
Paraaortic lymphadenectomy			
No	56 (57.1)	46.7%	.65
Yes	42 (42.9)	36.2%	
Paraaortic lymph node involvement			
No	39 (79.6)	33.2%	.41
Yes	10 (20.4)	25.7%	

DDS, disease-specific survival.

[a] After surgery (includes patients with stage I-IIA disease only).

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COMMENT

Small cell cervical carcinoma is rare and is associated with a poor prognosis.[47] The Gynecologic Oncology Group attempted to study small cell cervical carcinoma in protocol 66 between 1982 and 1986, but failed to recruit sufficient numbers of patients. As a result, treatment decisions have been based on these small single institution studies, and have extrapolated treatment approaches from the management of small cell cancer of the lung. With 188 patients in this report, to our knowledge, this is the largest study to date that analyzes the demographic, clinicopathologic, and detailed treatment-associated survival outcomes.

Our data showed that early-stage disease is an independent prognostic factor. However, survival is poor even for early-stage patients with a 5-year survival of only 36.8%. This is consistent with a prior report on 34 patients showing a 32% 5-year survival rate in those with stage I-IIA disease.[43] In this current report, we provide an update on those patients, included another 18 cases from 2 other institutions, and 136 patients from published literature. Previous analyses from 3 of the larger cohorts available have identified stage of disease as the only significant prognostic factor.[5,25,43] Another series of 26 patients showed that no patients with disease > stage IB1 or lymph node metastases achieved a cure; with an overall survival of only 29% at 5 years.[44] Others have used the SEER database and demonstrated that age, stage, and race were prognostic factors for survival in women with small cell cervical carcinoma.[48] In that analysis, the overall 5-year survivals ranged from approximately 50% for stage I patients, 40% for stage II patients, 25% for stage III patients, and under 10% for stage IV patients. Likewise, our study showed that those with stage I-IIA disease had a 5-year survival of 36.8% compared with 9.8% for those with stage IIB-IVA and 0.0% for those with stage IVB ($P < .001$). The SEER database study also showed that age and race are important prognostic factors. However, we were unable to demonstrate a similar difference associated with age and race, most likely because of the smaller sample size. Nevertheless, studies from large population databases are limited due to incomplete information on adjuvant or concurrent chemotherapy; as such, it is difficult to analyze treatment effects and associated outcomes.

Although most studies have confirmed that stage is an important prognostic indicator, the optimal treatment for small cell cervical carcinoma remains to be determined. To our knowledge, this is the first paper to demonstrate a potential benefit in survival associated with radical hysterectomy (odds ratio [OR], 0.62). The prior series by Chan et al[43] also showed that the only long-term survivors were those with small tumors

FIGURE 1
Overall survival based on stage (n = 188)

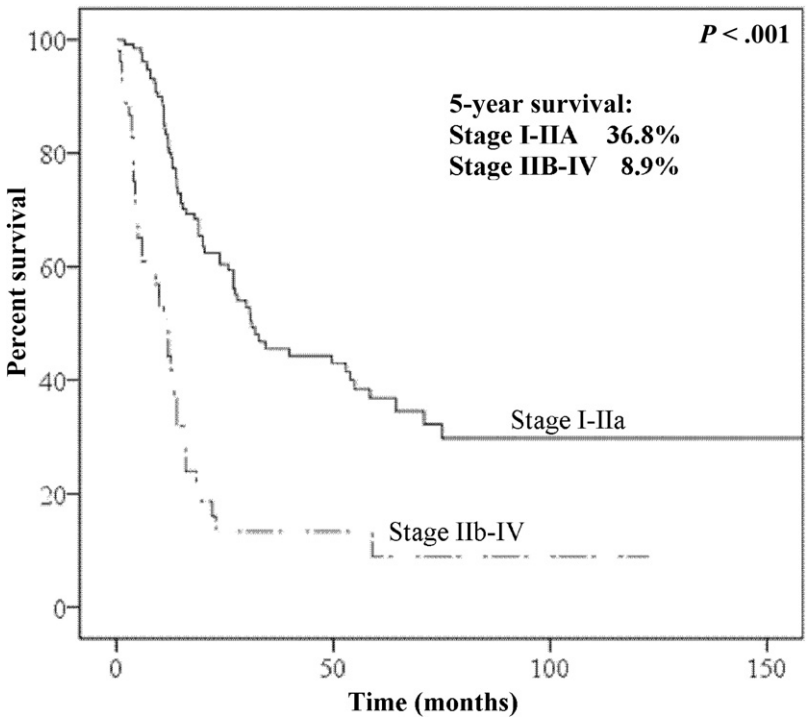

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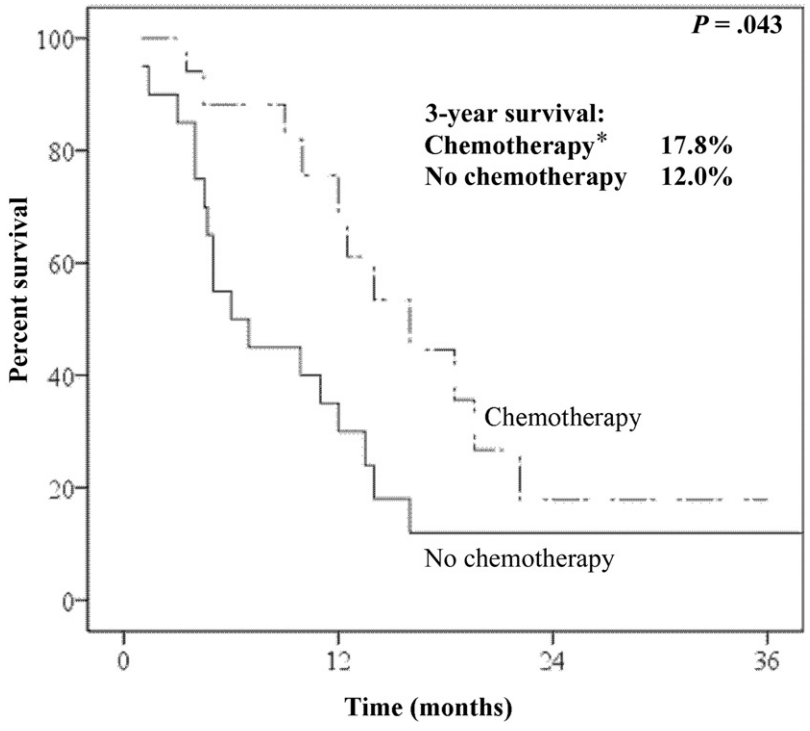
FIGURE 2
Overall survival in stage IIB-IVA patients based on chemotherapy (n = 37)



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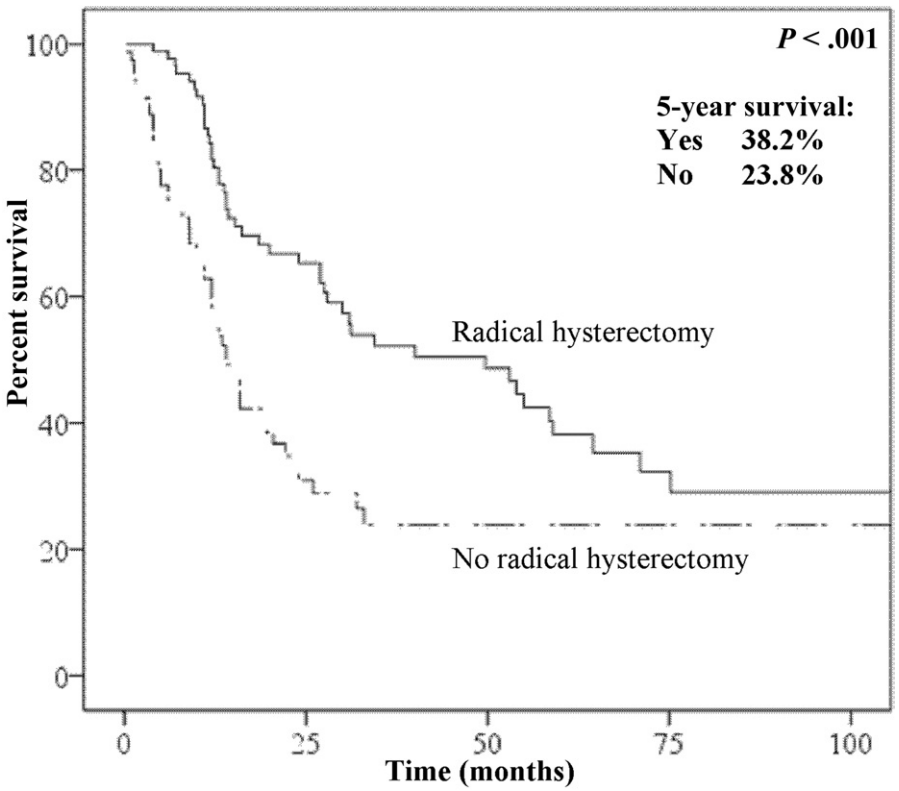
amenable to surgery. The additional 154 patients from this report confirmed the results from the previous study. As shown in a previous report by Chan et al, radical hysterectomy remains as the primary treatment for those with localized disease.[43] In fact, this initial study showed that the only long-term survivors were those with small tumors (<2 cm) amenable to radical surgery. This is not surprising given that radical hysterectomy remains an important component of the standard treatment in early-stage squamous cell cervical cancer.

Previous reports have not been able to show benefit associated with chemotherapy in the treatment of this aggressive cancer. It is possible that these small retrospective studies lacked the statistical power to see such a benefit. In our prior report on 34 patients, we were unable to show that chemotherapy improved survival. In this current larger series, we showed that chemotherapy improved the outcome in those with stage IIB-IVA disease. However, chemotherapy did not significantly impact the survival in those with early-stage neuroendocrine tumors. Although the survival of those who underwent chemotherapy was 47.3% vs 38.7% in those without chemotherapy, this difference was not statistically significant. Larger numbers of patients may be required to show a difference.

There are no studies that directly compare radical surgery or multimodality treatment in early-stage disease. Thus, although we found a benefit associated with chemotherapy in the stage IIB-IVA group, it remains to be determined whether patients with early-stage disease may benefit from chemotherapy after surgical treatment (Figure 3). A recent analysis of 68 patients with stage IB-IIA small cell carcinoma of the cervix showed no benefit from adjuvant chemoradiation therapy compared with adjuvant chemotherapy alone and a worse outcome with neoadjuvant chemotherapy.[49] However, given the aggressive nature of this tumor, the use of multimodality treatment with chemotherapy even in early-stage disease should be considered. As reported, the 5-year disease-specific survival of those with early-

FIGURE 3
Overall survival based on radical hysterectomy (n = 169)



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stage I-IIA disease was only 36.8%. The optimal chemotherapy regimen is difficult to distinguish based on our study; however, cisplatin combined with etoposide appears to be the most commonly used regimen. Given the overall poor prognosis, even in those with early-stage disease, further studies are warranted to develop novel therapies with systemic regimens for this aggressive cancer. For instance, there are ongoing trials evaluating targeted agents such as gefitinib, bevacizumab, temsirolimus, sorafenib, and thalidomide in small cell lung cancer.[50]

Our study was limited by the fact that the majority of patients were extracted from small case series making it difficult to validate the quality of information. Thus, there is a lack of information on surgeon's specialty, reason for choice of adjuvant therapy, standardization of chemotherapy, and lack of central pathology review in most reports. Although it is possible that there exists some overlap in our patient population, we attempted to prevent patient overlap by using individual patient data in each of the studies. In addition, there exists heterogeneity in data due to a lack of uniform criteria between papers, as well as a bias of selection of patients, coming only from published trials, which tend to come from positive studies.[51,52] Furthermore, our study is limited by the potential heterogeneity of our patient population between local hospital data and literature data. As such, we performed a separate analysis comparing the results from our hospital data with those abstracted from the literature review. The stage distribution of the patients and 5-year disease-specific survival rates were not significantly different between the 2 groups. This lends support for our combining all patients in one large series. This represents the largest group of patients with small cell cervical carcinoma with surgery, chemotherapy, and survival analysis. Our data indicate that early-stage, chemotherapy, and radical hysterectomy are associated with improved survival. Further studies are warranted to confirm our findings in these patients. ■

TABLE 3
Multivariate analysis–independent predictors of survival

Variables	Odds ratio	95% CI	*P* value
Stage[a]	2.52	1.76–3.62	< .001
Radical hysterectomy[b]	0.62	0.41–0.94	.026
Chemotherapy[c]	0.62	0.41–0.92	.019

CI, confidence interval.

[a] IA-IIA vs IIB-IVA vs IVB; [b] No vs yes; [c] No vs yes (includes chemotherapy alone or chemoradiation therapy).

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