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Definitive pelvic radiation therapy improves survival in stage IVB neuroendocrine cervical carcinoma: A NeCTuR study

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HIGHLIGHTS

- In stage IVB neuroendocrine cervical carcinoma, definitive pelvic radiation therapy may confer a survival benefit
- Complete response rates were higher after chemotherapy and definitive pelvic radiation therapy than after chemotherapy alone
- Overall survival was longer in patients who received ≥5 cycles of chemotherapy, alone or with radiation therapy, vs <5 cycles

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ABSTRACT

Objective. To evaluate the survival impact of adding definitive pelvic radiation therapy (RT) to chemotherapy among patients with stage IVB neuroendocrine cervical carcinoma (NECC).

Methods. We retrospectively studied patients with FIGO 2018 stage IVB NECC diagnosed during 1998–2020 who received chemotherapy with or without definitive whole pelvic RT (concurrent or sequential). Demographic, oncologic, and treatment characteristics were summarized. Progression-free (PFS) and overall survival (OS) were plotted using the Kaplan-Meier method, and hazard ratios (HRs) were calculated using Cox regression.

Results. The study included 71 patients. Median age was 43 years (range, 24–75). Fifty-nine patients (83%) had pure neuroendocrine histology, and 57 (80%) had pretreatment tumor size >4 cm. Fifty-six patients (79%) received chemotherapy alone with ($n = 15$) or without ($n = 41$) palliative pelvic RT, and 15 (21%) received chemotherapy and definitive pelvic RT (chemo+RT). Median follow-up time was 20.1 months (range, 11.3–170.3) for the chemo+RT group and 13.5 months (range, 0.9–73.6) for the chemotherapy-alone group. Median PFS was 10.3 months (95% CI, 7.5-∞) for the chemo+RT group vs 6.6 months (95% CI, 6.1–8.7) for the chemotherapy-alone group ($p = 0.0097$). At 24 months, the PFS rate was 24% for chemo+RT vs 7.8% for chemotherapy alone. Median OS was 20.3 months (95% CI, 18.5-∞) for the chemo+RT group vs 13.6 months (95% CI, 11.3–19.2) for the chemotherapy-alone group ($p = 0.0013$). At 24 months, the OS rate was 49.2% for chemo+RT vs 21.5% for chemotherapy alone. In a Cox regression model, definitive RT was associated with improved PFS (HR, 0.44; 95% CI, 0.23–0.83; $p = 0.0119$) and OS (HR, 0.31; 95% CI, 0.14–0.65; $p = 0.0022$).

Conclusions. Addition of definitive pelvic RT to chemotherapy may improve survival in patients with stage IVB NECC.

1. Introduction

Neuroendocrine cervical carcinomas are rare; they are estimated to account for only 1% to 2% of cervical cancer cases, for an estimated total of 150 to 250 new cases per year in the United States [1]. Although most patients with neuroendocrine cervical carcinoma present with clinically early-stage disease, nearly 25% of patients present with International Federation of Gynecology and Obstetrics (FIGO) stage IVB disease [2]. Most patients with stage IVB neuroendocrine cervical carcinoma are treated with chemotherapy alone, and the most

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commonly used regimen is platinum and etoposide [3–5]. Despite such treatment, the 5-year overall survival (OS) rate for patients with stage IVB disease is only 0% to 18% [6–9].

Patients with advanced neuroendocrine cervical cancer often present with bulky cervical tumors, which can cause vaginal bleeding, urinary obstruction, pelvic pain, and bladder or rectal fistula. These adverse events also may decrease survival [10–12]. To control such symptoms and improve quality of life, palliative pelvic radiation therapy may be recommended. For patients with squamous cell carcinoma and adenocarcinoma of the cervix with stage IVB and locally treatable pelvic disease, the addition of definitive radiation therapy as part of primary treatment may be considered [13]. This was explored in a retrospective study by Perkins et al. [14], who showed that addition of whole pelvic radiation therapy as part of primary treatment among patients with stage IVB disease lengthened median progression-free survival (PFS) by 7.0 months and median OS by 24.0 months.

The most recent National Comprehensive Cancer Network guideline for cervical cancer includes treatment recommendations for small cell carcinoma, a subtype of neuroendocrine carcinoma. As is the case for other histologic types, radiation therapy is considered an option for patients with stage IVB small cell cervical cancer amenable to local treatment [13]. However, data are scarce regarding the potential role of definitive radiation therapy for stage IVB neuroendocrine carcinoma of the cervix. The objective of this study was to evaluate the survival impact of adding definitive pelvic radiation therapy to chemotherapy among patients with stage IVB neuroendocrine cervical carcinoma.

2. Methods

This retrospective study was based on data from the Neuroendocrine Cervical Tumor Registry (NeCTuR), which 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 approved by the Institutional Review Board of MD Anderson Cancer Center (PA19–0571). Study data were collected and managed using REDCap electronic data capture tools hosted at MD Anderson [15].

We searched NeCTuR to identify patients with stage IVB neuroendocrine cervical carcinoma treated with chemotherapy with or without definitive pelvic radiation as primary treatment between February 1998 and September 2020. To be included, patients had to have pathologically confirmed pure neuroendocrine cervical carcinoma (small cell, large cell, or both small and large cell) or mixed neuroendocrine carcinoma in combination with another histology [1] and FIGO 2018 stage IVB disease. Patients entered in NeCTuR before publication of the FIGO 2018 classification system were re-classified using the 2018 system. Patients had to have received chemotherapy (any regimen and number of cycles) with or without definitive whole pelvic radiation therapy (delivered before, during, or after initial chemotherapy) as part of primary treatment. Exclusion criteria were as follows: no primary treatment, no chemotherapy as part of primary treatment, up-front simple or radical hysterectomy (before chemotherapy or chemotherapy and radiation therapy) as part of primary treatment, incomplete records, pregnant at diagnosis, age younger than 18 years at diagnosis, pathology report not available, and unknown radiation dose and/or intent of radiation therapy (definitive or palliative).

For the analysis, patients were divided into 2 groups: chemotherapy and definitive radiation or chemotherapy alone. Definitive radiation was defined as whole pelvic (with or without extended field) radiation therapy with intent to cure or definitive radiation therapy (≥45 Gy) with or without concurrent chemotherapy. In the chemotherapy and definitive radiation group no patient received 45 Gy only, all of them received in addition to the 45 Gy EBRT to the pelvis (cut off value to classify patients into chemotherapy and definitive radiation group) either a pelvic boost and/or brachytherapy which makes the final dose higher than 45 Gy. Patients in the chemotherapy alone group could not have received definitive radiation, but palliative radiation therapy (<45 Gy) was acceptable. Patients were subclassified according to the site of distant disease that caused the stage IVB classification: solid organ (liver, bone, lung, or brain), supraclavicular nodes, or other distant nodes. Response after primary treatment was evaluated with a CT (computed tomography) scan or PET/CT (positron emission tomography) scan to evaluate local and distant response. Complete response was defined as no evidence of disease at any site (pelvic and distant disease).

Descriptive statistics were used to summarize patient demographics and clinical characteristics. Fisher's exact test was used to compare categorical variables, excluding the "Not Reported" category, which is presented in the tables but was not included in statistical testing. Wilcoxon rank-sum tests were used to compare continuous variables between 2 groups. PFS was defined as the time from treatment initiation to the first recorded evidence of progression or death of any cause. Patients alive without disease were censored at the last follow-up. OS was defined as the time from diagnosis to death of any cause or last follow-up, with patients alive at last follow-up censored on that date. We estimated PFS and OS using the product-limit estimator of Kaplan and Meier. Median survival rates with 95% confidence intervals (CIs) are reported along with survival rates at 2 years. Cox proportional hazards regression was used to estimate hazard ratios (HRs) with 95% CIs. We tested for differences between survival curves using the log-rank test. Statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC) and R (R Core Team [2020], Vienna, Austria).

3. Results

3.1. Patient characteristics

Of the 87 patients in the NeCTuR database with stage IVB disease, 71 met the inclusion criteria (Supplemental Fig. 1). Of these 71 patients, 60 (85%) were diagnosed between January 2010 and September 2020. Fifty-six patients (79%) were treated with chemotherapy alone with ($n = 15$) or without ($n = 41$) palliative pelvic radiation therapy, and 15 patients (21%) were treated with chemotherapy and definitive radiation. The median age was 43 years (range, 24–75). Fifty-nine (83%) patients had pure and 12 (17%) had mixed neuroendocrine carcinoma. The 2 groups were balanced in terms of age, body mass index, ECOG performance status, histology (pure or mixed tumors), pretreatment tumor size, and location of disease at diagnosis. The patients' characteristics are summarized in Table 1.

3.2. Treatments and responses

Treatments are summarized in Table 2. Overall, 59 of 71 patients (83%) received cisplatin or carboplatin plus etoposide. Forty-nine patients (69%) received ≥5 cycles of chemotherapy. The chemotherapy and definitive radiation group and the chemotherapy alone group did not differ in terms of chemotherapy agents received or total number of chemotherapy cycles. Overall, 30 of 71 patients (42%) received definitive or palliative radiation, and 20 of those 30 patients (67%) received concurrent chemotherapy (cisplatin or carboplatin or cisplatin/carboplatin and etoposide).

Of the 15 patients in the chemotherapy and definitive radiation group, 10 received chemotherapy first (>7 days before radiation therapy was started), and 5 received concurrent chemotherapy and radiation therapy (chemoradiation) first followed by additional chemotherapy (with the same agents). Twelve of the 15 patients (80%) received brachytherapy.

Table 1
Demographic and clinical characteristics of patients with stage IVB high-grade neuroendocrine cervical carcinoma[a].

Characteristic	Overall cohort ($N = 71$)	Chemotherapy alone ($N = 56$)	Chemotherapy and radiation ($N = 15$)	P value
Age, median (range), yr	43 (24–75)	43.5 (24–75)	41 (28–66)	0.75
BMI, median (range), kg/m^2	28.9 (15.5–77.1)	27.4 (15.5–77.1)	32.7 (21.3–49.9)	0.42
ECOG performance status				
0	48 (68)	35 (63)	13 (87)	0.17
1	8 (11)	8 (14)	0 (0)	
2	2 (3)	2 (4)	0 (0)	
Missing	13 (18)	11 (20)	2 (13)	
Current or former smoker				
No	41 (58)	32 (57)	9 (60)	1.00
Yes	26 (37)	20 (36)	6 (40)	
Not reported	4 (6)	4 (7)	0 (0)	
Histology				
Pure NECC	59 (83)	46 (82)	13 (87)	1.00
Mixed (NECC + other histology)	12 (17)	10 (18)	2 (13)	
Pretreatment tumor size, cm				
≤2	2 (3)	2 (4)	0 (0)	0.45
>2−≤4	6 (8)	6 (11)	0 (0)	
>4	57 (80)	43 (77)	14 (93)	
Not reported	6 (8)	5 (9)	1 (7)	
Disease sites at diagnosis				
Solid organ only	35 (49)	29 (52)	6 (40)	0.26
Solid organ + DN	18 (25)	14 (25)	4 (27)	
DN only	5 (7)	2 (4)	3 (20)	
Solid organ + DN + Om/p	5 (7)	5 (9)	0 (0)	
Solid organ + Om/p	7 (4)	5 (9)	2 (13)	
DN + Om/p	1 (3)	1 (2)	0 (0)	

BMI, body mass index; DN, distant nodes; NECC, neuroendocrine cervical carcinoma; Om/p, omentum and/or peritoneum.
[a] Results reported as number of patients (%) unless otherwise specified.

At the completion of primary treatment, all patients underwent a CT scan or PET/CT to evaluate local and distant response to treatment. A clinical benefit (complete response, partial response, or stable disease) was seen in 31 of 71 patients (43%). Fifteen patients (21%) had a complete response, 13 (18%) had a partial response, and 3 (4%) had stable disease. The chemotherapy alone and chemotherapy plus definitive radiation groups had complete response rates of 13% and 53%, respectively; partial response rates of 18% and 20%, respectively; and stable disease rates of 5% and 0%, respectively ($p = 0.008$). There were no differences in terms of ECOG performance status at diagnosis ($p = 0.60$), total number of cycles of chemotherapy received ($p = 0.62$), or location of disease at diagnosis ($p = 0.67$) between patients with complete or partial response, patients with stable disease or mixed response, and patients with progressive or new disease (Supplemental Table 1).

3.3. Survival outcomes

Median follow-up time was 14.6 months (range, 0.9–170.2 for the entire cohort, 20.1 months (range, 11.3–170.3) for the chemotherapy and definitive radiation group, and 13.5 months (range, 0.9–73.6) for the chemotherapy alone group. The chemotherapy and definitive radiation group had a median PFS of 10.3 months (95% CI, 7.5-∞), vs 6.6 months (95% CI, 6.1–8.7) for the chemotherapy alone group ($p = 0.0097$) (Fig. 1A). At 24 months, the PFS rate for the chemotherapy and definitive radiation group was 24% vs 7.8% for the chemotherapy alone group. The chemotherapy and definitive radiation group had a median OS of 20.3 months (95% CI, 18.5-∞), vs 13.6 months (95% CI, 11.3–19.2) for the chemotherapy alone group ($p = 0.0013$) (Fig. 1B). At 24 months, the OS rate was 49.2% for the chemotherapy and definitive radiation group and 21.5% for the chemotherapy alone group.

Four patients had their disease staged as IVB solely because of supraclavicular lymph node involvement (2 patients each group). A subanalysis excluding those 4 patients showed that the chemotherapy and definitive radiation group had a median PFS of 10.3 months (95% CI, 7.5-∞), vs 6.4 months (95% CI, 6.0–8.8) for the chemotherapy alone group ($p = 0.015$) (Fig. 2A). At 24 months, the PFS rate was 23.1% for the chemotherapy and definitive radiation group and 8.0% for the chemotherapy alone group. The chemotherapy and definitive radiation group had a median OS of 40.9 months (95% CI, 16.3-∞), vs 13.6 months (95% CI, 11.3–19.2) for the chemotherapy alone group ($p = 0.0013$) (Fig. 2B). At 24 months, the OS rate was 52.7% for the chemotherapy and definitive radiation group and 20.3% for the chemotherapy alone group. A sub analysis comparing chemotherapy alone vs. chemotherapy and palliative radiation showed no difference in PFS ($p = 0.8652$) or OS ($p = 0.3576$).

In a sub-analysis limited to patients who had their disease staged as IVB solely because of solid organ (only) involvement ($n = 35$), the chemotherapy and definitive radiation group ($n = 6$) had a median PFS of 8.9 months (95% CI, 7.4-∞) vs 6.3 months (95% CI, 5.7–8.4) for the chemotherapy alone group ($n = 29$) ($p = 0.36$) (Supplemental Fig. 2A). At 24 months, the PFS rate for the chemotherapy and definitive radiation group was 0% vs 4.2% for the chemotherapy alone group. The chemotherapy and radiation group had a median OS of 28.2 months (95% CI, 13.0-∞) vs 13.9 months (95% CI, 10.6–22.6) for the chemotherapy alone group ($p = 0.09$) (Supplemental Fig. 2B). At 24 months, the OS rate was 50% for the chemotherapy and radiation group and 22.2% for the chemotherapy alone group.

We also examined PFS and OS according to the total number of chemotherapy cycles received as up-front treatment (cisplatin and/or carboplatin plus etoposide), including any cycles received concurrently with definitive or palliative radiation therapy. Patients who received ≥5 cycles had a median PFS of 7.5 months (95% CI, 6.5–10.0), vs 7.6 months (95% CI, 4.7–11.1) for those who received <5 cycles ($p = 0.68$) (Fig. 3A). At 24 months, the PFS rate was 6.6% for the ≥5 cycles group and 19.2% for the <5 cycles group. Patients who received ≥5 cycles had a median OS of 19.8 months (95% CI, 15.2–24.2), vs 11.0 months (95% CI, 6.6–19.2) for patients who received <5 cycles ($p = 0.02$) (Fig. 3B). At 24 months, the OS rate was 33.9% for the ≥5 cycles group and 18.0% for the <5 cycles group. Patients who received <5 cycles or ≥ 5 cycles of chemotherapy did not differ in terms of ECOG performance status ($p = 0.76$), location of disease at diagnosis ($p = 0.70$), or status at the completion of primary treatment ($p = 0.62$) (Supplemental Table 2).

In total, 8 patients underwent a simple ($n = 6$) or radical hysterectomy ($n = 2$) after chemotherapy alone (n = 6) or after chemotherapy and radiation therapy (n = 2). A subanalysis excluding patients who underwent surgery showed that the chemotherapy and definitive radiation group had a median PFS of 10.7 months (95% CI, 7.5-∞ vs 6.2) months (95% CI, 5.7–8.1) for the chemotherapy alone group ($p = 0.0032$) (Supplemental Fig. 3A). At 24 months, the PFS rate was 25.7% for the chemotherapy and definitive radiation group and 6.5% for the chemotherapy alone group. The chemotherapy and definitive radiation group had a median OS of 40.9 months (95% CI, 18.5-∞) vs 13.4 months (95% CI, 10.4–16.1) for the chemotherapy alone group ($p = 0.00047$) (Supplemental Fig. 3B). At 24 months, the OS rate was 53.1% for the chemotherapy and definitive radiation group and 19.3% for the chemotherapy alone group.

Patients in the chemotherapy and definitive radiation group who received brachytherapy (12/15) had a median PFS of 12.2 months (95% CI, 9.2-∞ vs 7.5 months (95% CI, 6.4-∞) for those who did not receive brachytherapy ($p = 0.11$), and a median OS of 81.8 months (95% CI, 20.3-∞) vs 18.5 months (95% CI, 15.5-∞) for those who did not receive brachytherapy ($p = 0.059$). Patients in the chemotherapy and radiation group who received brachytherapy ($n = 12/15$) were compared to

Table 2
Treatment received.

Treatment	Overall cohort (N = 71)	Chemotherapy alone (N = 56)	Chemotherapy and radiation (N = 15)	*P* value
Primary chemotherapy agents				0.50
Cisplatin/carboplatin + etoposide	52 (73)	38 (68)	14 (93)	
Cisplatin/carboplatin + other[a]				
Cisplatin/carboplatin + etoposide + other	10 (14)	9 (16)	1 (7)	
	7 (10)	7 (13)	0 (0)	
Other[a]	1 (1)	1 (2)	0 (0)	
Etoposide alone	1 (1)	1 (2)	0 (0)	
Pelvic radiation therapy intent				NA
Definitive	15 (21)	0 (0)	15 (100)	
Palliative	15 (21)	15 (27)	0 (0)	
No pelvic radiation therapy	41 (38)	41 (73)	0 (0)	
Total radiation dose received[b], mean (95% CI), Gy	56.3 (40.5, 72.1)	30.0 (16.3–43.8)	78.2 (58.3–98.0)	NA
Concurrent chemotherapy[c]				<0.0001
Yes	20/30 (67)	9/15 (60)	11/15 (73)	
No	10/30 (33)	6/15 (40)	4/15 (27)	
Concurrent chemotherapy agents				0.09
Cisplatin/carboplatin + etoposide	11/20 (55)	7/9 (78)	4/11 (36)	
Cisplatin/carboplatin alone	9/20 (45)	2/9 (22)	7/11 (64)	
Brachytherapy[d]				NA
Yes	12 (80)	–	12 (80)	
No	3 (20)	–	3 (20)	
Number of cycles of chemotherapy, median (range)	6 (1−12)	6 (1–12)	5 (2–9)	0.32
Number of cycles of chemotherapy[e]				0.24
<5	30 (42)	26 (46)	4 (13)	
≥5	41 (58)	30 (54)	11 (87)	
Order of treatments[d]				
Chemotherapy first, RT second	10 (67)	–	10 (67)	NA
Chemoradiation first, additional chemotherapy second	5 (33)	–	5 (33)	
Status at conclusion of primary treatment				
Progressive/new disease	30 (42)	26 (46)	4 (26)	0.008
Complete response	15 (21)	7 (13)	8 (53)	
Partial response	13 (18)	10 (18)	3 (20)	
Mixed response	8 (11)	8 (14)	0 (0)	
Stable disease	3 (4)	3 (5)	0 (0)	
Not reported	2 (3)	2 (4)	0 (0)	
Follow-up time, median (range), mo	14.6 (0.86–170.3)	13.5 (0.9–73.6)	20.1 (11.3–170.3)	0.0021
Recurrence[f] and/or death				
Yes	11/15 (73)	6/7 (86)	5/8 (63)	0.31
No	4/15 (27)	1/7 (14)	3/8 (38)	
Location of first recurrence/progression				
Local	4 (6)	3 (5)	1 (7)	0.78
Distant	35 (49)	27 (48)	8 (53)	
Both	20 (28)	17 (30)	3 (20)	
Unknown	12 (17)	9 (16)	3 (20)	

N/A, not applicable; RT, radiation therapy; mo, months.
[a] Bevacizumab, paclitaxel, or irinotecan.
[b] Total radiation dose includes pelvic, boost, and brachytherapy if received.
[c] Concurrent with either definitive or palliative radiation therapy.
[d] Among patients who received definitive radiation therapy.
[e] Cycles of chemotherapy, including any cycles received concurrently with definitive or palliative radiation therapy.
[f] Among patients with complete response after primary treatment.

those who did not ($n = 3/15$). The brachytherapy group had a median PFS of 12.2 months (95% CI, 9.2-∞), vs 7.5 months (95% CI, 6.4-∞) for the no brachytherapy group ($p = 0.11$). At 24 months, the PFS rate was 30% for the brachytherapy group and 0% for the no brachytherapy group. The brachytherapy group had a median OS of 81.8 months (95% CI, 20.3-∞) vs 18.5 months (95% CI, 15.5-∞) for the no brachytherapy group ($p = 0.059$). At 24 months, the OS rate was 62.9% for the brachytherapy group and 0% for the no brachytherapy group.

A Cox regression analysis to assess the association between variables and survival rate showed that receiving definitive radiation was associated with improved PFS (HR, 0.44; 95% CI, 0.23–0.83; $p = 0.0119$) and OS (HR, 0.31; 95% CI, 0.14–0.65; $p = 0.0022$). In addition, receiving ≥5 cycles of chemotherapy was associated with improved OS (HR, 1.83; 95% CI, 1.09–3.05).

4. Discussion

Our study showed that for patients with stage IVB neuroendocrine cervical carcinoma, addition of definitive pelvic radiation therapy to chemotherapy as part of the primary treatment was associated with longer PFS and OS. We also found that the rate of complete response was higher in the chemotherapy and definitive radiation group (53%) than in the chemotherapy alone group (13%). In addition, patients who received ≥5 cycles of chemotherapy, whether alone or in conjunction with radiation therapy, had longer OS than those who received <5 cycles.

Our finding of a 3.7-month increase in median PFS and a 6.7-month increase in median OS in favor of the chemotherapy and definitive radiation group is in agreement with similar studies in other types of cervical cancer. Perkins et al. [14] performed a multi-institutional

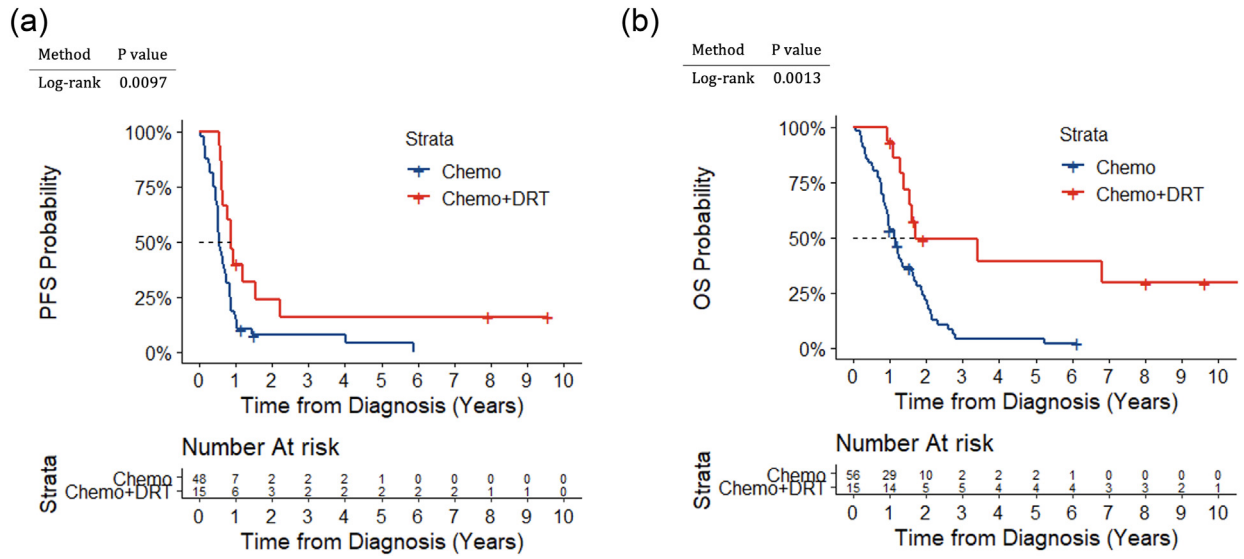

Fig. 1. Estimates of (A) progression-free survival (PFS) and (B) overall survival (OS) by treatment group. DRT, definitive pelvic radiation therapy.

retrospective review of addition of definitive radiation therapy to chemotherapy in patients with stage IVB squamous, adenocarcinoma, or adenosquamous cervical carcinoma. The 2 groups were balanced in terms of age, race, histology, grade, location of disease and number of sites at diagnosis, and chemotherapy agents used. OS was significantly improved in the chemotherapy and definitive radiation group (41.6 vs 17.6 months, $p < 0.01$), and the 2 groups had similar rates of complications (ureteral obstruction, vaginal bleeding, pelvic infection, pelvic pain, and fistula). PFS was also improved, by 7 months, with the addition of radiation (13 months vs 5.9 months; $p = 0.0006$). However, no patients with neuroendocrine cervical carcinoma were included in that study.

Bajaj et al. [16] published a case report of a 31-year-old patient with stage IVB (positive inguinal node) small cell neuroendocrine cervical carcinoma who had a complete response after pelvic chemoradiation and additional etoposide and cisplatin for a total of 6 cycles. At the time of publication, the patient had no evidence of disease after 6 years.

Patients with cervical cancer staged as IVB (squamous, adenocarcinoma, and adenosquamous) solely because of supraclavicular nodal disease have been reported to have better survival than patients with stage IVB cervical cancer with extranodal disease [17–19]. The previously mentioned study by Perkins et al. [14] included a subanalysis excluding patients with disease staged as IVB because of isolated supraclavicular nodal metastases ($n = 2$) and found that PFS remained significantly longer in the chemotherapy and definitive radiation group ($p = 0.015$) while the difference in OS was no longer significant ($p = 0.083$). In our study, 4 patients had disease staged as IVB solely because of supraclavicular nodal disease (2 in each group). When they were excluded from the analysis, both PFS and OS remained significantly longer in the chemotherapy and definitive radiation group.

The recently updated Society of Gynecologic Oncology guideline recommendation for treatment of stage IVB neuroendocrine cervical carcinoma is chemotherapy with at least 5 cycles of an etoposide-containing regimen with individualized radiation therapy to palliate symptoms [20]. Wang et al. [21] studied 179 patients with stage I-IV (stage I, $n = 104$; II, $n = 42$; III, $n = 9$; IV $n = 24$) neuroendocrine cervical carcinoma and found that for patients with stage IIB-IVB disease, primary treatment regimens that included etoposide and platinum for at least 5

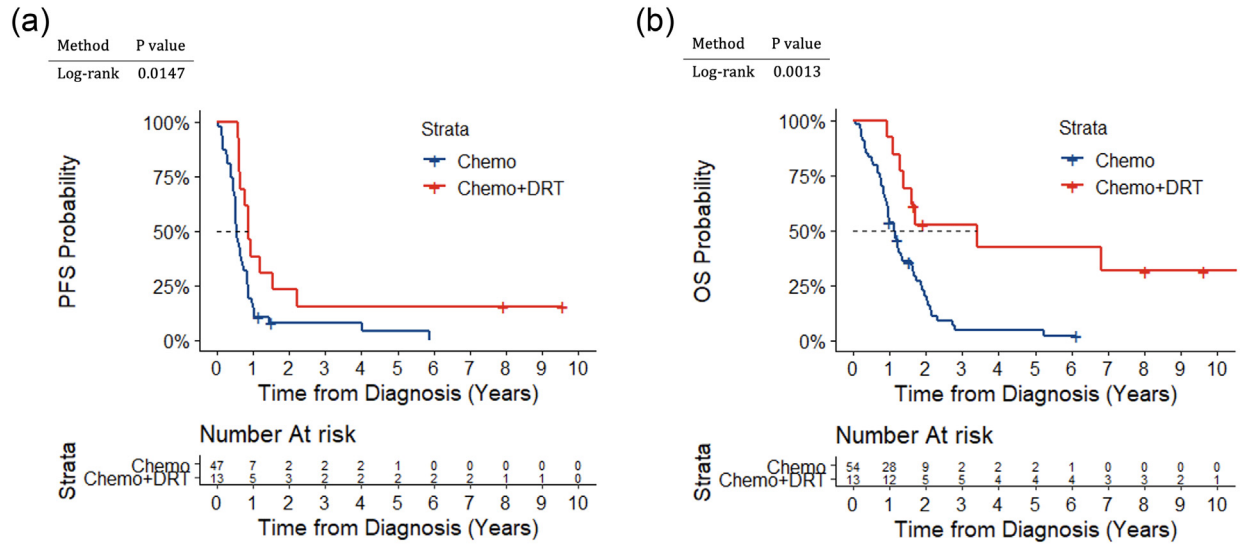

Fig. 2. Estimates of (A) progression-free survival (PFS) and (B) overall survival (OS) by treatment group excluding patients with disease diagnosed as stage IVB solely because of supraclavicular nodal disease. DRT, definitive pelvic radiation therapy.

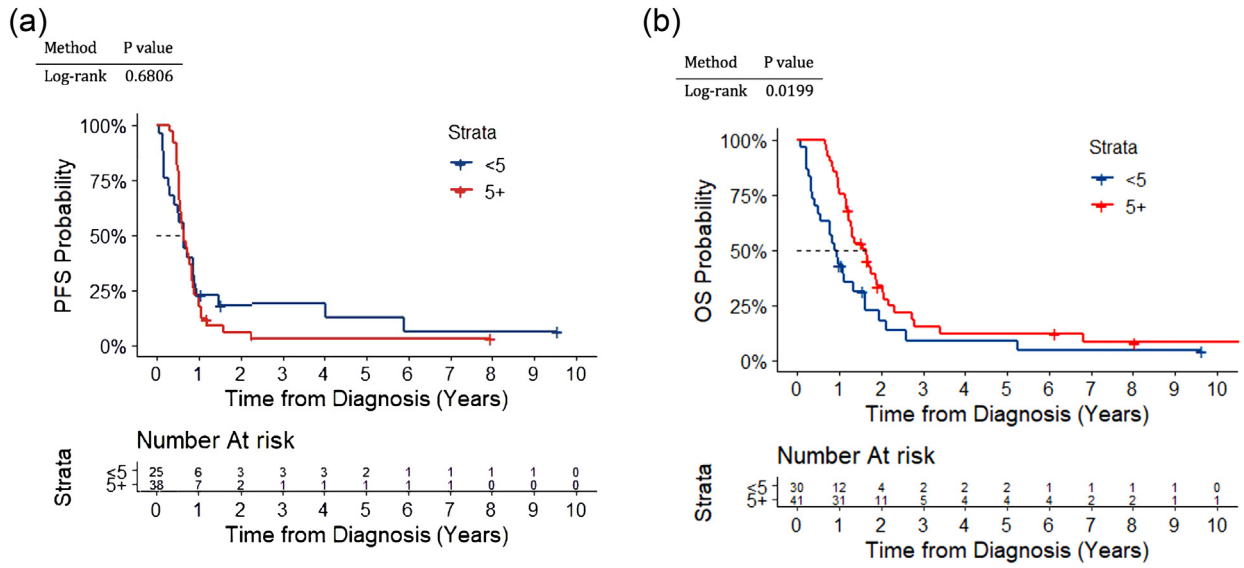

Fig. 3. Estimates of (A) progression-free survival (PFS) and (B) overall survival (OS) for patients who received ≥5 cycles of chemotherapy (including any cycles received concurrently with definitive or palliative radiation therapy) vs <5 cycles.

cycles were associated with a significantly higher 5-year disease-free survival rate (42.9**% vs** 11.8%, $\boldsymbol{p} = 0.041$) and OS rate (45.6**% vs** 17.1%, $\boldsymbol{p} = 0.035$) compared to other treatments. Furthermore, concurrent chemoradiation with etoposide and platinum for at least 5 cycles improved the 5-year disease-free survival rate (62.5% vs 13.1%, $p = 0.025$) and OS rate (75.0% vs 16.9%, $p = 0.016$) compared to regimens with fewer cycles. Pei et al. [22] showed the benefit of receiving at least 5 cycles of chemotherapy in patients with stage I-II small cell neuroendocrine cervical carcinoma. In multivariate analysis, the number of cycles of etoposide plus platinum was an independent prognostic factor for disease recurrence. Adjuvant chemotherapy for at least 5 cycles of etoposide plus platinum in the up-front setting was associated with improved 5-year recurrence-free survival compared with other treatments (67.6% vs 20.9%, $p < 0.001$). In agreement with these previous studies, our study showed an OS benefit for patients who received ≥5 cycles of chemotherapy in comparison to those who received <5 cycles. However, in a retrospective study, it is difficult to discern the reasons proposed by the treating physician for the additional number of cycles. The improved outcome may be directly related to the higher number of cycles, but patients who received more chemotherapy cycles might have been more fit to withstand treatment not only initially but also at times of progression or recurrence. Also, the patients who received more cycles may have been responding to initial treatment. In other words, some patients may have experienced disease progression after 3 cycles and not been offered additional chemotherapy.

As in other cervical cancer subtypes, in neuroendocrine cervical cancer, an improvement in median OS has been shown with the addition of brachytherapy to external beam radiation therapy. In a National Cancer Database study, Robin et al. [23] analyzed 100 patients diagnosed with locally advanced (FIGO IB2-IVA) neuroendocrine cervical cancer from 2004 through 2012 and treated with definitive chemoradiation to determine if the addition of brachytherapy improved outcomes. In multivariate analysis, these authors found that the median OS was 48.6 months with the addition of brachytherapy, compared with 21.6 months with external beam radiation therapy alone (HR, 0.475; 95% CI, 0.255–0.883; $\boldsymbol{p} = 0.019$). They concluded that brachytherapy is an essential component of definitive chemoradiotherapy for neuroendocrine cervical cancer.

Bajaj et al. [24] evaluated oncologic outcomes in patients with stage IB2-IVA small cell carcinoma of the cervix treated with definitive chemoradiation and found that among the factors associated with higher recurrence risk were receipt of <50 Gy vs 71–80 Gy (HR, 3.3; $p = 0.07$) and lack of brachytherapy (HR, 0.05; $p < 0.01$). A more recent National Cancer Database study by Lin et al. [25] evaluated the effect of brachytherapy on OS in 621 patients with small cell neuroendocrine cervical carcinoma (FIGO stage I, 178; II-IVA, 239; and IVB, 204) diagnosed from 2004 to 2014. The study showed that the addition of brachytherapy to external beam pelvic radiation therapy was associated with improved OS in patients with stage II-IVA disease ($p = 0.03$) but not in those with stage I or IVB disease. Only 38% (91/239) of the patients with stage II-IVA disease received brachytherapy. Of the 204 patients with stage IVB disease, 51% ($n = 105$) received no radiation therapy as part of their primary treatment, 38% ($n = 77$) received definitive external beam radiation therapy alone, 6% ($n = 12$) received external beam radiation therapy and brachytherapy, and 5% (n = 10) received brachytherapy alone. The authors concluded that brachytherapy may improve OS for stage II-IVA small cell cancer of the cervix but appears underutilized. In our study, we did not see a difference in PFS ($p = 0.11$) or OS ($p = 0.06$) between patients who received brachytherapy (n = 12) and those who did not ($n = 3$), but this is likely due to the small number of patients who received brachytherapy.

4.1. Strengths and limitations

The strengths of our study include the fact that it is the largest cohort study examining the impact of definitive pelvic radiation therapy on survival outcomes in patients with stage IVB high-grade neuroendocrine cervical carcinoma. We performed stratification according to subcategories of stage IVB based on location of metastatic disease and also evaluated oncologic outcomes based on number of cycles of chemotherapy administered. In addition, the NeCTuR database on which this study is based contains prospectively collected information and is routinely audited for accuracy against source documents. Furthermore, cases from outside MD Anderson must be submitted along with copies of the pathology to verify that the tumor is a neuroendocrine carcinoma and of cervical origin.

This study has several limitations. First, the retrospective nature of the study limits information regarding patient selection for the specified treatments. Second, although the sample size was the largest reported to date, the results should be interpreted with caution as the number of patients was still too low to support robust and definitive recommendations. Third, most patients who received definitive radiation did so

after induction chemotherapy. As patients who had a good response to chemotherapy were more likely to be dispositioned to definitive radiation, the oncologic benefits seen in this group might be due not only to the addition of definitive radiation but also to selection bias.

The statements made in this study are hypothesis generating only and may not be applicable to all patients with stage IVB neuroendocrine cervical carcinoma. The sample size is too small to control for confounders in a multivariable analysis. Furthermore, the small sample size did not permit a propensity score analysis to balance confounders. Moreover, the reason why patients were assigned to receive definitive radiation or to receive ≥5 cycles of chemotherapy is unknown. This decision was at the discretion of the treating physician. An intent-to-treat analysis including patients who were assign a priori to receive fewer than 5 or 5 or more cycles or to receive definitive radiation or not would have been ideal but was not possible owing to lack of this information in the database. Fourth, the ECOG performance status may have deteriorated during treatment, causing chemotherapy to be stopped before 5 cycles and not allowing radiation to be completed or even started. Lastly, the NeCTuR database does not include information on pelvic-related adverse events and the impact of radiation on pelvic-related morbidity and does not require central pathology review.

5. Conclusions

Our study demonstrated that in patients with stage IVB neuroendocrine cervical carcinoma, PFS and OS were longer when definitive pelvic radiation therapy was added to standard chemotherapy as part of primary treatment. These results suggest that patients who have a favorable response to initial chemotherapy should be considered for definitive pelvic radiation therapy with concurrent cisplatin and etoposide with the aim to achieve more than 5 cycles total (counting cycles delivered concurrently with radiation therapy) provided treatment is well tolerated. The role of brachytherapy for patients with stage IVB neuroendocrine cervical carcinoma remains elusive; however, studies suggest a possible benefit. Future studies should evaluate adverse events in patients with stage IVB neuroendocrine cervical carcinoma treated with chemotherapy and radiation. Similarly, additional studies are needed to determine which subgroup of patients with stage IVB neuroendocrine cervical carcinoma may benefit the most from this combined approach.

Author contributions

All authors contributed to the study described in this manuscript and contributed to writing and critical revision of this manuscript. All authors have given final approval of this version, and all authors accept responsibility for its contents.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.03.022.

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