Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence

Akila N. Viswanathan, a Michael T. Deavers, b Anuja Jhingran, c Pedro T. Ramirez, d Charles Levenback, d and Patricia J. Eifel c, *

a Department of Radiation Oncology, Brigham and Women's Hospital, Boston, MA, USA
b Department of Pathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
c Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
d Department of Gynecologic Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

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Abstract

Objective. To analyze the sites of relapse and overall survival in women with neuroendocrine marker-positive small cell carcinoma of the cervix.

Methods. The records of all women who had their initial treatment for cervical cancer at The University of Texas M.D. Anderson Cancer Center between 1980 and 2000 were reviewed. Fifty-one patients had stages I–III cancers that were originally described as “small cell” or “neuroendocrine.” Histological material was available for reexamination in 45 cases; of these, 21 were found to have small cell neuroendocrine carcinoma (SCNEC) as indicated by positive staining for chromogranin, synaptophysin, or CD56. Local treatment consisted of a radical hysterectomy in six patients and radiation therapy in 15. Thirteen patients received chemotherapy as part of their initial treatment. The median follow-up for surviving patients was 83 months (range, 25–209 months).

Results. Fourteen (66%) of the 21 patients had a relapse. The median time to first relapse from the initiation of treatment was 8.4 months (range, 3.6–28 months). Most patients developed hematogenous distant metastases before their death. Only 2 of 15 patients who were treated with radiation therapy had a recurrence within the radiation fields. However, five patients had a recurrence above the radiation fields in the paraaortic lymph nodes, and two patients had a recurrence distal to the pelvic fields in the vagina. No patient had brain metastases as the sole site of first recurrence. However, two patients developed brain metastases concurrently with lung metastases. The overall survival rate was 29% at 5 years; none of the patients who had disease more extensive than stage IB1 or clinical evidence of lymph node metastases survived their disease.

Conclusions. Patients with small cell neuroendocrine cervical cancer have a poor prognosis. Their course is frequently characterized by the development of widespread hematogenous metastases; locoregional recurrence outside irradiated fields is also frequent. Brain metastases were seen only in patients who also had lung metastases, suggesting that prophylactic cranial irradiation would be of little benefit.

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Introduction

Small cell neuroendocrine carcinoma of the uterine cervix (SCNEC) is a rare malignancy, representing less than 5% of all cases of cervical cancer. It is characterized by frequent and early nodal and distant metastases, resulting in a relatively poor prognosis. Histologically, SCNEC is indistinguishable from small cell carcinoma in other sites. Characteristic features include small (less than two to three times the diameter of a small resting lymphocyte or 14–21 μm) cells with hyperchromatic nuclei and scant cytoplasm. Nucleoli are inconspicuous or absent. Frequent mitoses as well as necrosis are commonly identified. Small cell carcinoma is diagnosed on hematoxylin–eosin staining alone and is independent of the extent of neuroendocrine differentiation [1]. However, neuroendocrine markers are commonly used to assist in classification. Up to 80% of

* Corresponding author. Department of Radiation Oncology, Box 97, U.T.M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Fax: +1-713-794-5573.
E-mail address: peifel@mdanderson.org (P.J. Eifel).
hematoxylin- and eosin-diagnosed small cell carcinomas also stain positive with neuroendocrine markers [2].

Most clinicians favor the use of chemotherapy to treat SCNEC because of the strong evidence supporting concurrent chemoradiation in other types of cervical cancer and high incidence of distant metastases in the SCNEC subgroup. However, the regimen, timing, and duration of chemotherapy remain controversial. Although patients with locoregionally advanced disease are usually treated with radiation therapy, the optimal locoregional treatment for women with early-stage cancers has not been determined. On the basis of similarities between SCNEC and small cell lung cancer, it has been suggested that prophylactic cranial irradiation may be indicated; however, its role has not been clearly defined [3].

We performed a retrospective review to learn more about patterns of relapse, treatment effectiveness, and overall survival in women with neuroendocrine marker-positive small cell carcinoma of the cervix.

Methods

A database of patients treated for carcinoma of the uterine cervix at The University of Texas M.D. Anderson Cancer Center was searched to identify patients whose tumors were described in the original pathology reports as “small cell” or “neuroendocrine” cervical carcinoma. Patients who had hematogenous distant metastases at diagnosis were excluded. Fifty-one patients met these criteria.

For this study, a gynecologic pathologist (M.D.) reexamined all the available biopsy and hysterectomy material. When material was available, additional sections were obtained and stained for synaptophysin, chromogranin, and CD56 (neural cell adhesion molecule). Six of the 51 cases were excluded because slides or tissue blocks were unavailable for histological review. In addition, 23 patients were excluded because they did not have small cell carcinoma on the basis of hematoxylin–eosin staining. The diagnoses in this group were large cell neuroendocrine cancer (nine patients), papillary squamous carcinoma (nine patients), carcinoid (two patients), primitive neuroectodermal tumor (two patients), and adenocarcinoma (one patient). Of the 22 patients with available paraffin blocks who were diagnosed as having small cell carcinomas on the basis of hematoxylin–eosin staining, 21 (95%) had positive staining for one or more neuroendocrine markers. These 21 patients form the final study population.

Patient, tumor, and treatment characteristics were obtained from the patients’ medical records. Follow-up

Table 1

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<td>chemotherapy</td>
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Note: Syn, synaptophysin; Chr, chromogranin; RT, radiation therapy; RH, radical hysterectomy; D, dead; A, alive; SCV, supraclavicular nodes; PAN, paraaortic node(s); P, cisplatin; E, etoposide; A, doxorubicin.

a Alive with unknown disease status at 25 months; subsequently lost to follow-up.

b Patients also had radiographic evidence of lymph node involvement.
and relapse information were obtained from chart review of records of clinic visits and correspondence with patients and physicians. The Department of Patient Studies at M.D. Anderson Cancer Center contacted patients annually to obtain information on current health status for those patients no longer having follow-up visits at M.D. Anderson.

The staging evaluation included a detailed clinical history and physical examination; in most cases, an attending radiation oncologist and a gynecologic oncologist performed a gynecologic examination in a multidisciplinary clinic. At the staging evaluation, tumor measurements were diagrammed, and a permanent copy of this diagram was placed in the patient’s chart. The results of other studies, including chest radiography, intravenous pyelography, proctoscopy, and cystoscopy, were documented in the medical chart. In addition to these routine diagnostic tests, seven patients had CT or MRI of the brain, three patients had CT of the chest, and two patients had bone scans as part of their diagnostic workup. Routine blood work was performed, and hemoglobin levels at diagnosis were recorded.

Local treatment was radical hysterectomy in 6 patients and radiation therapy in 15 patients (Table 1). Radiation was delivered using external-beam radiation therapy and intracavitary brachytherapy. External-beam therapy was delivered using anterior–posterior fields and 18-MV photons. Intracavitary treatment was delivered using Fletcher-Suit or Fletcher-Suit-Delclos afterloading low-dose-rate applicators. Chemotherapy was given to 13 (62%) of the 21 patients. Four patients received cisplatin, doxorubicin, and etoposide (three patients) or cisplatin and etoposide (one patient) after surgery. Seven patients received neoadjuvant cisplatin, doxorubicin, and etoposide before radiation therapy. One patient received neoadjuvant cisplatin and etoposide before radiation therapy and weekly cisplatin concurrent with radiation therapy. One patient received cisplatin and 5-fluorouracil concurrent with radiation therapy as her only chemotherapy.

Overall survival rates were calculated using life-table analysis and were compared using the log-rank test. Surviving patients were followed for a median of 83 months (range, 25–209 months).

**Results**

**Patient characteristics**

The median patient age was 46 years (range, 26–78 years) (Table 1). Race was recorded as white in 14 patients, African American in 2, Hispanic in 3, and Asian in 2. Five patients reported a history of tobacco use. The mean hemoglobin concentration at diagnosis was 12 g/dl.

Fifteen patients had stage I disease, and six had stage II or III disease. None of the six patients treated with radical hysterectomy had evidence of lymph node involvement. However, 6 of the 15 patients treated with radiation therapy had radiographic evidence of lymph node metastases; these were confirmed by fine-needle biopsy in two cases. All six patients treated with a radical hysterectomy had stage I disease and had negative surgical margins.

Synaptophysin staining was noted in 19 patients, chromogranin staining was noted in 16, and CD56 staining was noted in 15. Samples from 11 patients stained positive for all three neuroendocrine markers.

**Patterns of failure**

Of the 21 patients in the final study population, 14 had a relapse, and all 14 died of their disease. The mean time to first relapse was 8.4 months (range, 3.6–28 months); only one patient had a relapse more than 24 months after diagnosis. The sites of relapses are detailed in Table 1. Twelve patients developed hematogenous distant metastases before their death.

Fifteen patients received radiation therapy. Of these 15, only 2 were alive and had no evidence of disease recurrence. However, of the 13 recurrences that occurred in 15 patients treated with radiation, only 2 recurrences occurred in the radiated field. In six cases, an initial site of failure was in tissues adjacent to the radiation fields; five patients had a recurrence above the radiation fields in the paraaortic lymph nodes, and two patients had a recurrence distal to the pelvic fields in the distal vagina. Patients who were treated with radical hysterectomy tended to have less advanced disease than irradiated patients. Of the six patients treated with a radical hysterectomy, only two recurred, both in the pelvis. Of note, no patient had brain metastases as the sole site of first recurrence. Two patients had brain metastases diagnosed simultaneously with lung metastases.

**Survival**

Overall survival rates were 43% and 29% at 2 and 5 years, respectively. Survival was strongly correlated with...
tumor size and stage; none of the women who had disease more extensive than stage IB1 survived more than 30 months (Fig. 1). The survival rate of patients with stage IB1 disease was significantly poorer than that of patients with stage IB1 squamous carcinoma or adenocarcinoma treated at M.D. Anderson Cancer Center during the same time period (between 1980 and 2000) (Fig. 2). All six survivors were nonsmokers. Of the 14 patients that recurred, 7 were current or past smokers; however, a comparison of the survival rates of smokers versus nonsmokers did not achieve statistical significance ($P = 0.4$). Treatment with chemotherapy did not result in a significant increase in relapse-free survival ($P = 0.4$). There were no significant correlations between marker status and outcome.

**Discussion**

For this study, we restricted our analysis to patients with neuroendocrine marker-positive small cell carcinoma. A key component of our review was that all pathologic material was rereviewed by one pathologist using modern classification methods and staining techniques. Our approach is important because confusion about definitions of disease has made it difficult to interpret the results of previous reports on small cell carcinomas of the cervix. Albores-Saavedra et al. [4] published the first descriptions of so-called endocrine carcinomas of the cervix in 1976. Their early series included several poorly differentiated cancers that had a histological appearance similar to that of small cell or “oat cell” carcinomas of the lung. In subsequent years, there have been more than 40 reports of small series of patients with “small cell” or “neuroendocrine” carcinomas of the cervix. However, the inconsistent terminology used to describe endocrine cancers of the cervix has made it difficult to clearly define their incidence and behavior. Many series have included a mix of neuroendocrine-marker-positive and -negative tumors or have included neuroendocrine tumors with various cytological appearances. Classification of these cancers has evolved and many of our cases were reclassified on rereview of the pathology. In 1996, the College of American Pathologists and the National Cancer Institute sponsored a workshop designed to “reduce the number of terms used to describe these lesions” [5]. They suggested dividing endocrine tumors of the cervix into four categories: typical (classical) carcinoid tumor, atypical carcinoid tumor, large cell neuroendocrine carcinoma, and small (oat) cell carcinoma. Their definition of small cell carcinoma was “[a cancer with] small round or fusiform cells with scant cytoplasm and hyperchromatic nuclei having finely granular chromatin and absent or inconspicuous nucleioli. Numerous mitotic figures and extensive necrosis are common features” [5]. They went on to state, “because approximately 60% of small cell carcinomas show no reactivity for chromogranin and synaptophysin and 33% do not express neuron-specific enolase, immunohistochemical stains are not necessary to make the diagnosis” [5]. Small cell carcinomas, which exhibit no squamous differentiation, should not be confused with small cell nonkeratinizing squamous cell carcinomas. The latter belong to one of three categories of squamous carcinoma that were included in a system proposed by Reagan et al. [6] and subsequently adopted by the World Health Organization.

In our series, only 1 (4%) of 25 small cell carcinomas that were identified on review of hematoxylin–eosin-stained slides failed to demonstrate positivity for at least one neuroendocrine marker (three patients had no material available for immunohistochemical staining). Various authors have reported negative staining for neuroendocrine markers in 20–70% of cases of histologically diagnosed small cell carcinoma of the cervix [1,5,7]; however, not all studies used three markers. Only 11 of the 21 tumors included in our study stained positive for all three markers. Sites of failure of SCNEC of the cervix have not been detailed in most prior publications. However, the literature does suggest that small cell cancers behave aggressively with a frequency and manner of recurrence that is unusual for other types of cervical cancer. A number of the patients in our series experienced widespread dissemination involving bone, liver, lung, lymph nodes, and other soft tissues in a manner much more characteristic of small cell lung cancer than of cervical cancer in general. However, an appreciation of this aggressive behavior of small cell carcinoma of the cervix should not diminish understanding of the probable importance of locoregional disease control. Both of the patients who had recurrence after radical hysterectomy developed locoregional recurrence before dissemination to other organs. We believe that treatment with radical hysterectomy should be limited to patients with small tumors and favorable features. Although in-field pelvic recurrence was rare after radiation therapy, for many of our patients, the
initial recurrence included sites marginal to the radiation field in the distal vagina (two patients) or paraaortic lymph nodes (5 patients). Radiation therapy may prove critical for effective management of this disease as it has for patients with limited-stage small cell carcinoma of the lung. Surgical staging or more sensitive diagnostic imaging methods such as positron emission tomography could improve detection of paraaortic metastases that require extended regional radiation.

Several authors have commented on the unusually high incidence of brain metastases in patients with small cell carcinoma of the cervix [8–10]. This is another feature that draws comparison with small cell carcinoma of the lung. In small cell lung cancer, the rate of brain metastases is 50% or more in patients who experience an initial complete remission; a recent metaanalysis suggested that prophylactic cranial irradiation improved survival in patients with small cell lung cancer by decreasing the rate of brain metastases [3]. However, our data do not support the routine use of cranial irradiation in patients with small cell carcinoma of the cervix. Although none of the patients in our series received prophylactic cranial irradiation, only two had recurrences in the brain, and both of these were associated with simultaneous lung metastases, suggesting that hematogenous metastases to the lung may have been necessary before tumor could spread to the brain.

Many authors have emphasized the poor prognosis of patients with small cell carcinomas [1,2,7,9–15]. In a large population-based study from Norway, Alfsen et al. [14] identified 417 patients with adenocarcinoma, 29 patients with small cell carcinoma, and 59 patients with other non-squamous cell carcinomas of the cervix. Multivariate analyses showed that the most important prognostic variable was the presence of positive lymph nodes. Small cell carcinoma was the only histological subtype that was significantly correlated with outcome, with a 5-year survival rate of only 33% for patients with stage I disease and no survivors among patients with more advanced tumors. In our series, survival was strongly correlated with tumor size and disease stage; all of the long-term survivors had stage IB1 cancers (<4 cm in diameter). Several authors have previously noted a correlation between small tumor size and survival for patients with stage I small cell carcinoma of the cervix [10,12,15,16]. Survival is rare for patients who have cancers that are more extensive than stage IB, are larger than 2–4 cm, or involve lymph nodes [1,7,8,11–15]. Other prognostic factors identified as important by Chan et al. [15] included smoking status, pure histology, treatment with surgery, and margin status. Non of our operated patients had positive margins; like that of Chan et al., our study suggested a correlation between smoking status and outcome. Straughn et al. [7] investigated the relationship between molecular markers and survival. In their series, 14 (88%) of 16 small cell carcinomas were positive for neuron-specific enolase, chromogranin, or synaptophysin. Patients whose tumors were positive for chromogranin had a significantly poorer survival rate than those whose tumors were chromogranin negative. The authors also found a trend toward poorer survival for patients whose tumors did not express p53. However, they found no correlation between survival and expression of erbB2, proliferating cell nuclear antigen, or c-myc. We could not confirm Straughn et al.’s finding of a correlation between chromogranin staining and poor prognosis. In fact, all of our long-term survivors had tumors that stained positive for chromogranin. We did not find any significant correlations between marker status and outcome in this study.

Because SCNEC is a very rare tumor, it has not been possible to evaluate the impact of various treatments on outcome in prospective randomized trials. Variable inclusion criteria in retrospective studies and the small size of most series make it difficult to generalize the results of retrospective analyses. In recent years, novel treatment approaches to small cell carcinoma of the cervix have attempted to replicate successful treatments for small cell carcinoma of the lung. The success of concurrent chemoradiation for other types of locally advanced cervical cancer has also influenced the management of small cell carcinoma of the cervix.

The local treatment for small cell cancer of the cervix, as in other cervical cancers, is dependent on the stage and extent of the disease at presentation. Patients with early-stage disease have routinely been treated with radical hysterectomy. Sheets et al. [10] studied 14 patients with stage IB or IIA SCNEC treated with hysterectomy with or without postoperative radiation therapy; 57% of the patients had nodal disease. There were only two survivors, both of whom had small tumors (smaller than 2 cm) with negative nodes. In another series of patients treated with radical hysterectomy for early-stage disease, the survival rate was 36% [2]. Patients with more advanced disease are usually treated with radiation therapy alone. Although their overall outcome is poor, results are difficult to compare with results in surgical series because of the more advanced disease in patients treated with radiation. In our series, seven patients had stage IB1 tumors without radiographic evidence of lymph node metastases and with complete follow-up; two of the three who were treated with radiation and two of the four who were treated with hysterectomy had recent follow-up without evidence of recurrence.

Although several case reports and small series have indicated encouraging outcomes in patients treated with a combination of radical hysterectomy or radiation therapy and chemotherapy, the number of patients and follow-up is insufficient to permit determination of whether chemotherapy can improve the outcome of patients with small cell carcinoma of the cervix [11,17–21]. Delaloe et al. [11] reported that only 2 of 10 patients survived after treatment with various combinations of surgery or radiation therapy with chemotherapy. In another series of patients treated with sequential chemotherapy and radiation therapy at M.D. Anderson [20], 4 of 10 patients were alive without disease 7–60 months after treatment; 5 of these patients met the inclusion criteria for and are included in our current study.
Chang et al. [22] reported some of the most encouraging results with chemotherapy for this disease. In their study of 23 patients treated with radical hysterectomy for stage I or IIA small cell carcinoma, 10 of 14 patients were alive after adjuvant treatment with a regimen that alternated vincristine, doxorubicin, and cyclophosphamide with cisplatin and etoposide; only 3 of 9 patients treated with other chemotherapy regimens were alive. More recently, Hoskins et al. [23] reported encouraging results using concurrent chemoradiation in patients with more advanced disease. Interestingly, after they noted a high rate of paraaortic metastases in their patients, these authors also began to include routine paraaortic irradiation in their protocol. In their analysis, the 3-year survival rate for patients with stages I–II, node negative disease was 80%, and the survival rate for patients with more advanced disease was 38%. In our study of patients with SCNEC, the use of chemotherapy was not correlated with significantly improved outcome. Most of the patients in our study and in other reports of combined radiation therapy and chemotherapy received sequential treatment, an approach that has not been found to improve survival for patients with other types of cervical cancer. It is possible that the inclusion of concurrent chemotherapy for patients treated with radiation or the use of more intensive sequential chemotherapy regimes, like that advocated by Chang et al. [22] will improve the results of combined modality treatment.

We recognize the limitations of our study. This is a retrospective analysis of a single institutional experience with a small number of patients. However, it also reflects one of the largest reported experiences with this disease and one of the few that includes only patients with SCNEC, identified using modern classification and diagnostic techniques. Our study confirms the aggressive nature of this disease and suggests that a combination of accurate diagnostic methods, carefully selected locoregional treatment, and aggressive multi-agent chemotherapy may offer the best hope for improved cure rates. Although experience with treatment of small cell lung cancer may suggest fruitful avenues for improvement, SCNEC of the cervix differs from small cell lung cancer in SCNEC’s lower risk of brain metastasis. It is not yet known whether chemotherapy will be as effective as it has been in patients with small cell lung cancer. Currently, our typical approach is to treat patients with SCNEC using concurrent chemoradiation followed by several additional cycles of chemotherapy. However, the rarity of SCNEC limits the ability of single institutions to determine the value of different management approaches and suggests the need for well-designed multi-institutional group trials.

References

