Role of radical hysterectomy in patients with early-stage high-grade neuroendocrine cervical carcinoma: a NeCTuR study

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HIGHLIGHTS

- Parametrial involvement was present in 10% of patients and was never the only high-risk factor.
- The false-negative rate for sentinel lymph node biopsy was zero.
- Adjuvant radiotherapy decreased the likelihood of local recurrence by 60%.

ABSTRACT

Objective Patients with early-stage, high-grade neuroendocrine cervical carcinoma typically undergo radical hysterectomy with pelvic lymphadenectomy followed by adjuvant radiotherapy and/or chemotherapy. To explore the role of radical surgery in patients with this disease, who have a high likelihood of undergoing postoperative adjuvant therapy, we aimed to determine the rate of parametrial involvement and the rate of parametrial involvement without other indications for adjuvant treatment in these patients.

Methods We retrospectively studied patients in the Neuroendocrine Cervical Tumor Registry (NeCTuR) at our institution to identify those with International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IA1-IB2, high-grade neuroendocrine cervical carcinoma who underwent up-front radical surgery with or without adjuvant therapy.

Results One hundred patients met the inclusion criteria. The median age was 35 years (range 22–65), and 51% (51/100) had pure high-grade neuroendocrine carcinoma. No patient had a tumor >4 cm or suspected parametrial or nodal disease before surgery. Ten patients (10%) had microscopic parametrial compromise in the final surgical specimens. Ninety-four (94%) patients underwent nodal assessment, and 19 (19%) had positive nodes. Ten patients underwent both sentinel lymph node biopsy and pelvic lymphadenectomy, and none had false-negative findings. Patients with parametrial compromise were more likely to have positive pelvic nodes (80% vs 12%, p<0.0001), and a positive vaginal margin (20% vs 1%, p=0.03). All patients with parametrial compromise had lymphovascular space invasion (100% vs 73%, p=0.10). Of the 100 patients, 95 (95%) were recommended adjuvant therapy and 89 (89%) were known to have received it. Adjuvant pelvic radiotherapy reduced the likelihood of local recurrence by 62%.

Conclusions In carefully selected patients with high-grade neuroendocrine cervical carcinoma, the rate of microscopic parametrial involvement is 10%. As most patients receive adjuvant treatment, we hypothesize that simple hysterectomy may be adequate when followed by adjuvant radiotherapy with concurrent cisplatin and etoposide followed by additional chemotherapy.

INTRODUCTION

Neuroendocrine tumors of the cervix are rare.[1] They are classified as low-grade or high-grade, and high-grade tumors are more common.[2] Annually, neuroendocrine carcinomas account for only 1–2% of the estimated 13 800 new cases of cervical cancer in the USA.[3] High-grade neuroendocrine cervical carcinomas are aggressive tumors with a high rate of spread outside the pelvis at initial presentation. Lymphovascular space involvement and nodal metastases occur more frequently in early-stage disease than in early-stage squamous cell carcinoma of the cervix. Hematogenous spread, most commonly to the lungs and liver, is not infrequent at diagnosis.[4–6] Despite multimodal therapy, the 5 year overall survival rate of patients with early-stage disease (International Federation of Gynecology and Obstetrics (FIGO) stage I or II) is only 31–51%.[7]

Given the rarity of neuroendocrine cervical carcinoma, current treatment recommendations are based on small retrospective studies and are often extrapolated from primary neuroendocrine carcinoma of the lung. The current recommendation for patients with clinically early-stage disease is radical hysterectomy and adjuvant pelvic radiotherapy and/or chemotherapy.[8–10] At our institution, the standard recommendation for patients with early-stage (≤4 cm) neuroendocrine cervical carcinoma is open radical hysterectomy and nodal assessment (sentinel lymph node (SLN) biopsy) followed by radiotherapy with concurrent platinum and etoposide and then additional chemotherapy (same regimen) to complete a total of six cycles.[10]

Parametrial resection is performed as part of radical hysterectomy for squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix because of the 4–11% risk of parametrial involvement in patients with tumors ≤4 cm.[11–15] If the parametrium is involved, adjuvant therapy would be recommended. However, complications of parametrial resection

increase when surgery is combined with adjuvant treatment.[16 17] Furthermore, in patients with neuroendocrine cervical carcinoma, because the standard recommendation is adjuvant chemotherapy and radiotherapy regardless of parametrial status, the information provided by parametrial resection may not be needed.[8–10]

We wished to explore the role of radical surgery in patients with early-stage high-grade neuroendocrine cervical carcinoma. The primary objective of our study was to determine the rate of parametrial involvement in such patients. Secondary objectives were to determine the frequency of a positive parametrium alone without other high-risk features in the surgical specimen, and to identify factors that may impact oncologic outcomes.

METHODS

We searched the Neuroendocrine Cervical Tumor Registry (NeCTuR) at our institution to identify patients with high-grade neuroendocrine cervical carcinoma who underwent up-front radical surgery (hysterectomy or trachelectomy) as primary treatment. This Institutional Review Board approved registry is voluntary, international, and open to patients undergoing treatment, survivors, and legal representatives of deceased patients. The registry collects a wide range of data on patients with high-grade neuroendocrine cervical carcinoma. Participants give written informed consent, are active in the study for up to 10 years, and agree to allow the research team to collect information from their medical records. The study detailed in this manuscript is a retrospective analysis of patients from the registry that met the study inclusion criteria. This study is Institutional Review Board approved.

Inclusion criteria were: treatment between January 1991 and February 2020; pathologically confirmed high-grade neuroendocrine cervical carcinoma with pure (small cell, large cell, small and large cell, or high-grade not otherwise specified) or mixed histology (high-grade neuroendocrine carcinoma in combination with other histology); the source document of the pathology report must be available for review; tumor size ≤4 cm with no parametrial involvement by either pre-operative imaging (any modality) or pre-operative physical examination; no suspicion of metastatic disease on pre-operative imaging; and upfront radical surgery (trachelectomy or hysterectomy) with or without nodal assessment (full pelvic lymphadenectomy with or without para-aortic lymphadenectomy, with or without SLN mapping, or SLN mapping alone) with intent to cure. Parametrial involvement information must be available in the pathology report. Parametrial involvement was defined as any evidence of disease in the parametrial tissue on final pathologic examination: direct microscopic spread, positive parametrial nodes, and/or lymphovascular space invasion in the parametrial tissue. Patients were eligible regardless of the type of adjuvant treatment (radiotherapy with or without concurrent chemotherapy, chemotherapy alone (any regimen and number of cycles), or no adjuvant treatment), but surgery must have been first.

Patients were excluded if they had received chemotherapy and/or radiotherapy before radical hysterectomy, <18 years old, had no pathology report available, had unknown parametrial status, or underwent surgery for palliative reasons.

Of note, selection for surgery was based on clinical assessment (physical examination and imaging evaluation), but staging was based on the FIGO 2018 classification and therefore surgical pathologic findings were included to determine final stage. All patients were reclassified using the 2018 FIGO staging system. Thus, stages included ranged from stage IA1 to IIIC.

Study data were collected and managed using REDCap electronic data capture tools hosted at MD Anderson.[18] We used descriptive statistics to summarize demographic and clinical characteristics stratified by whether patients had parametrial compromise or not in up-front primary treatment. We used Fisher's exact test to compare categorical variables, excluding the 'Not reported' category, which is presented in tables but was not included in statistical testing. We used the Wilcoxon rank-sum test to compare median age and body mass index. We estimated overall survival from the date of diagnosis to death or last follow-up, with patients alive at last follow-up censored on that date. We estimated progression-free survival from the date of treatment initiation to first recurrence or death, with patients alive without recurrence at the last clinic visit censored on that date. We estimated overall survival and disease-free survival using the Kaplan-Meier product-limit estimator. We used Cox proportional hazards regression to model overall survival and disease-free survival as a function of parametrial compromise, tumor size at imaging, and adjuvant therapy (yes or no). Variables with univariate log-rank p values <0.10 were included in the disease-free and overall survival multivariable Cox regression models. Statistical analyses were performed using SAS/STAT software, version 9.4, for Windows (SAS Institute Inc). Graphics were generated using R software version 4.0.0 (R Foundation for Statistical Computing).

In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if requested.

RESULTS

One hundred patients met the inclusion criteria. The timeframe of the study was 1991 to 2020, with 90% of the included patients having surgery from 2003 to 2020 (Online supplemental figure 1). The median age was 35 years (range 22–65), and the median body mass index was 25.1 kg/m^2 (range 14.4–60.5). (Table 1) Fifty-one (51%) patients had pure and 49 (49%) had mixed high-grade neuroendocrine carcinomas. In 17 patients with mixed histology the neuroendocrine component of the tumor was diagnosed in the final surgical specimen. Tumor size before surgery was ≤2 cm in 48 (48%) patients, >2 cm and ≤4 cm in 47 patients (47%), and ≤4 cm without further specific differentiation in five (5%) patients. Ninety-five patients (95%) underwent radical hysterectomy, and five (5%) patients underwent radical trachelectomy. Ten patients (10%) had microscopic parametrial compromise in the final surgical specimens. Two of the 48 (4%) patients with pre-operative tumor size ≤2 cm, and eight of the 47 (17%) patients with pre-treatment tumor size >2 cm, had parametrial involvement.

Ninety-four patients (94%) had nodal assessment, which consisted of full pelvic lymphadenectomy with (n=10) or without (n=64) SLN mapping in 74 patients (79%); pelvic and para-aortic lymphadenectomy in 14 (15%); and SLN mapping alone in six (6%). Overall, 20 of the 94 patients (21%) had positive lymph nodes. The rate of pelvic nodal involvement was 13% (6/47) in patients with tumors ≤2 cm and 30% (13/44) in patients with tumors >2 cm.

Table 1 Demographic and clinical characteristics of patients with clinically early-stage high-grade neuroendocrine cervical carcinoma*

Characteristic	Overall cohort (n=100)	Parametrial involvement (n=10)	No parametrial involvement (n=90)	P value
Age, median (range), years	35.0 (22.0–65.0)	41.5 (30.0–63.0)	35.0 (22.0–65.0)	0.06
BMI, median (range), kg/m^2	25.1 (14.4–60.5)	25.3 (16.7–32.8)	25.1 (14.4–60.5)	0.43
Current or former smoker				0.48
Yes	43 (43)	6 (60)	37 (41)	
No	56 (56)	4 (40)	52 (58)	
Not reported	1 (1)	0 (0)	1 (1)	
FIGO (2018) stage				
IA1, IA2	11 (11)	0 (0)	11 (12)	
IB1	43 (43)	0 (0)	43 (48)	
IB2	23 (23)	0 (0)	23 (26)	
IIA1	1 (1)	0 (0)	1 (1)	
IIB	2 (2)	2 (20)	0 (0)	
IIIC1p	20 (20)	8 (80)	12 (13)	
Histology†				0.46
Pure HGNECC	51 (51)	4 (40)	47 (52)	
Mixed (HGNECC+other histology)	49 (49)	6 (60)	43 (48)	
Pre-treatment tumor size				0.05
≤2 cm	48 (48)	2 (20)	46 (51)	
>2 cm	47 (47)	8 (80)	39 (43)	
Not reported	5 (5)	0 (0)	5 (6)	
Tumor size in surgical specimen				0.06
No residual disease	19 (19)	0 (0)	19 (21)	
≤2 cm	27 (27)	2 (20)	25 (28)	
>2 cm and ≤4 cm	41 (41)	7 (70)	34 (38)	
>4 cm	2 (2)	1 (10)	1 (1)	
Not reported	11 (11)	0 (0)	11 (12)	
Positive nodes	20/94 (21)	8/10 (80)	12/84 (14)	<0.0001
Number of positive nodes, median (range)	2.0 (1.0–6.0)	2.0 (1.0–4.0)	2.0 (1.0–6.0)	0.49
Depth of invasion				0.13
≤10 mm	49/72 (68)	4/9 (44)	45/63 (71)	
>10 mm	23/72 (32)	5/9 (56)	18/63 (29)	
Lymphovascular space invasion				0.11
No	19/24 (19)	0/10 (0)	19/69 (28)	
Yes	60/79 (76)	10/100 (100)	50/69 (72)	
Positive vaginal margin	3 (3)	2 (20)	1 (1)	0.03
Ovarian compromise‡	1/57 (2)	0/6 (0)	1/51 (2)	1

*Results reported as number of patients (%) except when otherwise specified.
†Final histology: combination of pre-treatment histology and final specimen pathology.
‡Only reported for patients with bilateral salpingo-oophorectomy or unilateral oophorectomy.
BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics ; HGNECC, high-grade neuroendocrine cervical carcinoma .

One patient had a tumor <4 cm but not otherwise specified. Of the 16 patients who underwent SLN mapping, two had at least one positive SLN. One patient had a positive SLN diagnosed with hematoxylin-eosin staining and also had a positive non-SLN, and the other patient had a positive SLN with micrometastasis diagnosed by ultrastaging and negative non-SLNs. All patients who underwent SLN mapping alone had bilateral detection with all nodes negative. Among the 10 patients with both SLN mapping

and pelvic lymphadenectomy, the false-negative rate for SLN mapping was zero.

Patients with parametrial compromise were more likely to have positive pelvic nodes (8/10 (80%) vs 12/84 (14%), p<0.0001), and positive vaginal margins (2/10 (20%) vs 1/90 (1%), p=0.03) (Table 1). Parametrial involvement was more common in patients with nodal involvement than in those without nodal involvement (p<0.0001). Deep stromal invasion (>10 mm) was present in five of nine (56%) patients with parametrial involvement versus 18 of 63 (29%) of those without (p=0.13). Lymphovascular space invasion was present in all patients with parametrial compromise (100%) and in 50 of the 69 (72%) patients in the negative parametrium group (p=0.11). All patients with parametrial involvement also had other indications for adjuvant therapy, such as positive pelvic nodes (8/10) or in those two patients with negative nodes a combination of lymphovascular space invasion, tumor >2 cm, and deep stromal invasion (2/10). (Online supplemental table 1)

There was no difference in parametrial involvement (p=0.52), positive nodes (p=0.80), progression-free survival (log-rank p=0.33), or overall survival (log-rank p=0.15) between patients with pure versus mixed high-grade neuroendocrine carcinomas. The final specimen contained no residual disease in 19% (19/100) of patients. All patients with parametrial compromise had residual disease in the cervix. Of the 19 patients with no residual disease, 10 received adjuvant chemotherapy, five received adjuvant radiation and chemotherapy, three did not receive adjuvant therapy, and one patient was lost to follow-up with adjuvant therapy status unknown. Ten patients had no tumor size reported in the final specimen. Although all 100 patients in the series had a pre-treatment tumor size estimated to be ≤4 cm clinically, two (2.0%) patients had tumors pathologically measuring >4 cm in the final specimen. Of the 48 patients with pre-operative tumor size ≤2 cm clinically, six (14%) had a tumor >2 cm pathologically measured in the final specimen.

Ninety-five patients (95%) were recommended adjuvant therapy, and 89 (89%) were known to have received adjuvant treatment. Of the 11 patients (two with positive and nine with negative parametrium) who did not receive adjuvant therapy, five were advised surveillance after surgery, and six were recommended but refused adjuvant therapy (n=3) or were lost to follow-up and no information was available on whether they received it or not (n=3). Of the 89 patients known to have received adjuvant therapy, 47 (53%) received surgery and radiotherapy (with or without concurrent chemotherapy) and adjuvant chemotherapy; 26 (29%) received surgery and chemotherapy alone; and 16 (18%) received surgery and radiotherapy (with or without concurrent chemotherapy) (Table 2). Overall, 85% (80/94) of the patients in our series had no evidence of disease by physical examination and imaging at the conclusion of primary treatment.

Median follow-up time was 42 months (IQR 20–88) for patients with parametrium involvement and 35 months (IQR 17–81) for patients with no parametrium involvement. Overall, 52% (50/97) of patients had a recurrence and one died of the disease without having a recurrence but progressive disease after primary treatment. Recurrences were seen in eight of 10 (80%) patients with parametrium involvement and 43 of 87 (49%) patients in the negative parametrium group (p=0.01). Of the 50 patients who recurred with known location of recurrence, 23 (58%) had distant recurrence, 10 (25%) had local recurrence, and seven (18%) had both distant and local recurrence (p=0.72). (Table 2) Among the 50 patients with recurrence, 75% (9/12) of the patients who did not receive adjuvant radiotherapy had a local recurrence or both a local and a distant recurrence, versus 29% (8/28) of the patients who received radiotherapy (p=0.013). In other words, radiated patients were 62% less likely to have a local recurrence or both a local and distant recurrence than patients who did not receive adjuvant radiation. However, there was no significant difference between patients who did or did not receive adjuvant radiotherapy among

Table 2 Adjuvant treatment and recurrences

Adjuvant treatment or recurrence status	Overall cohort (n=100)	Parametrial involvement (n=10)	No parametrial involvement (n=90)	P value
Adjuvant treatment*				0.11
Chemo+RT	47 (48)	6 (60)	41 (46)	
Chemo	26 (26)	0 (0)	26 (29)	
RT	16 (16)	2 (20)	14 (16)	
None	10 (11)	2 (20)	9 (10)	
Recurrence†				0.1
No	46/98 (46)	2/10 (20)	44/88 (51)	
Yes	51/98 (51)	8/10 (80)	43/88 (48)	
Location of recurrence‡				0.72
Distant	23/40 (58)	4/7 (57)	19/33 (58)	
Local	10/40 (25)	1/7 (14)	9/33 (27)	
Both distant+local	7/40 (18)	2/7 (29)	5/33 (15)	

*One patient was lost to follow-up with unknown adjuvant treatment status.
†Information about recurrence was available for 98 of the 100 patients. One patient died of the disease without recurrence.
‡Location of recurrence was available for 40 of the 50 patients with recurrence.
Chemo, chemotherapy; RT, radiotherapy.

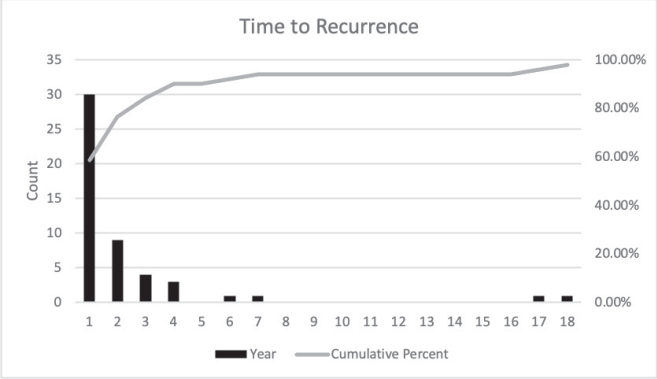

Figure 1 Time to recurrence. Bar graph shows the number of recurrences per year after diagnosis; curve shows cumulative proportion of patients with recurrence.

patients who recurred in median progression-free survival (14.0 months (range 8.9–18.4) vs 9.8 months (range 5.1–30.2), p=0.45) or median overall survival (53.1 months (range 22.4–71.5) vs 52.7 months (range 22.4–93.6), p=0.70).

Seventy-eight percent (39/50) had recurrence within the first 2 years and 86% (43/50) had recurrence within the first 3 years after diagnosis (Figure 1).

Progression-free and overall survival rates for the entire cohort at 5 years were 44% (95% CI 33% to 56%) and 61% (95% CI 50% to 73), respectively (Figure 2A). The progression-free survival rates at 5 years for patients with and without parametrial involvement were 13% (95% CI 0% to 35%) and 49% (95% CI 37% to 61%), respectively (log-rank p=0.14) (Figure 2B). Median progression-free survival was 25.2 months (range 3.2–45.8) for patients with parametrial involvement and 51.6 months (range 18.3–207.8) for patients without parametrial involvement (log-rank p=0.13). The overall survival rates at 5 years for patients with and without parametrial involvement were 58% (95% CI 27% to 90%) and 61% (95% CI 49% to 74%), respectively (log-rank p=0.18) (Figure 2C). Median overall survival was 93.7 months (95% CI 60 to ∞) overall, 62.9 months (95% CI 8.3 to ∞) in patients with parametrial involvement, and 217.2 months (95% CI 56.8 to ∞) in patients without parametrial involvement.

DISCUSSION

Summary of Main Results

Our study showed that the overall rate of parametrial involvement in patients with early-stage (≤4 cm) high-grade neuroendocrine cervical cancer and no pre-operative evidence of parametrial or nodal involvement was 10%. In patients with pre-operative tumor size ≤2 cm, this rate was 4% (2/48). We also found that 95% of patients were recommended adjuvant therapy. Importantly, no patient had parametrial involvement as the sole indication for adjuvant therapy besides the neuroendocrine histology.

These findings raise the question of whether patients with early-stage high-grade neuroendocrine cervical carcinoma require a radical hysterectomy. The question of whether radical hysterectomy is required is particularly important as one should aim to reduce rates of dual treatment with parametrectomy and radiotherapy to minimize postoperative morbidity.

Results in the Context of Published Literature

Ishikawa et al[19] evaluated patients with high-grade neuroendocrine carcinoma of FIGO stages I-II treated in 26 hospitals in Japan. Seventy patients underwent up-front radical surgery. The authors found that the rate of parametrial compromise was 20%. Our study showed a lower rate of parametrial compromise (10%). This difference may be related to the different inclusion criteria for up-front surgery as we only included patients with no suspicion of parametrial compromise before surgery and tumors ≤4 cm. In Japan, patients with FIGO 2009 stage IIB neuroendocrine cervical carcinoma are frequently treated with radical hysterectomy, which likely led to higher reported rates of parametrial compromise.[20]

In earlier studies of squamous, adenocarcinoma, and adenosquamous cervical carcinomas, other investigators have reported rates of parametrial involvement of 4–11%, similar to the rate found in our study.[11 13–15] However, for those types of tumors, parametrial involvement is considered in the decision making regarding recommendations for adjuvant treatment. In addition, factors such as tumor size, lymphovascular space invasion, and depth of invasion are integrated in the decision-making algorithm, along with parametrial involvement and lymph node status, to decide whether to recommend adjuvant chemotherapy and radiotherapy. Most

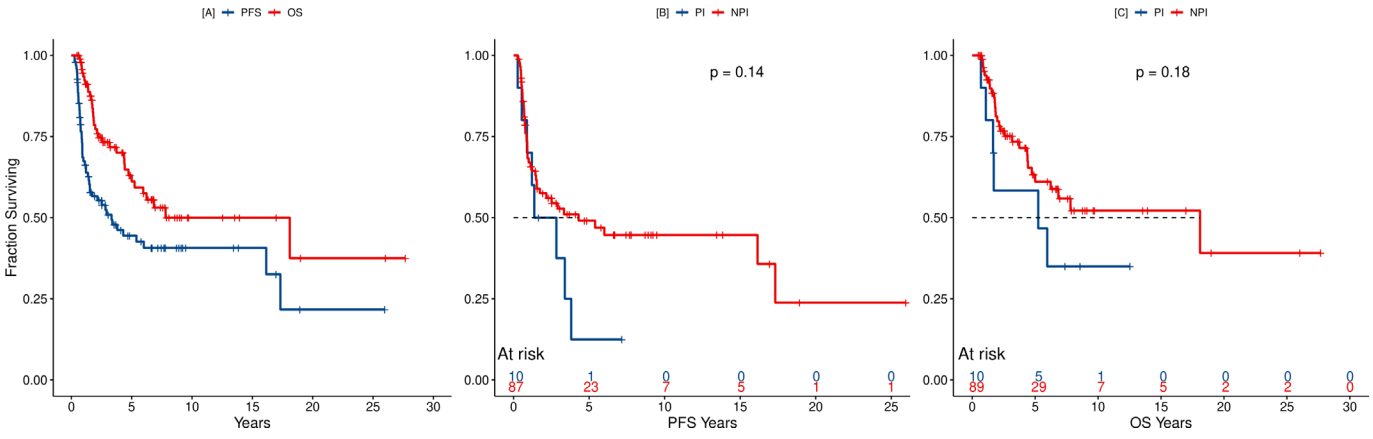

Figure 2 Estimates of (A) overall survival and progression-free survival for the entire cohort. Estimates of (B) progression-free survival and (C) overall survival by status of parametrial involvement. OS, overall survival; NPI, no parametrial involvement; PI, parametrial involvement; PFS, progression-free survival.

guidelines and treatment recommendations support multimodal treatment for patients with clinically early-stage high-grade neuroendocrine cervical cancer; most authors consider that surgery alone without adjuvant chemotherapy and/or radiotherapy is not appropriate for such patients.[8–10] In the multicenter study by Ishikawa et al,[19] the authors found that in a series of 70 patients who underwent up-front radical surgery, 80% (56/70) received adjuvant treatment. The authors did not report the reason why 20% of the patients (n=14) did not receive adjuvant treatment. In our study, 95% (95/100) of patients were recommended adjuvant treatment and 89% (89/100) actually received adjuvant treatment in the form of combined radiotherapy and chemotherapy. The fact that the majority of patients with neuroendocrine cervical tumors will undergo adjuvant radiotherapy, regardless of not only parametrial involvement but also margin status and lymph node involvement, calls into question the need for radical hysterectomy in patients with this disease.

In our study, we found that patients who received adjuvant radiotherapy were 62% less likely to have a local recurrence (with or without distant recurrence) than patients who did not receive radiotherapy (p=0.013), supporting the recommendation of adjuvant pelvic radiotherapy as part of the treatment for early-stage high-grade neuroendocrine cervical carcinoma. Previous studies have reported higher rates of locoregional failure in patients who did not receive adjuvant radiotherapy, although the difference did not reach statistical significance.[19 21] There might be a group of patients with negative SLN and no residual disease in the surgical specimen that may not benefit from adjuvant radiation therapy.

Our overall rate of positive lymph nodes was 20%. Although not being the primary objective of the study, we found that in the 10 patients who underwent both SLN mapping and full lymphadenectomy, the false-negative rate for SLN mapping was zero. Given that the majority of patients with clinically early-stage high-grade neuroendocrine cervical cancer undergo adjuvant pelvic radiotherapy in combination with chemotherapy regardless of lymph node status, one might also question the rationale for complete lymphadenectomy at the time of hysterectomy in patients with this disease. SLN mapping for cervical cancer is a standard procedure at our institution. We previously reported unilateral and bilateral SLN detection rates of 62% and 80%, respectively, in patients with cervical cancer; there was one false-negative finding, yielding a sensitivity of 96.4%, a negative predictive value of 99.3%, and a false-negative rate of 3.6%.[22] By omitting routine lymphadenectomy, one might decrease the rate of complications related to dual treatment (surgery and radiotherapy). SLN mapping with ultrastaging certainly may offer benefit in terms of diagnosing low-volume disease and detecting positive nodes in atypical locations that would have been missed with pelvic lymphadenectomy alone.

Strengths and Weaknesses

A strength of this study is its sample size, which is among the largest in the literature for studies examining the rate of parametrial compromise in patients with clinically early-stage high-grade neuroendocrine carcinoma undergoing radical hysterectomy. Weaknesses of this study include its retrospective nature, the fact that the registry does not require central pathology review, and a lack of uniformity in the recommendation of chemotherapy regimen and number of cycles. In addition, information on complications is not collected in the registry. We also recognize that patients were treated over a long time period during which treatment recommendations and indications might have varied.

Implications for Practice and Future Research

Noting that the majority of patients with early-stage high-grade neuroendocrine cervical carcinoma undergo adjuvant therapy after radical surgery regardless of parametrial involvement or lymph node status, we call into question the role of parametrectomy and complete pelvic lymphadenectomy in this patient population. We propose further considerations of simple hysterectomy and SLN mapping followed by adjuvant radiotherapy with concurrent chemotherapy (cisplatin and etoposide) followed by additional chemotherapy with the same treatment regimen. This strategy might minimize the rate of short- and long-term complications in patients with early-stage high-grade neuroendocrine cervical carcinoma.

CONCLUSIONS

We found that the rate of parametrial involvement in patients with high-grade neuroendocrine cervical carcinoma was similar to other histologic subtypes. In addition, the false-negative rate for SLN mapping was zero, and the bilateral detection rate was 100%. Furthermore, patients who received adjuvant radiotherapy were 62% less likely to have a local recurrence.

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Supplemental table 1. Findings in patients with parametrial involvement

Patient	Age, years	FIGO stage 2018	T category	Histology	Tumor size, mm	DOI, mm	LVSI	Vaginal margin	Nodal status (pelvic and/or SLN)	Number of positive nodes	Parametrial nodes positive	Ovaries[a]	DOI, mm	Adjuvant treatment[b]	Status at the end of treatment	Recurrence	Location of recurrence
1	31	IIB	T2	HGNECC (small and large cell)	30	6*	Yes	Negative	Negative		Yes	Negative	6	RT + Chemo	Complete response	Yes	Both
2	41	IIIC1p	T2	Mixed: small + SCC	20	7	Yes	Negative	Positive	2	Yes	Negative	7	RT	Complete response	Yes	Both
3	42	IIB	T2	Mixed: small + SCC	32	11	Yes	Negative	Negative			Negative	11	RT + Chemo	Complete response	Yes	Distant
4	48	IIIC1p	T2	Mixed: small + AC	20	11	Yes	Negative	Positive	2			11	RT + Chemo	Complete response	Yes	Distant
5	63	IIIC1p	T1	HGNECC (small cell)	15		Yes	Positive	Positive	1		Negative		Chemo + RT	Complete response	Yes	Distant
6	36	IIIC1p	T1	HGNECC (small cell)	13	17	Yes	Negative	Positive	1		Negative	17	RT	Complete response	No	
7	58	IIIC1p	T2	Mixed: small + SCC	30	14	Yes	Positive	Positive	3		Negative	14	RT + Chemo	Unknown	Yes	Distant
8	30	IIIC1p	T2	Mixed: large + AC	20	8	Yes	Negative	Positive	1	Yes		8	Chemo + RT	Complete response	Yes	Local
9	33	IIIC1p	T2	HGNECC (small cell)	39	25	Yes	Negative	Positive	2	Yes		25	No	Complete response	No	
10	42	IIIC1p	T2	Mixed: small + SCC	75	18	Yes	Negative	Positive	6			18	No	Unknown	Yes	Unknown

BMI, body mass index; Chemo, chemotherapy; DOI, depth of invasion; FIGO, International Federation of Gynecology and Obstetrics; H radiotherapy.

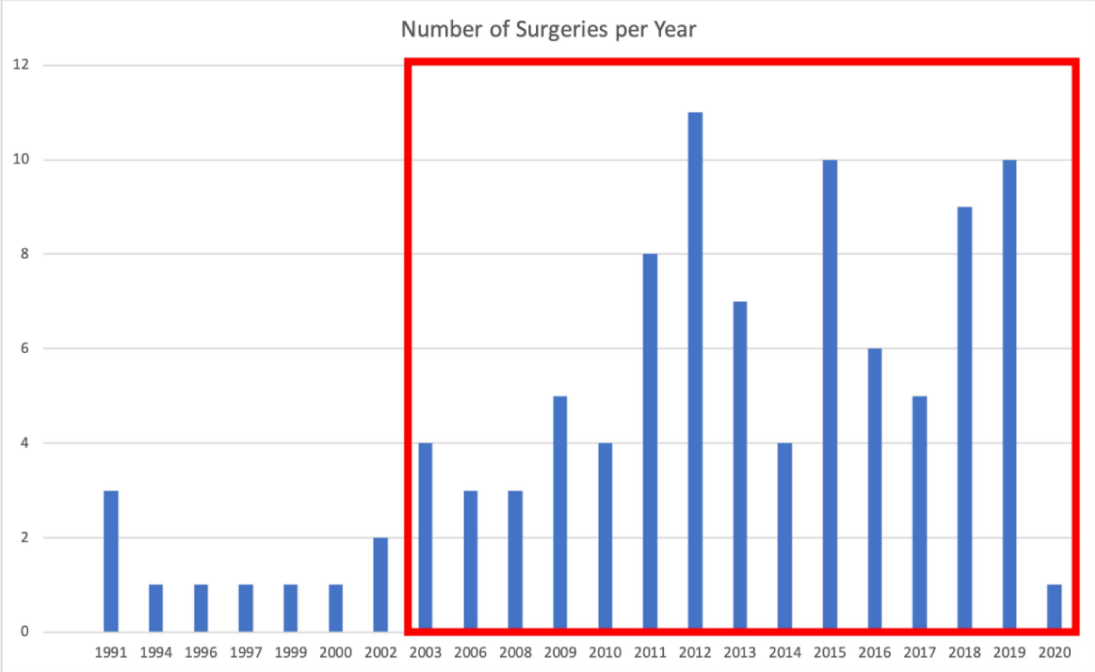
T category, T1: ≤2cm, T2: >2 - ≤4

*6 mm of 12 mm of stromal thickness

[a] Only reported for patients with bilateral salpingo-oophorectomy or unilateral oophorectomy.

b Listed in order received.

Supplemental Figure 1
Surgeries per year.



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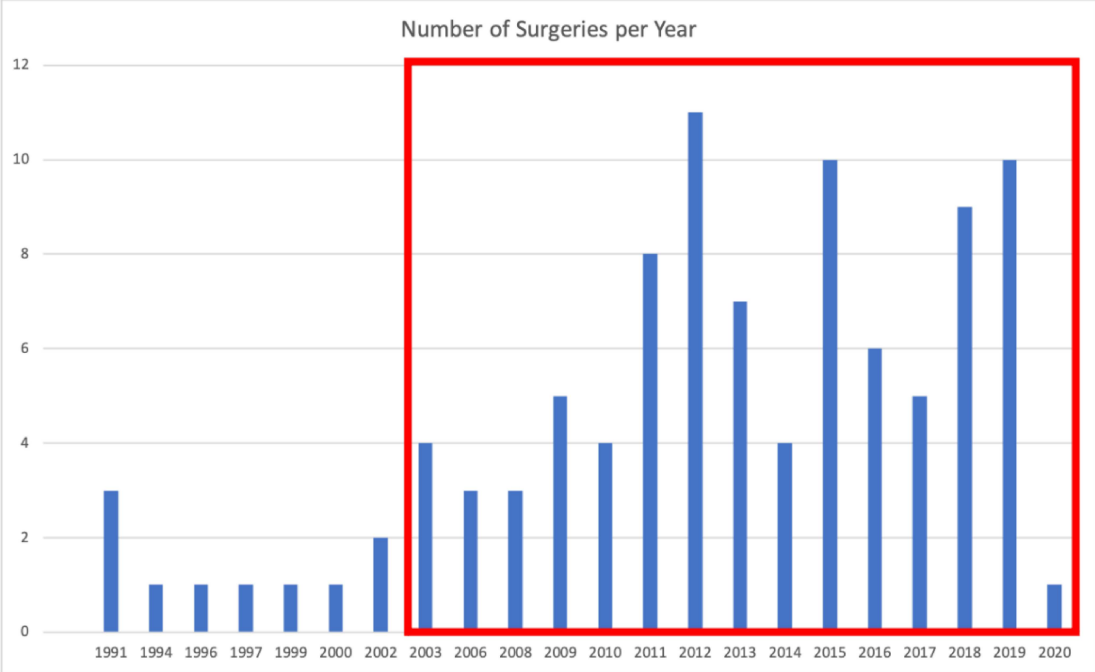

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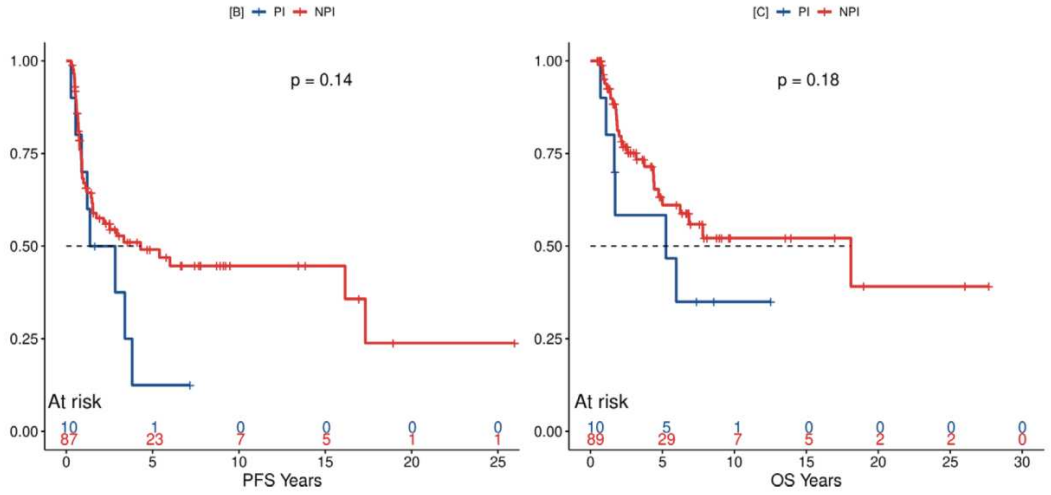
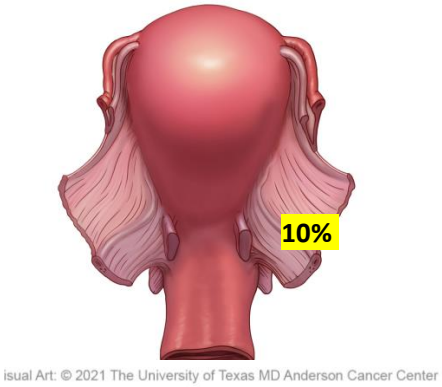
Role of Radical hysterectomy in Patients with Early-Stage High-Grade Neuroendocrine Cervical Carcinoma: a NeCTuR Study

Gloria Salvo, Preetha Ramalingam, Alejandra Flores Legarreta , Anuja Jhingran, Naomi Gonzales, Gary Chisholm, Michael Frumovitz

Objective: To determine the rate of parametrial involvement in FIGO stage IA1-IB2 (≤ 4cm) high-grade neuroendocrine cervical carcinoma undergoing upfront radical surgery with or without adjuvant therapy.



PI: Parametrial involvement NPI: No parametrial involvement



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95% were recommended adjuvant therapy

These findings raise the question of whether patients with early-stage high-grade neuroendocrine cervical carcinoma require a radical hysterectomy.

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