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Outcomes of patients undergoing radical hysterectomy for cervical cancer of high-risk histologic subtypes

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Structured Abstract

Introduction—The most common types of cervical cancer are squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma, referred to here collectively as SA cervical cancer. Other types of cervical cancer, referred to here collectively as nonsquamous/nonadenocarcinoma (NSNA) cervical cancer, include neuroendocrine, small cell, clear cell, sarcomatoid, and serous tumors. Anecdotally, NSNA tumors seem to have a worse prognosis than their SA counterparts. We sought to determine whether patients with early-stage NSNA have a worse prognosis than those with early-stage SA cervical cancer.

Methods—We retrospectively reviewed charts of women with stage IA1-IB2 NSNA cervical cancer treated by radical hysterectomy and lymph node staging at MD Anderson Cancer Center from 1990 to 2006. NSNA patients were matched 1:2 to patients with grade 3 SA lesions on the basis of stage, age at diagnosis, tumor size, and date of diagnosis.

Results—Eighteen patients with NSNA primary cervical cancer subtypes [neuroendocrine (n=7), small cell (5), clear cell (4), papillary serous (1), and sarcomatoid (1)] were matched to 36 patients with grade 3 SA lesions. There were no differences between the 2 groups in age, body mass index, clinical stage, or lesion size. The 2 groups also did not differ with respect to number of nodes resected, lymphovascular space invasion, margin status, lymph node metastasis, or adjuvant radiation therapy or chemotherapy. At a median follow-up of 44 months, median progression-free and overall survivals had not been reached; however, both progression-free survival ($p=0.018$) and overall survival ($p=0.028$) were worse for the NSNA group. The 5-year progression-free and overall survival rates were 61.2% and 67.6%, respectively, for the NSNA group, compared to 90.1% and 88.3%, respectively, for the SA group.

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Conclusions—Patients with early-stage NSNA cervical cancer undergoing radical hysterectomy and pelvic lymphadenectomy have a worse prognosis than patients with grade 3 SA lesions. Patients with NSNA tumors may require a multimodality approach to their cancer care.

Keywords

Neuroendocrine; small cell; clear cell; radical hysterectomy; cervical cancer

INTRODUCTION

Carcinoma of the uterine cervix is the second most common cancer and the third most common cause of cancer-related mortality among women worldwide (1). Although cervical cancer incidence and mortality rates have declined approximately 50% in the United States over the past 3 decades, the disease remains a serious health threat. Squamous cell carcinoma is the predominant histologic subtype; next most common are adenocarcinoma and adenosquamous carcinoma. These 3 subtypes collectively are referred to here as SA cervical cancer. Other types of cervical cancer, referred to here collectively as nonsquamous/nonadenocarcinoma (NSNA) cervical cancer, include neuroendocrine, small cell, clear cell, sarcomatoid, and serous carcinomas. These NSNA subtypes represent less than 5% of all cervical malignancies (2, 3) and therefore have not been widely studied in the literature due to their exceedingly low incidence. However, while the incidence of invasive cervical cancer and in particular SA cervical cancer has declined over time, the incidence of the NSNA histologic subtypes has shown no change or has even increased, especially in younger women (4).

There are conflicting reports on the prognosis of patients with various histologic subtypes. In a Norwegian study of 505 patients with stages I-IV non-squamous-cell carcinomas, small cell carcinoma was the only histologic subtype independently associated with a worse prognosis (5). A review of Surveillance, Epidemiology, and End Results data found histologic subtype to be an important independent prognostic factor in cervical cancer (1). The histologic subtypes associated with poorest survival were small cell carcinoma, adenosquamous carcinoma, and rare subtypes of adenocarcinoma (e.g., mucinous). These studies included women with all stages of cervical cancer.

In early-stage disease, however, it is unknown if NSNA histologic subtypes portend a worse prognosis. For example, a recent study by dos Reis et al. [6] compared patients diagnosed with early-stage adenocarcinoma and patients diagnosed with early-stage adenosquamous carcinoma to determine if there was a difference in overall outcomes. A total of 126 patients who underwent radical hysterectomy were compared. The study demonstrated that histology alone was not a prognostic indicator in these women with tumors amenable to surgical resection, and there was no difference in recurrence rates between the 2 histologic groups, although time to recurrence was shorter for patients with adenosquamous carcinoma (7.9 months versus 15 months; $p=0.01$) (6). Overall, the NSNA histologic subtypes of primary cervical cancer have often been associated with more aggressive behavior and poorer prognosis than the SA subtypes. However, given the rarity of the NSNA subtypes,

determining the exact clinical features and natural history of these tumors in early-stage disease when radical hysterectomy may be a therapeutic option has been challenging.

The aim of the present study was to determine whether women with NSNA cervical cancers have a worse prognosis than women with SA cervical cancers after radical hysterectomy and pelvic lymphadenectomy. We examined the survival and recurrence rates in these 2 groups of women.

MATERIALS AND METHODS

This study was conducted with approval from the Institutional Review Board at The University of Texas MD Anderson Cancer Center. We reviewed our institution's electronic medical records to identify patients with NSNA of the cervix stages IA1-IB2 who underwent a radical hysterectomy and pelvic lymphadenectomy performed by a gynecologic oncologist at MD Anderson between 1990 and 2006. NSNA histologic subtypes included neuroendocrine, small cell, clear cell, sarcomatoid, and serous carcinomas. Lymphoepithelioma-like and adenoid basal tumors were excluded because of their favorable prognosis (7-9). These patients with NSNA cancers were matched 1:2 with patients with SA cervical cancers who underwent a radical hysterectomy and pelvic lymphadenectomy performed by a gynecologic oncologist at MD Anderson during the same time period. Patients were matched on the basis of stage, age at diagnosis, size of tumor, and date of diagnosis. Women who had their radical hysterectomy aborted were excluded. In all patients (cases and controls), the diagnosis was confirmed by review of all histopathologic slides by an MD Anderson gynecologic pathologist.

Data on cases and controls were obtained using electronic medical records and reviewed retrospectively to obtain patient demographics, surgical-pathologic data (histologic subtype, grade, depth of tumor invasion, presence of lymph-vascular space invasion, presence of nodal metastasis, and surgical margin status), and clinical outcomes. Patients presenting to MD Anderson with early-stage cervical carcinoma routinely undergo a pretreatment staging evaluation, which includes a physical examination and chest radiography. In addition, many patients, particularly those with high-risk histologic subtypes, undergo a preoperative computed tomography scan. Our department policy is to only consider patients with cervical tumors ≤ 4 cm (stages IA1-IB1) as candidates for radical hysterectomy, although occasionally patients with stage IB2 cervical tumors < 6 cm undergo a radical hysterectomy. Follow-up data were obtained from documentation in the medical record of clinic visits and correspondence with patients and their primary physicians.

Parametric continuous variables were compared using the t test for independent samples. Nonparametric continuous and dichotomous variables were compared using the Mann-Whitney U test and χ^2 test, respectively. Disease-free and overall survival were calculated using the method described by Kaplan and Meier. Two-sided p values are reported. A p value of less than 0.05 was considered statistically significant. SPSS 17 for Windows (SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

We identified 18 patients with NSNA primary cervical cancer who met the inclusion criteria. Their histologic subtypes were as follows: neuroendocrine carcinoma, 7 patients; small cell carcinoma, 5 patients; clear cell carcinoma, 4 patients; serous carcinoma, 1 patient; and sarcomatoid carcinoma, 1 patient. Demographic and tumor factors are shown in Table 1. Patients in the NSNA group did not differ from the 36 matched patients in the SA group with respect to age, body mass index, racial/ethnic distribution, lesion size, and visibility of the primary tumor. The majority of patients in both groups had stage IB1 disease (NSNA, 83.3%; SA, 88.9%).

Intraoperative and postoperative pathologic findings are summarized in Table 2. On pathologic examination, the lymph node counts as well as the rates of positive margins, nodal disease and lymphovascular space invasion were similar in the 2 patient groups. There were trends toward a higher frequency of postoperative chemotherapy in the NSNA group and a higher frequency of radiotherapy in the SA group, but these differences were not statistically significant.

The median length of follow-up for the entire sample was 44 months (NSNA, 43.8 months; SA, 44.8 months). The median length of follow-up for patients alive at last contact was 61.8 months (NSNA, 63.4 months; SA, 61.8 months). Median progression-free and overall survivals were not reached in either group. Figure 1 shows the Kaplan-Meier progression-free survival curves for both groups. Log-rank test for the 2 curves showed a statistically significant difference ($p=0.02$). Five-year progression free survival rates were 61.2% (95% confidence interval [CI], 36-83%) for the NSNA group and 90.1% (95% CI, 82-100%) for the SA group. Figure 2 shows the overall survival curves for both groups. Log-rank test for the 2 curves showed a statistically significant difference ($p=0.03$). Five-year overall survival rates were 67.6% (95% CI, 46-88%) for the NSNA and 88.3% (95% CI, 70-95%) for the SA group.

DISCUSSION

To our knowledge, the NSNA cohort reported herein ($n=18$) is the largest cohort reported to date of surgically treated patients with stage I NSNA cervical cancer. Although the 2 groups were similar with respect to pathologic findings (presence of lymphovascular space invasion, nodal status, and margin status) and rates of postoperative adjuvant therapies, we found a decreased overall survival in women with NSNA cervical carcinoma compared to a matched group of women with SA cervical carcinoma after radical hysterectomy and pelvic lymphadenectomy, although 5-year overall survival was not statistically different between the 2 groups. In addition, the NSNA subtypes were associated with a worse 5-year progression-free survival rate: 61% for the NSNA group versus 90% for the SA group. However, the difference was not statistically significant as the 95% CIs overlapped.

Most reports, like our study confirm the aggressive behavior of NSNA carcinomas of the cervix. In a Surveillance, Epidemiology, and End Results population study, histologic subtype was found to be an important independent prognostic factor in cervical cancer (1).

The poorest survival was associated with small cell carcinoma, adenosquamous carcinoma, mucinous carcinoma, and clear cell carcinoma (1). In a retrospective study of 2443 patients diagnosed with International Federation of Gynecology and Obstetrics stage IA-IIA cervical cancer (all histologic subtypes), nonsquamous histology, parametrial involvement, higher rate of distant metastasis, and poorer prognosis were more common in women aged 30 years or younger than in older women (10). A study on large cell neuroendocrine tumors of the cervix including patients with stage IA2-IB2 tumors (7 cases) reported a median survival time of 17.2 months and only 1 long-term survivor (>5 years) (11). The results of this study also support poorer outcomes for patients with NSNA primary cervical cancers. In a Norwegian study of 505 patients, 417 with tumors classified as adenocarcinoma and 88 with tumors classified as other non-squamous-cell carcinoma, small cell carcinoma was the only histologic subtype with independent prognostic importance and was associated with worse prognosis (5). Our finding that early stage NSNA cervical tumors were associated with worse overall and progression-free survival agrees with the findings of most previous studies.

Due to the rarity of this disease, the most effective therapeutic approach to these patients with early stage NSNA cervical cancer remains unknown. A retrospective analysis of 17 patients with stages I-IV small cell neuroendocrine carcinoma of the uterine cervix treated at Memorial Sloan-Kettering Cancer Center showed a poor prognosis due to the tumor's propensity for distant spread and showed improved survival rates with chemotherapy even in early-stage cancers (3). The primary treatment of the patients in this series consisted of surgery with or without individualized adjuvant, definitive radiation therapy or chemoradiation therapy or chemotherapy alone. Of the 11 patients with early-stage disease, all 5 who did not receive chemotherapy as part of their initial treatment developed recurrent disease, versus 2 of 6 patients (33.3%) who did receive chemotherapy (3). Like the early stage patients in the Memorial Sloan-Kettering study, the stage I NSNA patients in our study also received more adjuvant chemotherapy compared to the SA patients (28% vs. 8%), although this difference was not significant. A report of 12 patients with sarcomatoid carcinoma treated at MD Anderson showed 4 patients (stage I or II) to be disease free from 5-42 months. All of these disease free patients had radiotherapy as part of their initial treatment (12). Although there are no randomized clinical trials comparing multimodality and other types of therapy for patients with small cell cervical cancer, it appears that multimodality therapy is associated with the best results in patients with this subtype (13).

The major limitation of this study is the small number of patients in the high risk group owing to the disease rarity. Due to small patient cohorts, we believe the study to be underpowered and therefore a type II error very likely exists. In other words, if we had larger sample sizes the differences in progression free and overall survivals would probably reach statistical significance. We are currently collaborating with another large cancer center to accrue similar data for a larger study. Also, this study is limited by many of the factors that plague retrospective studies, which rely on the quality of chart documentation. In addition, as MD Anderson is a tertiary referral center, a selection bias may exist in the patients who present to us. Given the rarity of NSNA primary cervical cancers, this analysis included only a small number of patients. Furthermore, the patients were treated over 16 years, so consistency with respect to surgical techniques, radiation application, and

chemotherapy prescription likely varies. Finally, grouping the 5 histologic subtypes into 1 group (NSNA) was not ideal but is necessary in the study of such rare tumors.

Even though this study has these limitations, it is important because this case-controlled study revealed outcomes for the largest series reported to date of patients with NSNA primary cervical cancer (n=18). There was a trend toward poorer survival for patients with the NSNA histologic subtype, although the differences were not statistically significant. However, it seems reasonable to conclude that NSNA primary cervical cancers have a worse prognosis than their SA counterparts. A recent Cochrane review suggests there may be a role for adjuvant chemotherapy following definitive chemoradiation for locally advanced cervical cancer. (14) Although the small sample sizes of this study preclude us from making definitive treatment recommendations, we hypothesize that patients with NSNA tumors would likely benefit from a multimodality approach combining surgery and radiation for local control with chemotherapy for distant control. In a disease process as rare as NSNA cervical cancer, prospective studies comparing different treatment approaches will never be possible; therefore, decision making may have to be based on small cohort studies such as this one.

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Figure 1.
Kaplan-Meier curves for progression-free survival.

Figure 2.
Kaplan-Meier curves for overall survival.

Table 1

Patient and tumor characteristics

Characteristic	NSNA (n=18)	SA (n=36)	<i>p</i>
Median age, years	40.7	42.3	0.58
Range	16.7–72.2	24.5–68.3	
Mean BMI (kg/m ²)	26.9	28.5	0.14
Range	15.9–45.2	17.4–42.2	
Race/ethnicity			NC
Caucasian	12	26	
Hispanic	4	8	
Asian	2	1	
African American	0	1	
Stage			0.88
IA1	1	1	
IA2	0	1	
IB1	15	32	
IB2	2	2	
Median size of lesion, cm	3.8	2.9	0.22
Range	1.0–6.0	0.5–5.0	
Visible lesion			
Yes	11	21	0.54
No	7	15	

NSNA, nonsquamous/nonadenocarcinoma; SA, squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma; BMI, body mass index; NC, not calculable because of small subgroup sizes.

Table 2

Intraoperative and postoperative pathologic findings

Finding	NSNA (n=18)	SA (n=36)	p
Median hospital LOS	6.4	5.5	0.76
Median estimated blood loss (ml)	668	722	0.61
LVSI			1.0
Present	9	18	
Absent	7	13	
Unknown	2	5	
Parametrial involvement			
Positive			
Negative			
Median number of lymph removed	19.5	17	0.67
Margins			0.29
Positive	0	4	
Negative	17	32	
Number of nodes removed			
Lymph node spread			0.76
Present	5	12	
Absent	13	24	
Adjuvant chemotherapy			0.09
Yes	5	3	
No	13	33	
Adjuvant radiation therapy			0.24
Yes	6	20	
No	12	16	

NSNA, nonsquamous/nonadenocarcinoma; SA, squamous carcinoma, adenocarcinoma carcinoma, or adenosquamous carcinoma; LOS, length of stay; LVSI, lymphovascular space invasion.