Clinicopathologic characteristics, oncologic outcomes, and prognostic factors in neuroendocrine cervical carcinoma: a Neuroendocrine Cervical Tumor Registry study

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ABSTRACT

Objective To evaluate clinicopathologic features and oncologic outcomes of patients with neuroendocrine cervical carcinoma in an institutional neuroendocrine cervical tumor registry.

Methods Retrospective study including patients with neuroendocrine cervical carcinomas diagnosed between 1986 and 2022. Patients were categorized into International Federation of Gynecology and Obstetrics 2018 stage groups: early-stage (IA1–IB2, IIA1); locally advanced (IB3, IIA2–IVA); and advanced (IVB). Clinicopathologic characteristics and oncologic outcomes were evaluated by stage. Survival was compared between patients diagnosed in 1986–2003 and those diagnosed in 2004–2016. Progression-free and overall survival were estimated using the Kaplan-Meier product-limit estimator.

Results A total of 453 patients was included, 133 (29%) with early-stage, 226 (50%) with locally advanced, and 94 (21%) with advanced disease. Median age was 38 years (range 21–93). Sixty-nine percent (306/453) had pure and 32% (146/453) had mixed histology. The node positivity rate (surgical or radiological detection) was 19% (21/108) for tumors ≤2 cm, 37% (39/105) for tumors >2 to ≤4 cm, and 61% (138/226) for tumors >4 cm (p<0.0001). After primary treatment, rates of complete response were 86% (115/133) for early-stage, 65% (147/226) for locally advanced, and 19% (18/94) for advanced disease (p<0.0001). The recurrence/progression rate was 43% for early-stage, 69% for locally advanced, and 80% for advanced disease (p<0.0001). Five-year progression-free and overall survival rates were 59% (95% CI 50% to 68%) and 71% (95% CI 62% to 80%), respectively, for early-stage, 28% (95% CI 22% to 35%) and 36% (95% CI 29% to 43%), respectively, for locally advanced, and 6% (95% CI 0% to 11%) and 12% (95% CI 5% to 19%), respectively, for advanced disease. For early-stage disease, the 5-year progression-free survival rate was 68% for tumors ≤2 cm and 43% for tumors >2 to ≤4 cm (p=0.0013). Receiving cisplatin/carboplatin plus etoposide (HR=0.33, 95% CI 0.17 to 0.63, p=0.0008) and receiving curative radiotherapy (HR=0.32, 95% CI 0.17 to 0.6, p=0.0004) were positive predictors of survival for patients with advanced disease.

Conclusion Among patients with neuroendocrine cervical carcinomas, overall survival is favorable for patients with early-stage disease. However, most patients present with locally advanced disease, and overall survival remains poor in this subgroup. For patients with advanced disease, receiving cisplatin/carboplatin plus etoposide and curative radiation therapy is associated with improved overall survival.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neuroendocrine cervical tumors account for 1–2% of all cervical cancer and are more aggressive than squamous or adenocarcinomas.

WHAT THIS STUDY ADDS

⇒ This study, is based on the largest registry of cervical neuroendocrine carcinomas and adds valuable data on prognosis, treatment options, and survival.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study is the starting point for future research on the topic, both retrospectively and prospectively. It also gives physicians additional data to better counsel and treat patients with this disease.

INTRODUCTION

The National Cancer Institute defines 'rare tumors' as cancers that occur in fewer than 15 of 100 000 people each year, affecting fewer than 40 000 people per year in the United States.[1] Each year, one-quarter of all cancer deaths are due to rare cancers.[1] Neuroendocrine cervical carcinomas are rare tumors of the gynecological tract, estimated to account for only 1% to 2% of all cervical cancers. Given that the incidence of cervical cancer is approximately 569 847 cases per year worldwide,[2] it is estimated that 5000 to 11 000 new cases of neuroendocrine cervical carcinoma occur each year across the globe.

Consensus is lacking about the best strategies for prevention, screening, diagnosis, and treatment of rare tumors. In addition, the low prevalence of rare tumors prevents investigators from conducting adequately powered studies and thereby impedes understanding of epidemiological, clinical, and pathological characteristics of such tumors. Prospective

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randomized studies in rare tumors are hard to complete, even with multi-institutional international collaborations.

Disease-specific tumor registries allow aggregation of well-curated data from a large pool of patients treated worldwide and thereby make it possible for researchers to evaluate and compare treatment strategies (both primary treatment and treatment for recurrence), survival outcomes, and surveillance strategies. Registries can also become the starting point for international collaborative studies and prospective randomized trials.

In 2011, a small group of patients diagnosed with neuroendocrine cervical carcinoma and their caregivers started raising funds to support the mission of better understanding the natural course and treatment of this disease. This organization, Small/Large Cell Carcinoma of the Cervix: Sisters United, joined forces in 2013 with The University of Texas MD Anderson Cancer Center, and together they established the Neuroendocrine Cervical Tumor Registry (https://necervix.com/). The goal of this study was to evaluate clinicopathological characteristics, treatments, oncologic outcomes, and prognostic factors in patients with neuroendocrine cervical cancer included in the registry.

METHODS

This retrospective study included patients diagnosed between June 1986 and February 2022 with pure or mixed neuroendocrine cervical carcinoma. Participants in the Neuroendocrine Cervical Tumor Registry 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. This analysis 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.[3 4]

Patients with pathology reports unavailable or disease reported as neuroendocrine features or differentiation, FIGO 2018 stage unknown, or no follow-up after primary treatment were excluded. All patients had their disease restaged using the International Federation of Gynecology and Obstetrics (FIGO) 2018 classification system[5] and categorized as early-stage (IA1–IB2, IIA1), locally advanced (IB3, IIA2–IVA), or advanced (IVB). This meant that patients with FIGO 2009 clinical early-stage disease with documented positive lymph nodes were classified as having locally advanced disease in this analysis. Patients were classified as IIIC1 or C2r (radiologically positive nodes) if the radiology reports classified the nodes as unequivocally positive. Nodes 'suspicious or concerning for disease' were not considered positive in our classification of the data points. Histologic types were classified as pure (high-grade neuroendocrine carcinoma not otherwise specified small cell, large cell, or small cell plus large cell neuroendocrine carcinoma) or mixed (any pure histology in combination with adenocarcinoma, squamous cell carcinoma, and/or adenosquamous carcinoma). Participation in the Neuroendocrine Cervical Tumor Registry does not require a central pathology review; however, when patients are being seen at MD Anderson even for a second opinion, a formal pathology review is performed by expert pathologists at the MD Anderson Cancer Center. Pathology reports and consultations (if done) are requested when no tissue is available for central review. Only patients with an initial biopsy report and, if surgery was performed, a surgical pathology report available in English or Spanish, were included in the analysis.

Tumor size was obtained from the surgical pathology report whenever available or from reports on pre-treatment conization, imaging studies, or physical examination. After completion of primary treatment (surgery, radiotherapy, and/or chemotherapy), most patients had a positron emission tomography–CT or CT scan of the chest, abdomen, and pelvis for evaluation of response. For patients who received cisplatin or carboplatin plus etoposide (concurrently with radiation therapy or as additional chemotherapy), all cycles were added to determine the total number of cycles received.

For a subanalysis of survival by time frame, patients were divided into those diagnosed in 1986–2003 and in 2004–2016. The cut-off point of 2003 was based on the 2003 publication by Hoskins et al, which showed the benefits of concurrent cisplatin plus etoposide for cervical neuroendocrine tumors treated with radiation.[6] 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. Wilcoxon rank-sum tests were used to compare continuous variables between the two groups.

Progression-free and overall survival were analyzed for all patients; time from first recurrence or progression to death was analyzed for patients with recurrence or progression after primary treatment. Survival analyses were done for all patients and for each stage group separately. Progression-free survival 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. Overall survival 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. Survival was estimated using the Kaplan-Meier product-limit estimator. We tested for differences between survival curves using the log-rank test. Median survival rates with 95% confidence intervals (CIs) are reported along with 3-year and 5-year survival rates. Cox proportional hazards regression was used to estimate hazard ratios (HRs) with 95% CIs.

Multivariate analyses were performed to evaluate potential prognostic factors for progression-free and overall survival in all patients and time from first progression/recurrence to death in patients with recurrence or progression after primary treatment. Stage was not included in the model as a multivariate analysis was performed for each stage group separately because not all variables are clinically relevant for all stages. The variables were chosen prior to analysis and included age, chemotherapy agents, adjuvant radiation therapy (for early-stage disease), number of chemotherapy cycles (for early-stage disease), nodal status (for locally advanced and advanced disease), tumor size, histology, and intent of pelvic radiation therapy (for advanced disease). In summary, the selection of variables for the multivariate analysis was performed based on clinically relevant variables deemed appropriate for the endpoint of interest. Statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc.) and R Core Team 2020.

In accordance with the journal's guidelines, we will provide our data for independent analysis by a tean selected 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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RESULTS

Of 544 patients included in the Neuroendocrine Cervical Tumor Registry Database at data lock on November 19, 2022, 453 were included in this analysis (online supplemental figure 1). One hundred and thirty-three (29%) had early-stage disease, 226 (50%) had locally advanced disease (including 34 with clinical early-stage disease but pelvic or para-aortic lymph node involvement found post-operatively), and 94 (21%) had advanced disease.

Demographics and Patient Characteristics

The median age was 38 years (range 21–93), and the median body mass index was 26.2 kg/m2 (range 14.4–77.1). The proportions of patients with pure and mixed histology were 68% and 32%, respectively (table 1). The rate of positive nodes (surgical or radiological detection) for patients with nodal status and tumor size available was 19% (21/108) for tumors ≤2 cm, 37% (39/105) for tumors >2 to ≤4 cm, and 61% (138/226) for tumors >4 cm (p<0.0001).

Primary Treatments and Responses

Multimodality treatment was most common for patients with early-stage and locally advanced disease, and chemotherapy alone was most common for patients with advanced disease (table 2). Cisplatin/carboplatin plus etoposide was the most frequently used primary chemotherapy regimen across all stage categories (91% in early-stage (96/106), 88% in locally advanced (137/156), and 83% in advanced (70/84), p=0.24).

The complete response rate was 86% for early-stage disease, 65% for locally advanced disease, and 19% for advanced disease (p<0.0001) (table 2).

Recurrences

Sixty-three percent (287/453) of the patients had a recurrence or progression after primary treatment: 43% with early-stage, 69% with locally advanced, and 80% with advanced disease, (p<0.0001) (table 2). Among patients with early-stage disease, the recurrence rate was 33% (27/83) for tumors ≤2 cm and 59% (29/49) for tumors >2 to 4 cm. Seventy percent of recurrences occurred within 1 year and 93% occurred within 3 years after primary treatment initiation (online supplemental figure 2). Median survival after recurrence was 10.5 months (range 9.1–12.0).

Median, Progression-free, and Overall Survival

For early-stage, locally advanced, and advanced disease, median survival from recurrence was 18.5 months (range 13.8–31.0), 9.8 months (range 8.2–11.4), and 7.8 months (range 6.9–9.7), respectively. Median follow-up time for all patients in the study was 59.9 months (range 43.5–76.7), for early stage 65.8 months (range 43.2–86.7), for locally advanced 60.4 months (39.5–84.9), and for advanced 28.8 months (range 11.9–87.0). Progression-free and overall survival rates at 3 and 5 years according to disease stage and status at completion of primary treatment are shown in table 3. Five-year progression-free and overall survival rates were 59% (95% CI 50% to 68%) and 71% (95% CI 62% to 80%), respectively, for patients with early-stage disease; 28% (95% CI 22% to 35%) and 36% (95% CI 29% to 43%), respectively, for patients with locally advanced disease; and 6% (95% CI 0% to 11%) and 12% (95% CI 5% to 19%), respectively, for patients with advanced disease (figure 1). Among patients with early-stage disease, the 5-year progression-free survival rate was 68% for tumors ≤2 cm and 43% for tumors >2 to ≤4 cm (p=0.0013).

Survival by Time Frames

Median progression-free survival was 17 months (95% CI 12 to 193.8) for the 1986–2003 group versus 13.8 months (95% CI 11.1 to 20.7) for the 2004–2016 group (p=0.32) (figure 2A). Median overall survival was 32.7 months (95% CI 21.2 to 87.8) for the 1986–2003 group versus 43.3 months (95% CI 33.7 to 61.6) for the 2004–2016 group (p=0.55) (figure 2B). Median time from first progression/recurrence to death was 6.4 months (95% CI 5.2 to 12.9) for the 1986–2003 group versus 11.9 months (95% CI 9.8 to 14.6) for the 2004–2016 group (p=0.002) (figure 2C).

Survival by stage and time frame is summarized in online supplemental figure 3. For patients with early-stage disease, progression-free survival, overall survival, and time from first recurrence/progression to death did not differ by time frame. For patients with locally advanced disease, progression-free survival and overall survival did not differ by time frame, but time from first recurrence/progression to death was 6.6 months (95% CI 3.9 to 12.9) for the 1986–2003 group and 10.6 months (95% CI 9.5 to 14.7) for the 2004–2016 group (p=0.0021). For patients with advanced disease, treatment during 2004–2016 was associated with better median progression-free survival (8 months (95% CI 6.8 to 10.6) vs 5.3 months (95% CI 3.5 to NA), p=0.039); median overall survival (18.5 months (95% CI 14.6 to 25.2) vs 8.7 months (95% CI 6 to NA), p=0.0034); and median time from first recurrence/progression to death (9.7 months (95% CI 7.6 to 14.2) vs 4.9 months (95% CI 1.2 to NA), p=0.0042).

Prognostic Factors

Results of the analysis of potential prognostic factors are summarized in table 4.

For patients with early-stage disease, tumor size >2 cm to ≤4 cm vs ≤2 cm was a predictor of worse progression-free survival (HR=3.57, 95% CI 1.78 to 7.14, p=0.0003) and worse overall survival (HR=2.52, 95% CI 1.11 to 5.68, p=0.026). No prognostic factors were identified for time from first recurrence/progression to death.

For patients with locally advanced disease, node positivity was a predictor of worse progression-free survival (HR=1.46, 95% CI 1.01 to 2.12, p=0.043) and worse overall survival (HR=1.55, 95% CI 1.06 to 2.28, p=0.025). Pure histology was a predictor of shorter time from first recurrence/progression to death (HR=2.0, 95% CI 1.34 to 2.99, p=0.0007).

For patients with advanced disease, curative-intent radiotherapy as part of primary treatment was associated with better progression-free survival (HR=0.35, 95% CI 0.19 to 0.65, p=0.0009); better overall survival (HR=0.32, 95% CI 0.17 to 0.6, p=0.0004); and longer time from first recurrence/progression to death (HR=0.46, 95% CI 0.23 to 0.92, p=0.0331). Receiving cisplatin/carboplatin plus etoposide was a predictor of better overall survival (HR=0.33, 95% CI 0.17 to 0.63, p=0.0008). Tumor size >4 cm was a predictor of worse overall survival (HR=3.12, 95% CI 1.56 to 6.24, p=0.0013) and shorter time from first recurrence/progression to death (HR=3.18, 95% CI 1.56 to 6.46, p=0.0014). For patients with advanced disease receiving the 'Texas cocktail' (topotecan, paclitaxel, and bevacizumab)[7] at the time of recurrence or progression

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Table 1 Demographic and clinical characteristics of patients with neuroendocrine cervical carcinoma*

Characteristic	Overall cohort (n=453)	Early-stage disease (n=133)	Locally advanced disease (n=226)	Advanced disease (n=94)	P value
Age (years), median (range)	38 (21–93)	36 (22–72)	38 (21–93)	44 (24–75)	<0.0001
Age at diagnosis (years)					
<30	75 (16.6)	26 (19.5)	41 (18.1)	8 (8.5)	0.003
30–39	172 (38.0)	61 (45.9)	82 (36.73	29 (30.9)	
40–49	99 (21.9%)	27 (20.3)	48 (21.2)	24 (25.5)	
50–59	67 (14.8%)	16 (12.0)	36 (15.9)	15 (16.0)	
60–69	27 (6.0%)	2 (1.5)	12 (5.3)	13 (13.8)	
70–79	12 (2.6%)	1 (0.8)	6 (2.7)	5 (5.3)	
≥ 80	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	
BMI (kg/m^2) median (range)	26.2 (14.4–77.1)	25.5 (15.9–45.9)	26.1 (14.4–64.8)	28.9 (15.5–77.1)	0.0187
FIGO 2018 stage					
IA1	7 (1.5)	7 (5.3)	0 (0.0)	0 (0.0)	<0.0001
IA2	8 (1.8)	8 (6.0)	0 (0.0)	0 (0.0)	
IB	1 (0.2)	1 (0.8)	0 (0.0)	0 (0.0)	
IB1	76 (16.8)	76 (57.1)	0 (0.0)	0 (0.0)	
IB2	35 (7.7)	35 (26.3)	0 (0.0)	0 (0.0)	
IB3	46 (10.2)	0 (0.0)	46 (20.4)	0 (0.0)	
IIA1	5 (1.1)	5 (3.8)	0 (0.0)	0 (0.0)	
IIA2	5 (1.1)	0 (0.0)	5 (2.2)	0 (0.0)	
IIB	19 (4.2)	0 (0.0)	19 (8.4)	0 (0.0)	
IIIB	5 (1.1)	0 (0.0)	5 (2.2)	0 (0.0)	
IIIC1r	54 (11.9)	0 (0.0)	54 (23.9)	0 (0.0)	
IIIC1p	58 (12.8)	0 (0.0)	58 (25.7)	0 (0.0)	
IIIC2r	26 (5.7)	0 (0.0)	26 (11.5)	0 (0.0)	
IIIC2p	5 (1.1)	0 (0.0)	5 (2.2)	0 (0.0)	
IVA	8 (1.8)	0 (0.0)	8 (3.5)	0 (0.0)	
IVB	94 (20.8)	0 (0.0)	0 (0.0)	94 (100.0)	
Missing	1 (0.2)	1 (0.8)	0 (0.0)	0 (0.0)	
ECOG performance status					
0	272 (60.0)	101 (75.9)	116 (51.3)	55 (58.5)	<0.0001
1	16 (3.5)	0 (0.0)	7 (3.1)	9 (9.6)	
2	6 (1.3)	0 (0.0)	1 (0.4)	5 (5.3)	
3	2 (0.4)	0 (0.0)	0 (0.0)	2 (2.1)	
Missing	157 (34.7)	32 (24.1)	102 (45.1)	23 (24.5)	
Current or former smoker					
No	251 (55.4)	74 (55.6)	121 (53.5)	56 (59.6)	0.7593
Yes	174 (38.4)	53 (39.8)	89 (39.4)	32 (34.0)	
Not reported	28 (6.2)	6 (4.5)	16 (7.1)	6 (6.4)	
Histology					
Pure	307 (67.8)	69 (51.9)	157 (69.5)	81 (86.2)	<0.0001

Continued

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Table 1 Continued

Characteristic	Overall cohort (n=453)	Early-stage disease (n=133)	Locally advanced disease (n=226)	Advanced disease (n=94)	P value
Mixed	146 (31.4)	64 (48.1)	69 (30.5)	13 (14.0)	
Histology					
HGNEC	72 (15.9)	18 (13.5)	28 (12.4)	26 (27.7)	0.0206
Large cell	70 (15.5)	25 (18.8)	31 (13.7)	14 (14.9)	
Small cell	305 (67.3)	88 (66.2)	163 (72.1)	54 (57.4)	
Small and large cell	6 (1.3)	2 (1.5)	4 (1.8)	0 (0.0)	
Pelvic node status†					
Negative	245 (54.1)	133 (100.0)	77 (34.1)	35 (37.2)	<0.0001
Positive	207 (45.7)	0 (0.0)	148 (65.5)	59 (62.8)	
Missing	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	
Tumor size (cm)					
≤2	108 (23.8)	83 (62.4)	20 (8.8)	5 (5.3)	
>2–≤4	105 (23.2)	49 (36.8)	43 (19.0)	13 (13.8)	
>4	227 (50.1)	0 (0.0)	158 (69.9)	69 (73.4)	
Not reported	13 (2.9)	1 (0.8)	5 (2.2)	7 (7.4)	<0.0001
Pregnant at diagnosis					
Yes	20 (4.4)	7 (5.3)	11 (4.9)	2 (2.1)	0.4971
No	432 (95.4)	126 (94.7)	214 (94.7)	92 (97.9)	
Missing	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	
Post partum at diagnosis					
Yes	14 (3.1)	4 (3.0)	5 (2.2)	5 (5.3)	0.3236
No	438 (96.7)	129 (97.0)	220 (97.3)	89 (94.7)	
Missing	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	

*Results reported as number of patients (%) unless otherwise specified.
†Nodal positivity (pelvic and/or para-aortic) based on pathology report for patients who underwent surgery (sentinel lymph node biopsy and/or pelvic lymphadenectomy and/or para-aortic lymphadenectomy) and images for patients who did not undergo surgery.
BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HGNEC, high-grade neuroendocrine carcinoma.

was associated with a longer time from first recurrence/progression to death (HR=0.52, 95% CI 0.27 to 0.99, p=0.045).

DISCUSSION

Summary of Main Results

In this study of patients with neuroendocrine cervical carcinoma, 86% of patients with early-stage disease achieved a complete response to primary treatment; however, nearly half of those patients had a recurrence. Nevertheless, the 5-year overall survival rate for patients with early-stage disease was favorable, at 78%. Among patients with locally advanced disease, the complete response rate was lower (65%), and thus the 5-year overall survival rate was less favorable, at 52%. For early-stage disease, tumor size >2 cm was an independent predictor of progression and worse survival, and for locally advanced disease, lymph node compromise and pure histology were associated with worse survival. Among patients with advanced disease, consolidation radiation therapy with curative intent after induction chemotherapy was a predictor of improved survival. Over a 30-year period, survival increased only for patients with advanced disease in the primary and recurrence setting and for patients with locally advanced disease that progressed or recurred after primary treatment.

Results in the Context of Published Literature

Survival Outcomes

In a review published in 2019, we found that 5-year overall survival rates for early-stage (I–II) and advanced (III–IV) neuroendocrine cervical carcinoma were 31% to 51% and 0% to 7%, respectively.[8] In a previous analysis based on data from the Neuroendocrine Tumor Registry, we found that for patients with stage IA1–IB2 disease who underwent radical surgery, progression-free and overall survival rates at 5 years were 44% and 61%, respectively.[9] In our present study, patients with early-stage disease had

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Table 2 Primary treatment, response to primary treatment, and recurrence and progression*

Treatment	Overall cohort (n=453)	Early-stage disease (n=133)	Locally advanced disease (n=226)	Advanced disease (n=94)	P value
SX+CH+RT	124 (27.4)	52 (39.1)	67 (29.6)	5 (5.3)	<0.0001
SX+CH	66 (14.6)	41 (30.8)	14 (6.2)	11 (11.7)	
SX+RT	36 (7.9)	13 (9.8)	23 (10.2)	0 (0.0)	
CH+RT	97 (21.4)	13 (9.8)	71 (31.4)	13 (13.8)	
SX	19 (4.2)	13 (9.8)	6 (2.7)	0 (0.0)	
RT	44 (9.7)	1 (0.8)	40 (17.7)	3 (3.2)	
CH	59 (13.0)	0 (0.0)	4 (1.8)	55 (58.5)	
No treatment	8 (1.8)	0 (0.0)	1 (0.4)	7 (7.4)	
Primary chemotherapy agents					
Cisplatin/carboplatin+etoposide	303 (87.6)	96 (90.6)	137 (87.8)	70 (83.3)	0.2115
Cisplatin/carboplatin+other	33 (9.5)	6 (5.7)	15 (9.6)	12 (14.3)	
None	2 (0.6)	0 (0.0)	2 (1.3)	0 (0.0)	
Other	6 (1.7)	2 (1.9)	2 (1.3)	2 (2.4)	
Cisplatin/carboplatin alone	2 (0.6)	2 (1.9)	0 (0.0)	0 (0.0)	
Concurrent chemotherapy					
Yes	253 (84.1)	65 (82.3)	172 (85.6)	16 (76.2)	0.4288
No	48 (15.9)	14 (17.7)	29 (14.4)	5 (23.8)	
Concurrent chemotherapy agents					
C/C+E	122 (48.2)	32 (49.2)	85 (49.4)	5 (31.3)	0.0749
C/C alone	116 (45.8)	32 (49.2)	75 (43.6)	9 (56.3)	
C/C+other	7 (2.8)	1 (1.5)	4 (2.3)	2 (12.5)	
Other	8 (3.2)	0 (0.0)	8 (4.7)	0 (0.0)	
Brachytherapy					
Yes	237 (52.3)	57 (42.9)	158 (69.9)	22 (23.4)	0.0125
No	90 (19.9)	23 (17.3)	48 (21.2)	19 (20.2)	
Not reported	126 (27.8)	53 (39.8)	20 (8.8)	53 (56.4)	
Cycles of C/C+E, median (range)	5 (2–12)	4 (2–7)	4 (2–9)	6 (2–12)	0.007
Cycles of C/C+E chemotherapy					
<5	131 (44.1)	49 (52.7)	59 (44.0)	23 (32.9)	0.0423
≥5	166 (55.9)	44 (47.3)	75 (56.0)	47 (67.1)	
Response to primary treatment					
Complete response	280 (61.8)	115 (86.5)	147 (65.0)	18 (19.1)	<0.0001
Partial response	27 (6.0)	0 (0.0)	12 (5.3)	15 (16.0)	
Mixed response	15 (3.3)	2 (1.5)	4 (1.8)	9 (9.6)	
Stable disease	4 (0.9)	0 (0.0)	1 (0.4)	3 (3.2)	
Progressive or new disease	118 (26.0)	16 (12.0)	56 (24.8)	46 (48.9)	
Not reported	9 (2.0)	0 (0.0)	6 (2.7)	3 (3.2)	
Follow-up time, median (range), months	26.7 (22.4–30.4)	52.4 (39.5–63.8)	26.1 (22.4–30.8)	13.8 (11.6–16.1)	<0.0001
Recurrence and/or progression					
Yes	287 (63.4)	57 (42.9)	155 (68.6)	75 (79.8)	<0.0001
No	160 (35.3)	76 (57.1)	68 (30.1)	16 (17.0)	
Unknown	6 (1.3)	0 (0.0)	3 (1.3)	3 (3.2)	
Location of first recurrence/ progression					

Continued

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Table 2 Continued

Treatment	Overall cohort (n=453)	Early-stage disease (n=133)	Locally advanced disease (n=226)	Advanced disease (n=94)	P value
Distant	175 (61.0)	35 (61.4)	97 (62.6)	43 (57.3)	0.0394
Both	69 (24.0)	9 (15.8)	33 (21.3)	27 (36.0)	
Local	39 (13.6)	12 (21.1)	22 (14.2)	5 (6.7)	
Not reported	4 (1.4)	1 (1.8)	3 (1.9)	0 (0.0)	

*Results reported as number of patients (%) unless otherwise specified.
C/C+E, cisplatin or carboplatin+etoposide; CH, chemotherapy; RT, radiation therapy; SX, surgery.

5-year progression-free and overall survival rates of 59% and 71%, respectively, higher than rates previously reported. The difference may be a result of the fact that patients in our present study with clinical early-stage disease were reclassified as having locally advanced disease if nodal metastases were found at surgery. The better 5-year overall survival rate for patients with advanced disease in our present study (12%) than for patients in our earlier review is probably due to more aggressive use of consolidation radiation therapy after induction chemotherapy when favorable resolution of extrapelvic disease was noted.

Prognostic Factors

Our findings that larger tumor size and positive nodes were risk factors for poor survival in neuroendocrine cervical carcinoma are in line with findings from previously published studies, several of which identified stage (which is related to tumor size) and/or nodal metastases to be predictive of worse survival.[10–12] Other factors previously shown to be predictive of worse survival of patients with neuroendocrine cervical carcinoma include older age at diagnosis,[10 12] less than five cycles of chemotherapy,[11] and radical surgery.[12] We evaluated the role of surgery (radical surgery) in early stages without finding any significance in progression-free or overall survival. However, one must interpret this finding with caution as most patients with early-stage disease also underwent radiation therapy and outcomes may not be solely related to the impact of surgery. Our finding that receiving radiation therapy with curative intent was a predictor of improved overall survival in patients with advanced disease agrees with a previous report by our group,[13] and radiation therapy has also been shown to be beneficial in other histologic types of cervical carcinoma.[14 15]

Time Trends in Survival

Whereas we found no difference in progression-free or overall survival between 1986–2003 and 2004–2016, Yang et al,[12] in an analysis of data from the Surveillance, Epidemiology, and End Results (SEER) Registry, found that 5-year relative survival rates

Table 3 Three-year and 5 year progression-free survival (PFS) and overall survival (OS) rates by stage group and response to primary treatment*

Response to primary treatment	Early-stage disease	Locally advanced disease	Advanced disease	P value
Complete response				
3-year PFS	72% (64% to 81%)	48% (39% to 57%)	28% (7% to 48%)	<0.0001
5-year PFS	68% (59% to 78%)	42% (33% to 51%)	19% (0% to 39%)	
3-year OS	91% (86% to 97%)	63% (54% to 71%)	53% (29% to 77%)	<0.0001
5-year OS	78% (69% to 87%)	52% (43% to 61%)	39% (15% to 64%)	
Partial response				
3-year OS	NA	100% (NA-100%)	100% (0% to 100%)	0.8651
5-year OS	NA	100% (0% to 100%)	100% (0% to 100%)	
Stable disease				
3-year OS	NA	13% (0% to 35%)	13% (0% to 35%)	0.1823
5-year OS	NA	13% (0% to 35%)	13% (0% to 35%)	
Mixed response or progressive disease or new disease				
3-year OS	35% (11% to 60%)	9% (2% to 17%)	3% (0% to 8%)	0.0012
5-year OS	21% (0% to 42%)	2% (0% to 6%)	3% (0% to 8%)	

*Values in table are rate (95% CI).

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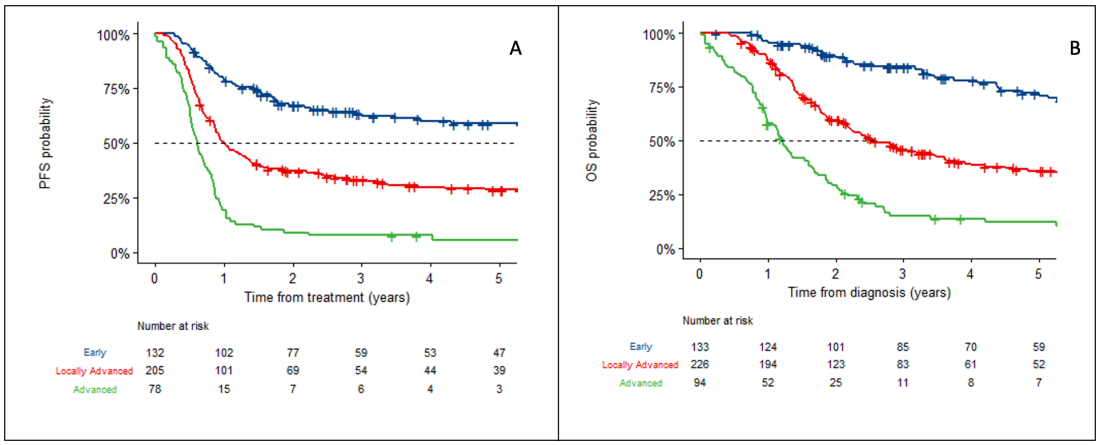

Figure 1 Progression-free survival (PFS) (A) and overall survival (OS) (B) by stage group.

and overall survival rates for patients with neuroendocrine cervical carcinoma gradually decreased over time between 1988 and 2015. Yang et al,[12] attributed the decrease in survival for neuroendocrine carcinoma to the decrease in the proportion of patients with localized disease and the increase in the proportion of patients with advanced disease. We noted similar changes in our study: the proportions of patients with early-stage, locally advanced, and advanced disease were 32%, 60%, and 8%, respectively, in 1986–2003 and 29%, 51%, and 20%, respectively, in 2004–2016.

Although we found no differences in progression-free or overall survival between 1986–2003 and 2004–2016, we found that the median time from first progression/recurrence to death increased by 5.5 months between the earlier and later periods. The improvements in time from first progression/recurrence to death were significant in patients with locally advanced and advanced disease. The so-called Texas cocktail of paclitaxel, topotecan, and bevacizumab, appears to play some role in the improvements in these groups. Our institution started treating patients with this three-drug regimen in 2013 and published the first results in 2017.[16] We recently published an updated analysis[7] including 62 patients treated with the three-drug regimen and 56 treated with other chemotherapy regimens as first-or second-line therapy for recurrence. The combination paclitaxel, topotecan, and bevacizumab was associated with improved progression-free survival (8.7 months vs 3.7 months, HR=0.27, 95% CI 0.17 to 0.48). Median overall survival was 16.8 months for topotecan, paclitaxel, and bevacizumab and 14.0 months for other regimens (HR=0.87, 95% CI 0.55 to 1.37) with more patients remaining on treatment at 6 months (67% vs 31%, p=0.0004) and 1 year (24% vs 9%, p=0.02) with topotecan, paclitaxel, and bevacizumab.

For patients with advanced disease, the addition of pelvic irradiation with curative intent as part of primary treatment has been shown to improve both progression-free and overall survival compared with chemotherapy alone for primary treatment with or without palliative radiation.[13] This treatment strategy for advanced disease may have contributed to the improvement in survival.

Strengths and Weaknesses

Our study has several strengths. The large sample size is one of the major strengths. Another strength is the quality control of the Neuroendocrine Cervical Tumor Registry Database, which is routinely audited for accuracy against source documents. For patients outside MD Anderson, all medical records related to the disease must be submitted for the patient to be included. The NeCTuR Registry contains important information unavailable in SEER, including intent of surgery (palliative vs curative) and other treatments received (chemotherapy, immunotherapy, or hormonal therapy), and information on recurrences, which allows consideration of the impact of these variables on outcomes.

Limitations of our study include the retrospective nature of the study, which restricts information about patient treatment selection; the lack of central pathology review for patients treated outside MD

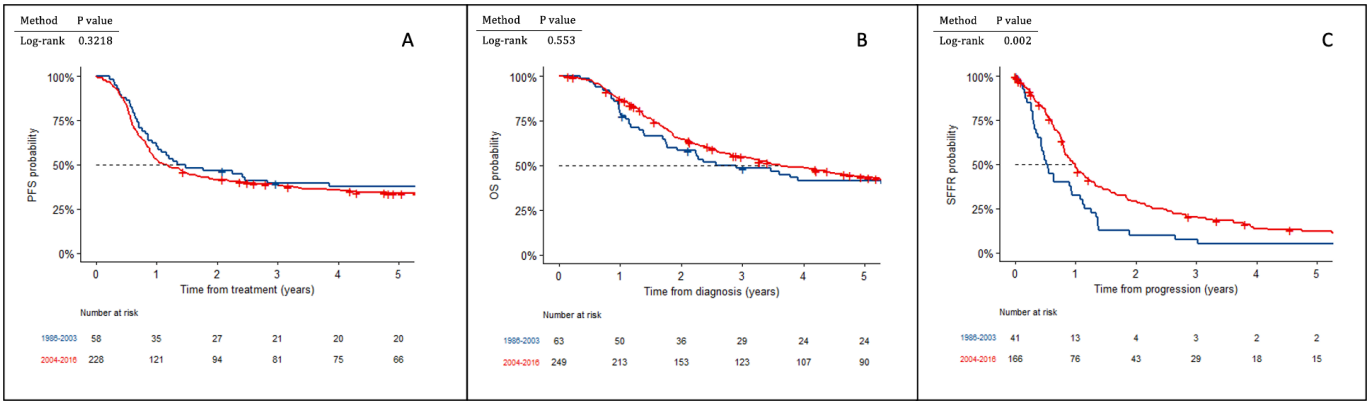

Figure 2 Progression-free survival (PFS) (A), overall survival (OS) (B), and survival from first recurrence/progression (SFFR) (C) by diagnosis year, 1986–2003 vs 2004–2016.

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Table 4 Multivariate Cox regression

Stage group	Parameter	Numerator	Reference	Hazard ratio (95% CI)	P value
Progression-free survival					
Early-stage	Age at diagnosis			0.99 (0.96 to 1.03)	0.6911
	C/C+E	Yes	No	1.14 (0.61 to 2.12)	0.6756
	Radiation*	Yes	No	0.68 (0.33 to 1.38)	0.2878
	Chemotherapy cycles†	≥5 cycles	<5 cycles	1.05 (0.57 to 1.92)	0.8826
	Tumor size	>2 cm–≤4 cm	≤2 cm	3.57 (1.78 to 7.14)	**0.0003**
	Histology	Pure	Mixed	1.54 (0.87 to 2.74)	0.1392
	Surgery‡	Yes	No	2.09 (0.74 to 5.91)	0.1634
Locally advanced	Age at diagnosis			1 (0.99 to 1.02)	0.5877
	C/C+E	Yes	No	0.75 (0.5 to 1.14)	0.1771
	Nodal positivity§	Positive	Negative	1.46 (1.01 to 2.12)	**0.0434**
	Chemotherapy cycles†	≥5 cycles	<5 cycles	0.96 (0.63 to 1.45)	0.8401
	Histology	Pure	Mixed	1.24 (0.86 to 1.8)	0.2491
	Tumor size	>4 cm	≤4 cm	1.11 (0.76 to 1.62)	0.5740
Advanced	Age at diagnosis			1.01 (0.99 to 1.04)	0.2265
	C/C+E	Yes	No	0.96 (0.51 to 1.82)	0.9014
	Radiation*	Yes	No	0.35 (0.19 to 0.65)	**0.0009**
	Nodal positivity	Positive	Negative	1.66 (0.96 to 2.87)	0.0689
	Chemotherapy cycles†	≥5 cycles	<5 cycles	1.14 (0.63 to 2.05)	0.6702
	Histology	Pure	Mixed	1.28 (0.62 to 2.66)	0.5097
	Tumor size	>4 cm	≤4 cm	1.19 (0.64 to 2.2)	0.5826
Overall survival					
Early-stage	Age at diagnosis			0.99 (0.95 to 1.03)	0.6187
	C/C+E	Yes	No	0.86 (0.44 to 1.7)	0.6674
	Radiation*	Yes	No	0.57 (0.26 to 1.29)	0.1792
	Chemotherapy cycles†	≥5 cycles	<5 cycles	0.92 (0.44 to 1.93)	0.8255
	Tumor size	>2 cm -≤4 cm	≤2 cm	2.52 (1.11 to 5.68)	**0.0265**
	Histology	Pure	Mixed	1.39 (0.71 to 2.75)	0.3382
	Surgery‡	Yes	No	1.9 (0.48 to 7.51)	0.3627
Locally advanced	Age at diagnosis			1.01 (0.99 to 1.02)	0.2462
	C/C+E	Yes	No	0.75 (0.49 to 1.15)	0.1859
	Nodal positivity§	Positive	Negative	1.55 (1.06 to 2.28)	**0.0248**
	Chemotherapy cycles†	≥5 cycles	<5 cycles	0.83 (0.53 to 1.3)	0.4235
	Pure vs mixed	Pure	Mixed	1.44 (0.99 to 2.12)	0.0592
	Tumor size	T3 (>4 cm)	≤4 cm	1.03 (0.7 to 1.51)	0.8975
Advanced	Age at diagnosis			1.02 (0.99 to 1.04)	0.1675
	C/C+E	Yes	No	0.33 (0.17 to 0.63)	**0.0008**
	Radiation*	Yes	No	0.32 (0.17 to 0.6)	**0.0004**
	Nodal positivity	Positive	Negative	1.38 (0.82 to 2.34)	0.2263
	Chemotherapy cycles†	≥5 cycles	<5 cycles	0.77 (0.45 to 1.33)	0.3550
	Histology	Pure	Mixed	1.06 (0.54 to 2.07)	0.8605
	Tumor size	>4 cm	≤4 cm	3.12 (1.56 to 6.24)	**0.0013**
Survival from first recurrence or progression					
Early-stage	Age at diagnosis			0.98 (0.94 to 1.02)	0.3703

Continued

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Table 4 Continued

Survival from first recurrence or progression					
	Texas cocktail	Yes	No	0.81 (0.33 to 1.98)	0.6472
	Curative radiation	Yes	No	0.8 (0.34 to 1.9)	0.6086
	Chemotherapy cycles†	≥5 cycles	<5 cycles	0.75 (0.34 to 1.66)	0.4757
	Tumor size	>2 cm–≤4 cm	≤2 cm	0.72 (0.32 to 1.64)	0.4312
	Histology	Pure	Mixed	0.97 (0.46 to 2.04)	0.9345
	Surgery‡	Yes	No	0.35 (0.07 to 1.74)	0.2010
Locally advanced	Age at diagnosis			1.01 (1 to 1.02)	0.1866
	Texas cocktail	Yes	No	0.74 (0.44 to 1.26)	0.2698
	Nodal positivity	Positive	Negative	1.22 (0.82 to 1.82)	0.3235
	Chemotherapy cycles†	≥5 cycles	<5 cycles	0.74 (0.49 to 1.11)	0.1447
	Histology	Pure	Mixed	2.00 (1.35 to 2.98)	**0.0006**
	Tumor size	T3 (>4 cm)	≤4 cm	1.08 (0.71 to 1.63)	0.7217
Advanced	Age at diagnosis			1.01 (0.98 to 1.03)	0.5367
	Texas cocktail	Yes	No	0.52 (0.27 to 0.99)	**0.0454**
	Radiation*	Yes	No	0.44 (0.22 to 0.89)	**0.0228**
	Nodal positivity	Positive	Negative	0.91 (0.52 to 1.57)	0.7324
	Chemotherapy cycles†	≥5 cycles	<5 cycles	0.78 (0.39 to 1.59)	0.5005
	Histology	Pure	Mixed	0.94 (0.48 to 1.85)	0.8659
	Tumor size	>4 cm	≤4 cm	3.18 (1.56 to 6.46)	**0.0014**

No C/C+E is defined as no chemotherapy or other chemotherapy agents.
Texas cocktail is defined as a combination of topotecan, paclitaxel, and bevacizumab.
*Curative radiation therapy with or without chemotherapy. No curative radiation therapy is defined as chemotherapy alone or with palliative radiation therapy.
†Chemotherapy cycles is defined as the total number of cycles of C/C+E (concurrently with radiation therapy and as additional chemotherapy).
‡Surgery is defined as a simple hysterectomy, radical hysterectomy, or radical trachelectomy. No surgery is defined as not having had any of those three types of procedure.
§Nodal positivity (pelvic and/or para-aortic) based on pathology report for patients who underwent surgery (sentinel lymph node biopsy and/or pelvic lymphadenectomy and/or para-aortic lymphadenectomy) and images for patients who did not undergo surgery.
C/C+E, cisplatin/carboplatin+etoposide.

Anderson; the long time frame of the study, during which diagnostic tools and treatments changed; and the lack of data on treatment-related complications.

Implications for Practice and Future Research

A multidisciplinary team will help to generate uniform algorithms, analyze treatment strategies, and establish the feasibility of phase I trials that seek to find better treatment options for neuroendocrine cervical carcinoma. Although restricted by the rarity of the disease, guidelines[8 17 18] have been published in recent years to guide physicians in formulating treatment recommendations for patients with neuroendocrine cervical cancer, and these may contribute to improved oncologic outcomes.

At MD Anderson, a phase II, single-center, open-label, single-arm clinical trial is underway of Cadonilimab (AK104) for previously treated patients with recurrent or metastatic high-grade neuroendocrine cervical cancer (NCT05063916). AK104 is a bispecific antibody that simultaneously binds to human programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), cell surface receptors expressed on activated T-cells, and blocks both PD-1 and CTLA-4, suppressing the immune system and activating anti-tumor immunity. Based on data for AK104 and the promising evidence of clinical activity and safety of other similar drugs (nivolumab plus ipilimumab) across a range of tumor types in early clinical trials, we hypothesize that AK104 will be effective in patients with recurrent or metastatic high-grade neuroendocrine cervical cancer as a second-line or third-line treatment. Eighteen patients will be enrolled. There is a significant unmet need for improved systemic therapies for patients with recurrent or metastatic high-grade neuroendocrine cervical cancer.

CONCLUSIONS

In patients with neuroendocrine cervical carcinoma, oncologic outcomes for patients with early-stage disease are favorable; however, even with combined treatment strategies, more than half of patients will experience recurrence or progression after primary treatment, with most recurrences occurring during the first 3 years after treatment completion. Recurrences are mostly distant. For early-stage disease, tumor size >2 cm is an independent predictor of progression and death, while for locally advanced disease, lymph

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node compromise and pure histology are associated with worse survival. For advanced disease, radiation therapy with curative intent is a predictor of improved survival. Over a 30-year period, survival has increased only for patients with advanced disease.

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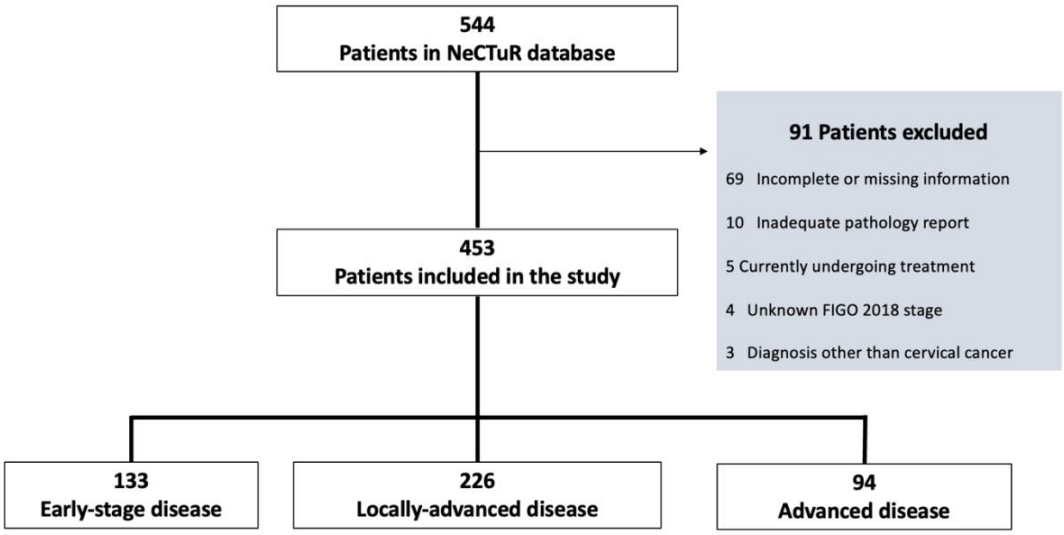
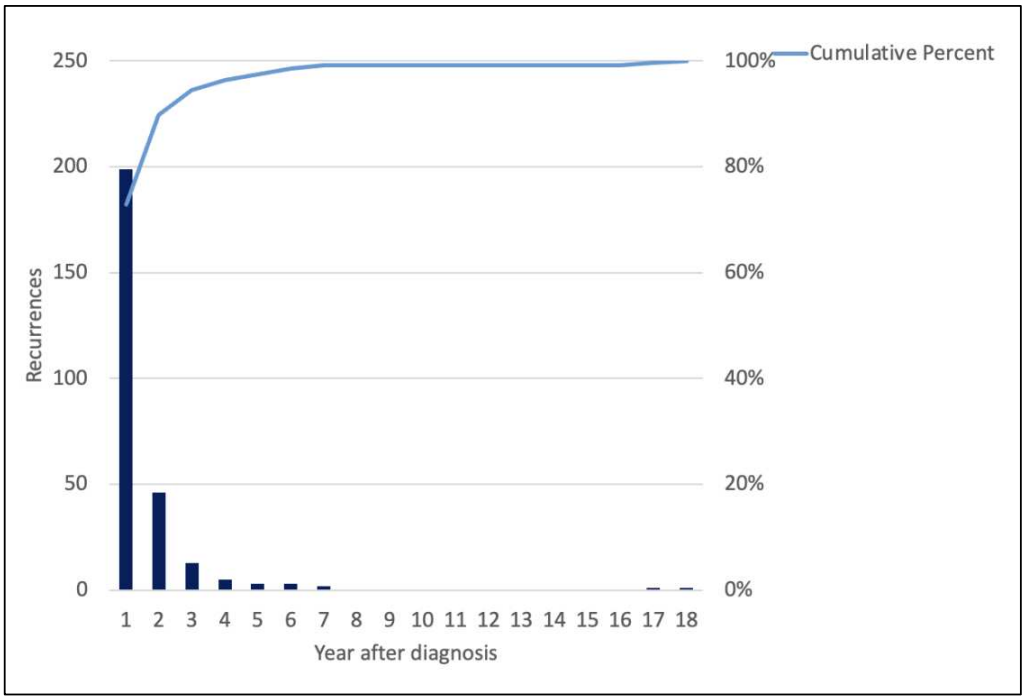
Supplemental Material

Supplemental Figure 1: Consort Diagram



Supplemental Figure 2: Time to first recurrence.



Supplemental Figure 3: Progression-free survival (PFS) (A, D, and G), overall survival (OS) (B, E, and H), and survival from first recurrence or progression (SFFR) (C, F, and I) by stage group for patients diagnosed in 1986-2003 and 2004-2016.