Impact of pelvic radiation therapy in patients with early neuroendocrine cervical carcinoma and no residual disease in the radical hysterectomy specimen: a NeCTuR study

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ABSTRACT

Objective The impact of adjuvant pelvic radiation therapy on the rate and location of recurrences was evaluated in patients with early-stage (IA1–IB2) neuroendocrine cervical carcinoma who underwent prior conization or polypectomy with no residual disease and negative nodes in the subsequent upfront radical hysterectomy specimen. As a secondary objective, disease-free and overall survival were analyzed.

Methods We searched the Neuroendocrine Cervical Tumor Registry (NeCTuR) to identify patients with clinical early-stage neuroendocrine cervical carcinoma with no residual disease in the specimen from upfront radical surgery and negative nodes. Patients who received pelvic radiation therapy were compared with those who did not, regardless of whether they received adjuvant chemotherapy.

Results Twenty-seven patients met the inclusion criteria, representing 17% of all patients with clinical early-stage disease who underwent upfront radical hysterectomy included in the NeCTuR registry. The median age was 36.0 years (range 26.0–51.0). Six (22%) patients had stage IA, 20 (74%) had stage IB1, and one (4%) had stage IB2 disease. Seven (26%) patients received adjuvant radiation therapy and 20 (74%) did not. All seven patients in the radiation group and 14 (70%) in the no-radiation group received adjuvant chemotherapy (p=0.16). Fifteen percent (4/27) of patients had a recurrence, 14% (1/7) in the radiation group and 15% (3/20) in the no-radiation group (p=0.99). In the radiation group the recurrence was outside the pelvis, and in the no-radiation group, 67% (2/3) recurred outside the pelvis and 33% (1/3) recurred both inside and outside the pelvis (p=0.99). In the radiation group the 5-year disease-free and overall survival rates were 100% while, in the no-radiation group, the 5-year disease-free and overall survival rates were 81% (95% CI 61% to 100%) (p=0.99) and 80% (95% CI 58% to 100%) (p=0.95), respectively.

Conclusions For patients with no residual disease and negative nodes in the upfront radical hysterectomy specimen, our study did not find that pelvic radiation therapy improves survival.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Most patients with early-stage neuroendocrine cervical tumors are treated with radical surgery, radiation, and chemotherapy. Whether radiation is needed is controversial, especially in patients with no disease in the radical hysterectomy specimen.

WHAT THIS STUDY ADDS

⇒ This study showed that 69% of patients with early-stage neuroendocrine cervical tumors who underwent upfront radical hysterectomy after a cone biopsy/loop electrosurgical excision procedure had no residual disease in the cervix. Among patients with no residual disease, recurrence rates and 3-year and 5-year disease-free and overall survival rates were similar in those who did and did not receive adjuvant radiation therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides physicians with additional data to counsel patients with early-stage disease during discussions about adjuvant radiation.

INTRODUCTION

Primary cervical neuroendocrine tumors are infrequent. They account for approximately 1.5% of all invasive carcinomas of the uterine cervix and approximately 100–200 new cases of neuroendocrine cervical carcinoma are diagnosed each year in the USA.[1] These tumors are associated with a high risk of recurrence, even in early-stage disease.[2 3] Due to the rarity of neuroendocrine cervical carcinoma, treatment is based on small retrospective studies, population-based studies, and extrapolation of treatment guidelines for neuroendocrine carcinoma of the lung.

Given the aggressiveness of neuroendocrine cervical carcinoma, a multi-modality therapeutic approach including surgery, chemotherapy, and pelvic radiation therapy is recommended.[4–7] For clinically early-stage disease (tumors ≤4 cm, localized to the

cervix, and negative nodes on imaging), most guidelines[5–7] recommend treatment with radical hysterectomy and pelvic lymph node assessment followed by chemoradiation to the pelvis with cisplatin and etoposide followed by additional chemotherapy with the same agents,[4–7] with the aim of delivering a total of at least five cycles.[8 9]

This approach differs from treatment recommendations for other types of cervical cancers such as squamous cell carcinomas and adenocarcinomas, for which pelvic radiation therapy is recommended after radical surgery only when pathologic examination of the hysterectomy specimen reveals intermediate-risk disease factors (large tumor, deep invasion into the cervical stroma, or lymphovascular space invasion)[10] and/or high-risk disease factors (positive surgical margins, positive lymph nodes, or parametrial invasion).[11] A combination of intermediate-risk factors or the presence of at least one high-risk factor indicates the need for adjuvant pelvic radiation therapy to decrease pelvic recurrences and improve survival.[10 11] The rationale behind this approach is that, although multi-modal therapy may add oncologic benefits such as a decrease in pelvic recurrences for some patients with early-stage disease, post-operative radiation can cause significant long-term morbidity, especially to the bladder and gastrointestinal tract.[11 12] As pelvic radiation for cervical cancer requires treatment of target areas such as pelvic lymph nodes and the vaginal apex, toxicity after radical hysterectomy may be lessened with newer radiation techniques that deliver a lower dose to non-target areas.[13]

For early-stage neuroendocrine carcinomas, whether adjuvant radiation therapy provides an oncologic benefit is controversial.[5] Our group previously showed that the addition of pelvic radiation therapy after radical surgery in patients with clinically early-stage neuroendocrine cervical carcinomas (with or without residual disease) reduces pelvic recurrences without improving overall survival.[14] We explored the impact of the addition of pelvic radiation therapy in a sub-group of patients with clinically early-stage (IA1–IB2) neuroendocrine cervical carcinoma: those with an upfront radical hysterectomy and no cervical residual disease in the surgical specimen. The primary objective was to determine the rate and location of recurrences and the secondary objective was to determine disease-free and overall survival rates.

METHODS

This retrospective study was based on data from the Neuroendocrine Cervical Tumor Registry (NeCTuR), which includes patients with pure (small cell, large cell, small cell and large cell, or neuroendocrine carcinoma not otherwise specified) or mixed neuroendocrine cervical carcinoma (any neuroendocrine carcinoma in combination with other histologies).

We searched the NeCTuR database to identify patients with clinically early-stage neuroendocrine cervical carcinoma treated with upfront radical hysterectomy and lymph node assessment (pelvic lymphadenectomy and/or sentinel lymph node biopsy) with or without adjuvant pelvic radiation therapy from July 1986 to November 2021 (70% (20/27) of patients received treatment in the past 10 years) and who had no cervical residual disease in the surgical specimen as the result of a surgical procedure performed before the hysterectomy (eg, conization, loop electrosurgical excision procedure (LEEP), or polypectomy). To be included, patients had to have pathologically confirmed pure or mixed neuroendocrine cervical carcinoma on the pre-operative procedure specimen, early-stage disease (IA1–IB2) per the International Federation of Gynecology and Obstetrics (FIGO) 2018 classification system, pre-treatment tumor size ≤4 cm, no residual disease in the radical hysterectomy specimen, and negative pelvic nodes. Patients entered in NeCTuR before publication of the latest FIGO classification system were re-classified using the 2018 system. All patients have a positron emission tomography scan or chest abdomen and pelvic CT scan prior to and after primary treatment is completed. Information on radiation-associated morbidity is not collected in the registry.

Exclusion criteria included advanced disease (IB3, IIA2–IVB), having received chemotherapy and/or radiation therapy before radical hysterectomy, incomplete records, age <18 years at diagnosis, and pathology reports not available. Patients were divided into two groups: those who received pelvic radiation therapy with curative intent (≥45 Gy) and/or brachytherapy and those who did not receive pelvic radiation therapy. The primary objective was to determine the rate and location of recurrences. The secondary objective was to determine disease-free and overall survival rates.

Study data were collected and managed using REDCap electronic data capture tools hosted at MD Anderson.[15 16] Descriptive statistics were used to summarize patient demographics and clinical characteristics. Fisher's exact test was used to compare categorical variables and to compare nodal status. The Kruskal–Wallis test was used to compare age and body mass index and to evaluate concurrent chemotherapy cycles, brachytherapy, final chemotherapy cycles, and total radiation dose in patients who received radiation. Disease-free survival and overall survival were estimated using the Kaplan–Meier product-limit estimator. Disease-free survival was defined as the time from diagnosis to the first recorded evidence of recurrence or death of any cause. Overall survival was defined as the time from diagnosis to death of any cause or last follow-up, with patients alive at the last follow-up censored on that date. Statistical analyses were performed using SAS 9.4 for Windows (SAS Institute, Cary, North Carolina, USA) and R (R Core Team 2020, Vienna, Austria)

RESULTS

Patient Characteristics

At data lock on January 12, 2023, a total of 160 patients in the NeCTuR database with clinically early-stage neuroendocrine cervical carcinoma had undergone upfront radical surgery. Of those, 27 (17%) patients had no residual disease found in the radical hysterectomy specimen after having a cone biopsy or LEEP (n=20) or polypectomy (n=7) before the radical surgery and were included in the study. In 29 patients who underwent cone/LEEP prior to definitive surgery, 20 (69%) had no residual disease in the final radical hysterectomy specimen. The median age was 36.0 years (range 26.0–51.0), and the median body mass index was 25.1 kg/m^2 (range 15.9–45.9). Seven (26%) patients received adjuvant radiation therapy and 20 (74%) did not. The two groups were balanced in terms of age, body mass index, FIGO stage, pre-treatment tumor size, and histology (Table 1).

Table 1 Demographic and clinical characteristics of patients with early-stage neuroendocrine cervical carcinoma

Characteristic	Overall (n=27)	Radiation (n=7)	No radiation (n=20)	P value*
Age, median (range), years	36.0 (26.0–51.0)	39.0 (30.0–49.0)	35.5 (26.0–51.0)	0.64†
BMI, median (range), kg/m^2	25.1 (15.9–45.9)	24.8 (21.7–28.1)	27.6 (15.9–45.9)	0.28†
Race				0.05‡
Asian	2 (7)	2 (29)	0 (0)	
Native Hawaiian	1 (4)	0 (0)	1 (5)	
White	22 (81)	4 (57)	18 (90)	
Missing	2 (7)	1 (14)	1 (5)	
Ethnicity				0.99‡
Not Hispanic	22 (81)	5 (71)	17 (85)	
Hispanic	1 (4)	0 (0)	1 (5)	
Missing	4 (15)	2 (29)	2 (10)	
FIGO 2018 stage				0.14‡
IA1	3 (11)	0 (0)	3 (15)	
IA2	3 (11)	0 (0)	3 (15)	
IB1	20 (74)	6 (86)	14 (70)	
IB2	1 (4)	1 (14)§	0 (0)	
Diagnostic specimen				0.35‡
Cone	20 (74)	4 (57)	16 (80)	
Polyp	7 (26)	3 (43)	4 (20)	
Histologic sub-type				0.31‡
Small cell	10 (37)	2 (29)	8 (40)	
Small cell+adeno	4 (15)	1 (14)	3 (15)	
NECC NOS	3 (11)	1 (14)	2 (10)	
Large cell	3 (11)	0 (0)	3 (15)	
NECC NOS+adeno	2 (7)	2 (29)	0 (0)	
Small cell+large cell	1 (4)	0 (0)	1 (5)	
Small cell+squamous	1 (4)	0 (0)	1 (5)	
Large cell+adeno	1 (4)	1 (14)	0 (0)	
Large cell+squamous	1 (4)	0 (0)	1 (5)	
Small cell+large cell + adeno	1 (4)	0 (0)	1 (5)	
Tumor size, cm				0.99‡
≤2	26 (96)	6 (86)	20 (100)	
>2–≤4	1 (4)	1 (14)§	0 (0)	
Status at end of primary treatment				0.99‡
Complete response	26 (96)	7 (100)	19 (95)	
New disease	1 (4)	0 (0)	1 (5)	

*Values in the table are n (%) of patients unless otherwise indicated.
†Wilcoxon rank-sum test.
‡Fisher's exact test.
§This patient underwent a polypectomy. The tumor was completely removed with this procedure and the hysterectomy specimen had no residual disease.
adeno, adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; NECC NOS, neuroendocrine cervical carcinoma not otherwise specified.

Treatment

Of the seven patients who received radiation, five received concurrent chemotherapy (cisplatin or carboplatin plus etoposide in four patients and cisplatin in one). Five patients received brachytherapy with radiation. Overall, 78% (21/27) of patients received additional chemotherapy, all patients in the radiation group and 70% (14/20) in the no-radiation group. The regimen used in the no-radiation group was cisplatin or carboplatin plus etoposide.

Recurrences and Survival

Twenty-six patients (96%) had a complete response after primary treatment, seven (100%) in the radiation group and 19 (95%) in the no-radiation group. One patient (5%) in the no-radiation group recurred in the lungs after completing adjuvant chemotherapy (Table 1). Fifteen percent (4/27) of patients had a recurrence, 14% (1/7) in the radiation group and 15% (3/20) in the no-radiation group (p=0.99). In the radiation group, the recurrence was outside the pelvis and, in the no-radiation group, 67% (2/3) recurred outside the pelvis and 33% (1/3) recurred both inside and outside the pelvis (p=0.99) (Table 2).

Median follow-up time was 44.0 months (IQR 30.6–112.9) for the radiation group and 36.1 months (IQR 21.6–84.3) for the no-radiation group (p=0.55). Median disease-free and overall survival were not reached for either group (Table 3); 3-year and 5-year disease-free and overall survival did not differ between the groups (Figure 1 and Table 3).

DISCUSSION

Summary of Main Results

In this study of patients with early-stage neuroendocrine cervical carcinoma who underwent upfront radical hysterectomy after conization/LEEP or polypectomy and had no disease in the final pathology specimen and negative nodes, the recurrence rate was similar in patients who received pelvic radiation therapy after radical hysterectomy and those who did not. Our study also showed that, after conization/LEEP, 69% of patients with early-stage neuroendocrine cervical carcinomas who underwent upfront radical hysterectomy had no residual disease in the final pathology specimen.

Results in the Context of Published Literature

Patients with clinically early-stage cervical cancer are recommended a radical hysterectomy with pelvic lymphadenectomy for all histologic types.[6] In an aim to decrease pelvic recurrences and improve survival while preventing long-term co-morbidities related to pelvic radiation after radical surgery, patients with early-stage squamous cell carcinomas, adenocarcinomas, or adenosquamous carcinomas are typically recommended adjuvant radiation based on the presence of a combination of intermediate-risk[10] or high-risk factors.[11] For these histologic types, it is recognized that not all early-stage diseases should be seen as a homogenous group that should receive the exact same treatment. Although it is a more tailored approach than for neuroendocrine carcinomas, there is also some controversy regarding the intermediate risk factors solely indicating the need for adjuvant radiation.[6 17]

Neuroendocrine cervical carcinomas have a high rate of nodal and distant (outside the pelvis) metastasis at the time of diagnosis. They are aggressive tumors, and lymphovascular space invasion and nodal metastases occur more frequently in early-stage disease than they do in early-stage squamous cell carcinoma of the cervix.[2 3 18] Although most guidelines and centers recommend radical surgery followed by chemotherapy for clinically early-stage neuroendocrine carcinoma,[4–7] whether adjuvant pelvic radiation therapy should be delivered to all patients with clinically early-stage neuroendocrine cervical carcinoma is controversial. The rationale for adjuvant pelvic radiation therapy is the aggressiveness of this histologic type, but does not take into account that most recurrences, which influence prognosis more than anything else, occur outside the pelvis and that not all early-stage disease ise exactly the same.

Ishikawa et al[19] retrospectively studied 93 patients with stage I–II neuroendocrine carcinoma, of whom 88 (95%) underwent radical surgery with pelvic lymphadenectomy and five underwent definitive radiation therapy. In the radical surgery group, 14 patients received adjuvant radiation therapy, 48 received adjuvant chemotherapy, and 11 received both. Patients who underwent upfront radical surgery had improved overall survival compared with those who received definitive radiation therapy. Moreover, adjuvant radiation therapy did not improve the prognosis of patients with early-stage neuroendocrine carcinoma. Recurrence in the pelvis occurred in 16% (4/25) of patients who received post-operative pelvic radiation therapy and 24% (15/62) of those who did not. The OR for recurrence inside the pelvis when radiation was added was 0.61 (95% CI 0.16 to 2.01, p=0.43). However, adjuvant chemotherapy decreased the risk of recurrence outside the pelvis with an OR of 0.37 (95% CI 0.13 to 0.99, p=0.05). On the basis of these findings, the authors concluded that patients with stage I–II high-grade neuroendocrine cervical carcinoma should receive adjuvant chemotherapy with either etoposide plus a platinum regimen or irinotecan plus a platinum regimen, but that post-operative radiation therapy might not add additional benefits.

Similarly, Salvo et al[9] retrospectively studied 100 patients with clinically early-stage, high-grade neuroendocrine cervical carcinoma who underwent upfront radical surgery with or without adjuvant therapy. Eighty-nine (89%) patients received adjuvant therapy, of whom 47 (53%) received surgery, radiation, and adjuvant chemotherapy; 26 (29%) received both surgery and chemotherapy; and 16 (18%) received surgery and radiation therapy. Fifty patients (52%) had a recurrence, and the rate of local recurrence or both local and distant recurrence was 75% (9/12) among the patients who did not receive adjuvant radiation therapy versus 29% (8/28) among those who did (p=0.01). Compared with patients who did not receive adjuvant radiation therapy, those who did were 62% less likely to have a local component to their recurrence. However, there were no survival differences between the two groups.

Table 2 Recurrences

	Recurrence			Location of recurrence		P
	No	Yes	P value	Distant	Local+distant	value
Radiation	6 (86%)	1 (14%)	0.99	1 (100%)	0 (0%)	0.99*
No-radiation	17 (85%)	3 (15%)		2 (67%)	1 (33%)	

*Fisher's exact test.

Table 3 3-year and 5 year disease-free and overall survival

	Radiation	No-radiation	P value
Follow-up time (months)	44.0 (IQR 30.6–112.9)	36.1 (IQR 21.6–84.3)	0.55*
DFS			0.10†
Median	NA (95% CI 71.2% to ∞)	NA (95% CI 46.7% to ∞)	
3-year	100% (95% CI 100% to 100%)	90% (95% CI 76% to 100%)	
5-year	100% (95% CI 100% to 100%)	81% (95% CI 61% to 100%)	
OS			0.95†
Median	NA (95% CI 84.3% to ∞)	NA (95% CI 63.3% to ∞)	
3-year	100% (95% CI 100% to 100%)	90% (95% CI 77% to 100%)	
5-year	100% (95% CI 100% to 100%)	80% (95% CI 58% to 100%)	

*Kruskal–Wallis test.
†Log-rank test.
DFS, disease-free survival; OS, overall survival.

Kim et al[14] recently published a meta-analysis comprising 13 studies that included patients with early-stage neuroendocrine carcinoma of the cervix who underwent upfront radical hysterectomy with or without adjuvant radiation therapy. In the five studies that reported recurrence data and the location of the recurrence, the recurrence rate was 52.5% (63/120) for patients who received post-operative radiation therapy and 37.8% (70/185) for those who did not. The rate of pelvic recurrence without distant recurrence was 12.5% (15/120) in the radiation group and 24.3% (45/185) in the no-radiation group (relative risk (RR) 0.60; 95% CI 0.34 to 1.08, p=0.09). The rate of distant recurrence without local recurrence was 33.3% (40/120) in the radiation group and 9.2% (17/185) in the no-radiation group (RR 2.47; 95% CI 1.28 to 4.76, p=0.007). The rate of both pelvic and distant recurrence was 6.7% (8/120) in the radiation group and 3.8% (7/185) in the no-radiation group (RR 0.87; 95% CI 0.30 to 2.49, p=0.79). In all 13 studies, the mortality rate was 34.8% (138/396) in the radiation group and 35.2% (223/632) in the no-radiation group (RR 1.08; 95% CI 0.75 to 1.56, p=0.66).

Based on these results, the addition of radiation therapy appears to decrease the pelvic recurrence rate but not improve overall survival. The lack of improvement in overall survival may be due to the small sample size not powered to show a statistically significant difference between the groups. Another possibility is that the impact of reduced local recurrence on overall survival is overshadowed by the impact of distant recurrences.

Lee et al[20] showed that tumor stage and tumor size are prognostic factors for survival in neuroendocrine cervical cancer. In all stages of neuroendocrine cervical cancer, patients with a tumor size >2 cm had a median survival time of 47 months compared with 133 months for those with a tumor size ≤2 cm. In early-stage disease, patients with a tumor size >2 cm had a median survival time of 44 months compared with 130 months for those with a tumor size ≤2 cm (p=0.06). Patients with small tumors (≤2 cm) tended to be long-term disease-free survivors. Thus, multi-modality treatment may be most appropriate for patients with a tumor size >2 cm. In the present study, only one patient had a pre-treatment tumor size of >2 but ≤4 cm, so median survival could not be estimated.

For other types of cervical carcinomas such as squamous cell carcinomas or adenocarcinomas, the rate of no residual disease in the radical hysterectomy specimen was reported to be approximately 9.5% for patients with clinically early-stage disease[21] and 60% for patients with low-risk tumors who underwent fertility-sparing radical trachelectomy.[22]

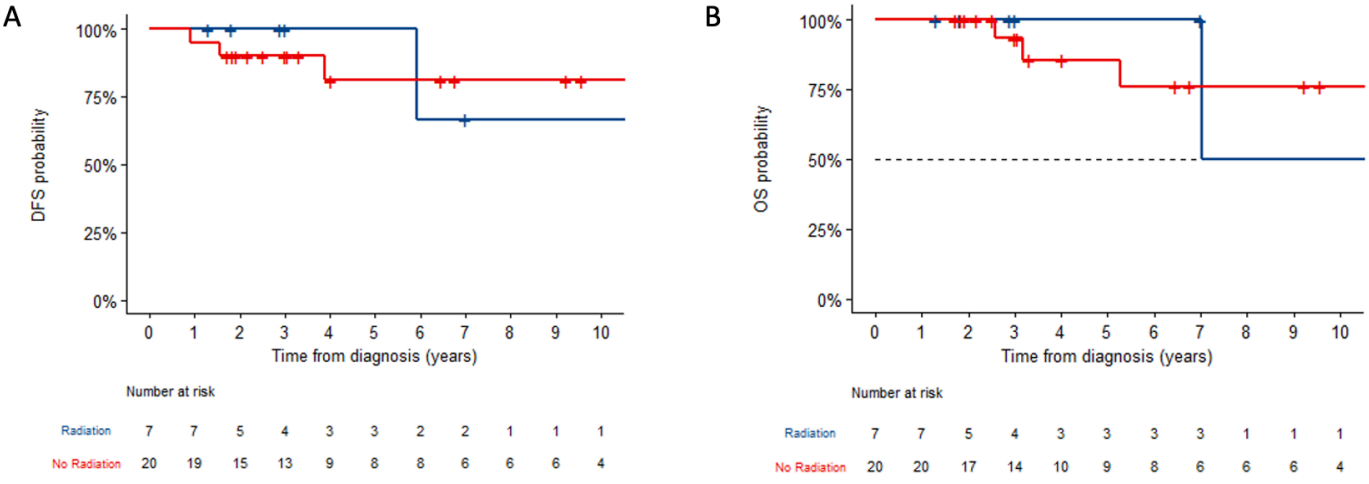

Figure 1 Estimates of (A) disease-free survival (DFS) and (B) overall survival (OS) for the radiation and no-radiation groups.

Strengths and Weaknesses

To our knowledge, this is the only study published so far evaluating the rate of no residual disease in the surgical specimen in patients with early-stage neuroendocrine cervical carcinomas as well as evaluating the impact of adjuvant radiation therapy on survival in these patients. Another major strength of this study is the quality of the NeCTuR database, which is routinely audited for accuracy against source documents and is prospectively maintained. The fact that NeCTuR is open to outside institutions allows for a heterogeneous patient pool.

Although the study included the largest series of patients with neuroendocrine cervical carcinoma treated with upfront hysterectomy and no residual disease published to date, this was also its major weakness which gave the study low statistical power and leaves uncertainty about whether the results are due to the intervention (radiation) or chance. In addition, all biases associated with a retrospective study should be considered. The addition of pelvic radiation therapy after surgery was based on the treating physician's decision. Moreover, the impact of surgery and post-operative radiation therapy might be overestimated as patients able to undergo post-operative radiation therapy may have had fewer medical co-morbidities than those who did not. Lastly, the reasons why the seven patients received post-operative radiation therapy were not included in the NeCTuR database.

Implications for Practice and Future Research

This study provides additional data to help physicians counsel and select the best treatment strategy for patients with early-stage disease who underwent a cone/LEEP or polypectomy and have no residual disease in the upfront radical surgery specimen. Further research on this topic including more cases is warranted.

CONCLUSIONS

In our study including patients with clinically early-stage neuroendocrine cervical carcinomas who underwent upfront radical surgery and had no residual disease in the final pathology specimen, we did not observe improved survival with the addition of adjuvant radiation therapy. Although patients who received adjuvant radiation therapy were less likely to have recurrence inside the pelvis, this difference was not statistically significant.

Decisions about whether a patient with no residual disease should receive radiation therapy might have to be individualized on the basis of appropriate patient counseling covering the controversies regarding radiation therapy in this patient population. Factors such as the patient's age, menopausal status, medical co-morbidities, and access to close follow-up should be taken into consideration. Due to the high risk of metastasis outside the pelvis even in early-stage disease, patients should continue to receive adjuvant chemotherapy.

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Competing interests MF has research support from AkesoBio and is a speaker/consultant for Stryker. The other authors have no competing interests.

Patient consent for publication Not applicable.

Ethics approval NeCTuR was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center (PA12-1006) and established in 2013. NeCTuR is voluntary, international, and open to patients undergoing treatment, survivors, and legal representatives of deceased patients, regardless of where they underwent treatment. 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 retrospective analysis described here was separately approved by the Institutional Review Board of MD Anderson Cancer Center (PA19-0571).

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Data availability statement In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

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