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J Gynecol Oncol. 2023 Jul;34(4):e50
https://doi.org/10.3802/jgo.2023.34.e50
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

RB1 alteration and poor prognosis in women with high-grade neuroendocrine carcinoma of the uterine cervix: a NeCTuR study

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Received: Jan 17, 2023
Accepted: Jan 18, 2023
Published online: Feb 9, 2023

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ABSTRACT

Objective: To describe the gene alteration status in high-grade neuroendocrine cervical carcinoma (NECC) specimens and to explore the potential association of unique gene alterations with survival.
Methods: Results from tumor-based molecular testing on specimens from women with high-grade NECC in the Neuroendocrine Cervical Tumor Registry were reviewed and analyzed. Tumor specimens could be from primary or metastatic sites and obtained at initial diagnosis, during treatment, or at recurrence.
Results: Molecular testing results were available for 109 women with high-grade NECC. The genes most frequently mutated were *PIK3CA* (mutated in 18.5% of patients), *TP53* (17.4%), and *MYC* (14.5%). Other targetable alterations identified were alterations in *KIT* (7.3%), *KRAS* (7.3%), and *PTEN* (7.3%). Women with tumors having an *RB1* alteration (6.4%) had a median overall survival (OS) of 13 months, compared to 26 months for women with tumors that did not have an *RB1* alteration (p=0.003). None of the other genes evaluated were shown to be associated with OS.
Conclusion: Although no individual alteration was found in a majority of tumor specimens from patients with high-grade NECC, a large proportion of women with this disease will have at least one targetable alteration. Treatments based on these gene alterations may offer additional targeted therapies for women with recurrent disease, who currently have very limited therapeutic options. Patients with tumors that harbor *RB1* alterations have decreased OS.

Keywords: Cervical Cancer; Neuroendocrine Carcinoma

Synopsis

Treatment options are limited for women with recurrent neuroendocrine cervical cancer, and molecular testing may increase opportunities for treatment with targeted therapies. We reviewed molecular tumor testing results in 109 women with high-grade neuroendocrine cervical cancer, the largest such study reported to date. We identified high rates of alterations in genes including *PIK3CA*, *MYC*, *KIT*, *KRAS*, and *PTEN*, which may offer expanded therapeutic options for women with recurrent disease. We also found that the presence of RB1 alterations was associated with shorter overall survival.

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Funding

This study was supported by the National Cancer Institute under award number P30CA016672, which supports the MD Anderson Cancer Center Clinical Trials Office, and by Small/Large Cell Carcinoma of the Cervix: Sisters United.

Conflict of Interest

Michael Frumovitz has research support from Astra Zeneca and GlaxoSmithKline and is a speaker/consultant for Stryker. R. Tyler Hillman receives research support from Sumitomo Dainippon Pharma. The remaining authors have no disclosures to report.

Author Contributions

Conceptualization: F.A., H.R.T., F.M.; Data curation: F.A., S.G.; Formal analysis: C.G.; Project administration: G.N.R.; Supervision: H.R.T.; Validation: S.G.; Writing - original draft: F.A.; Writing - review & editing: F.M.

INTRODUCTION

Neuroendocrine carcinomas of the gynecological tract are rare entities, and the uterine cervix is the most commonly affected organ. Around 1.0% to 1.5% of all cervical cancers are neuroendocrine carcinomas, which have an annual incidence of 0.06 case per 100,000 women [1,2]. Compared to the more common squamous cell carcinoma and adenocarcinoma of the cervix, neuroendocrine carcinoma of the cervix (NECC) is more likely to follow an aggressive course and is associated with significantly worse survival rates [1,2].

The World Health Organization classifies gynecological neuroendocrine carcinomas into 2 categories: low-grade carcinomas, which include carcinoid and atypical carcinoid tumors, and high-grade carcinomas, which include small cell and large cell carcinomas. Of all cases of NECC, 80% are small cell carcinomas and 12% are large cell carcinomas [3]. Most of the remaining cases are high-grade neuroendocrine tumors not otherwise specified. Primary low-grade NECC is exceedingly rare.

NECC is associated with a poor prognosis, with a mean recurrence-free survival of 16 months and a mean overall survival (OS) of 40 months [4]. Stecklein et al. [5] showed that patients with large cell NECC had better median OS (153 months) than patients with small cell or unclassified NECC (21 months). Tangjitgamol et al. [6] reported that among women with NECC, lack of immunohistochemical expression of HER-2/neu was associated with shorter survival (14.2 months) than positive expression.

Genomic alterations of NECC have been previously reported. Our group previously analyzed hotspot alterations in 44 patients with high-grade NECC and found that *PIK3CA* (altered in 18% of patients), *KRAS* (14%), and *TP53* (11%) were the most commonly altered genes [7].

The objective of this study was to update the gene alteration status of high-grade NECC in a larger cohort and to explore the potential association of unique gene alterations with survival.

MATERIALS AND METHODS

We searched the Neuroendocrine Cervical Tumor Registry (NeCTuR) at our institution to identify patients with high-grade NECC who had tumor-based molecular testing performed. NeCTuR is an Institutional Review Board (IRB)-approved registry that is voluntary, international, and open to patients undergoing treatment, survivors, and legal representatives of deceased patients. The registry collects a wide range of data on patients with high-grade NECC. Participants give written informed consent, are active in the registry for up to 10 years, and agree to allow the research team to collect information from their medical record. The study detailed in this manuscript is a retrospective analysis of patients from the registry who met the study inclusion criteria. This study was approved by the IRB at University of Texas MD Anderson Cancer Center (PA12-1006).

Inclusion criteria for this study included age over 18 years, primary high-grade NECC confirmed by a pathologist, and tumor-based molecular testing performed on primary or metastatic NECC at any point during treatment. Patients who had molecular tests performed only on blood, saliva, or any other type of tissue other than formalin-fixed, paraffin-embedded tissue were excluded from analysis. Patients who had a diagnosis of carcinoid

tumor, atypical carcinoid tumor, carcinoma with neuroendocrine features, or carcinoma with neuroendocrine differentiation were also excluded. NECC tissue samples from any organ (cervix or site of metastasis), at any point during treatment (at diagnosis, during treatment, or after any recurrence), and regardless of the patient's treatment status at sample collection (untreated or treated) were included. Study data were collected and managed using REDCap electronic data capture tools hosted at MD Anderson.

Thirteen different molecular sequencing panel tests were performed on NECC tissue samples from patients in the study cohort and had results available for review. The tests included MD Anderson CLIA-certified tests, FoundationOne, Caris Mollecular Intelligence, MSK-IMPACT, and Invitae (Multi-Center Panel). Each panel test and panel test version analyzed different genes and different numbers of genes, ranging from 46 to 400 genes per test.

Genes were classified as altered if 1) they were found to have any type of alteration (deletion, insertion, amplification, rearrangement, or point alteration) except a silent alteration and 2) the alteration was not a variant of unknown significance, a variant of uncertain origin, or a probable germline polymorphism.

A total of 303 unique genes were tested by at least one of the 13 panel tests. Of these, 45 genes were tested fewer than 10 times and were excluded from further analyses. Altogether, 258 unique genes were tested in at least 10 patients in the cohort and included in the analysis.

Survival analysis are reported as hazard ratio (HR) with 95% confidence interval (CI) and calculated using adjusted Cox regression models. OS was defined as the time from diagnosis to death from any cause or the last date of contact for surviving participants. OS was modeled as a function of gene alteration status (altered or not altered for the tested gene), age at diagnosis, body mass index (BMI) at diagnosis, International Federation of Gynecology and Obstetrics stage at diagnosis (modified stages I to IV), and Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis. BMI and ECOG performance status are important potential predictors of outcome. BMI results were missing for 20% of patients and ECOG performance status results were missing for 25%, so we performed multiple imputations using the fully conditional specification method of Van Buuren to create 100 datasets [8]. We used a Bonferroni significance cutoff of 0.005 based on the 10 genes analyzed. Statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

From more than 500 women who are participants of our registry, 109 women met the study inclusion criteria. For these 109 women, a total of 127 results from 13 panel tests were available. Nine women had multiple tests, and for each of these 9 women, the test results for each gene were coalesced into a single positive or negative (altered or not altered) result, i.e., if a specific gene was identified as altered on any test, that gene was considered altered.

Patient characteristics are summarized in **Table 1**. The median age at diagnosis was 37 years (range 24–66 years). At the time of diagnosis, 36 women (33%) had stage I, 7 (6%) had stage II, 30 (28%) had stage III, and 36 (33%) had stage IV tumors.

https://doi.org/10.3802/jgo.2023.34.e50

Table 1. Demographics and clinicopathological variables

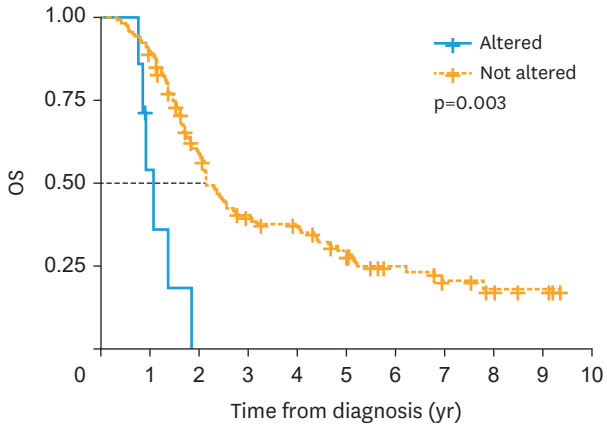
Characteristic	Value (n=109)
Age (yr)	37 (24–66)
BMI (kg/m^2)	26.2 (17.4–47.5)
Unknown	22
Race	
Asian	12 (11)
Black or African American	6 (5)
White	84 (77)
Other	2 (2)
Unknown	5 (5)
Ethnicity	
Hispanic or Latinx*	12 (11)
Not Hispanic or Latinx	88 (81)
Unknown	9 (8)
ECOG performance status at diagnosis	
0	76 (70)
1	5 (4)
2	1 (1)
Unknown	27 (25)
Stage	
I	36 (33)
II	7 (6)
III	30 (28)
IV	36 (33)
Specimen type	
Naïve of treatment	66 (61)
Received treatment	35 (31)
Multiple†	5 (5)
Unknown	3 (3)

Values are presented as median (range) or number (%).
BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.
*Includes patients who self-identified as or whose medical records indicated ethnicity as Hispanic, Latina, Latine, Latino, or Latinx.
†Both pretreatment and posttreatment samples were tested in the same patient.

Of the 258 genes included in the analysis, 10 were altered in at least 5 patients. When only those patients with tests that included the genes of interest were used as the denominator, the most frequently altered gene was *PIK3CA* (altered in 18.5% of patients), followed by *TP53* (17.4%), *MYC* (14.5%), *KIT* (7.3%), *KRAS* (7.3%), *PTEN* (7.3%), *RB1* (6.4%), *CTNNB1* (5.0%), *GNAS* (4.6%), and *MET* (4.6%).

Women with tumors having an *RB1* alteration had lower median OS than women without *RB1* alterations (13 months vs. 26 months, p=0.003) (**Fig. 1**). None of the other genes evaluated were associated with OS (**Table 2**). Cox regression analysis showed women with high-grade NECC that harbored an *RB1* alterations were 4.3 times more likely to die of their disease compared to women without *RB1* alterations (HR=4.34; 95% CI=1.66–11.32; p=0.003). No other genes had a significant effect on OS in multivariate analysis (**Table 3**).

The mean age at diagnosis of the 7 women who had *RB1* alteration was 43 years (27–55) all of which had either advanced or locally advanced stage at diagnosis (**Table 4**). From these women with *RB1* alterations, 5 (71%) had also *TP53* alterations, while 2 had no other alterations. The types of *RB1* alterations detected included point mutations (missense and frameshift mutations), a complex alteration (deletion plus insertion), and loss of exons. One patient was found to have a bi-allelic *RB1* alteration, while 2 different women shared the same point mutation that caused a missense mutation in codon 137, exon 4, which led to an



No. at risk											
Altered	7	3	0	0	0	0	0	0	0	0	0
Not altered	102	90	53	33	29	21	12	8	5	3	0

Fig. 1. OS of women with high-grade neuroendocrine cervical carcinoma with or without *RB1* alteration.
OS, overall survival.

Table 2. Kaplan-Meier OS results by gene alteration status

Gene	Group	OS (mo)	p-value*	Difference between 2 groups (mo)
CTNNB1	Altered	15.79 (11.51–NA)	0.068	10.13
	Not altered	25.92 (22.34–33.59)		
GNAS	Altered	60.00 (32.66–NA)	0.178	34.51
	Not altered	25.49 (22.04–30.76)		
KIT	Altered	21.35 (18.49–NA)	0.908	4.60
	Not altered	25.95 (22.37–33.59)		
KRAS	Altered	32.66 (25.49–NA)	0.967	7.43
	Not altered	25.23 (21.35–31.02)		
MET	Altered	NA (22.40–NA)	0.202	NA
	Not altered	25.72 (22.04–31.02)		
MYC	Altered	16.99 (13.88–NA)	0.325	8.50
	Not altered	25.49 (19.80–53.09)		
PIK3CA	Altered	25.49 (19.87–NA)	0.451	0.43
	Not altered	25.92 (22.37–32.66)		
PTEN	Altered	18.50 (11.28–NA)	0.325	7.45
	Not altered	25.95 (22.37–36.74)		
RB1	Altered	12.99 (10.62–NA)	<0.001	13.00
	Not altered	25.99 (23.85–36.74)		
TP53	Altered	20.26 (13.42–62.93)	0.264	5.69
	Not altered	25.95 (22.40–38.32)		

Values are presented as median (95% confidence interval).
NA, not available; OS, overall survival.
*Log-rank test.

exchange of glutamate to aspartate. Of the 7 patients with *RB1* alterations, 2 had large cell NECC, 4 had small cell NECC, and one had high-grade NECC, not otherwise specified. There was no relationship between *RB1* alteration and histologic subtype, such as small cell versus large cell or pure versus mixed. The mean OS was 13.5 months among these women.

Of the109 women in our cohort, 57 (52.3%) had human papillomavirus (HPV) data available from mRNA, DNA, in situ hybridization tests results or were reported by the pathologist (unspecified method). Of these, 43 women (75.4%) were found to have HPV positive tumors. Although most test reports did not specify the HPV genotype found, 6 of them described genotype 18 positivity. Our findings showed that all patients who had HPV data available and

https://doi.org/10.3802/jgo.2023.34.e50

Table 3. Adjusted Cox regression analysis of impact of alterations on overall survival

Gene	No. of patients			HR (95% CI)*,†	p-value‡
	Total	Not altered	Altered		
CTNNB1	101	96	5	1.45 (0.51–4.16)	0.486
GNAS	108	103	5	0.57 (0.19–1.73)	0.316
KIT	109	101	8	1.20 (0.48–3.02)	0.696
KRAS	109	101	8	1.25 (0.53–2.94)	0.601
MET	109	104	5	0.83 (0.21–3.18)	0.779
MYC	55	47	8	2.65 (0.96–7.30)	0.059
PIK3CA	108	88	20	0.73 (0.37–1.44)	0.360
PTEN	109	101	8	1.13 (0.44–2.91)	0.791
RB1	109	102	7	4.34 (1.66–11.32)	0.003
TP53	109	90	19	1.57 (0.84–2.92)	0.154

CI, confidence interval; HR, hazard ratio.
*Adjustment variables are age at diagnosis, International Federation of Gynecology and Obstetrics stage at diagnosis, Eastern Cooperative Performance Group performance status, and body mass index at diagnosis.
†All comparisons are altered vs. not altered.
‡Calculated using Barnard and Rubin (1999) method of adjusted degrees of freedom [13].

Table 4. Clinical data and OS in women with *RB1* alterations

Age at diagnosis	FIGO stage	Histologic subtype	Other altered genes	*RB1* alteration in standard nomenclature	Mean OS (mo)
27	IIIC1r	Small cell	None	c.411A>T (p.E137D)	22.3
46	IVB	Small cell	*BAP1*, *MYC*, *TP53*	c.1072C>T (p.R358*) and c.1174_1189delinsACCTG (p.A392fs*10)	8.2
33	IVB	Small cell	*CCNE1*, *TP53*	c.958C>T (p.R320*)	12.9
55	IIIC2r	Small cell	*MYC*, *TP53*	c.1183C>T (p.Q395*)	16.8
45	IVB	Large cell	*ERCC4*, *PTEN*, *MARCA4*, *TP53*	Loss of exons 3–27	11.2
46	IVB	High-grade NOS	*TP53*	E737fs*7	11.1
52	IVB	Large cell	*FGFR2*, *KIT*	c.411A>T (p.E137D)	10.6

The symbol "*" stands for 3' untranslated regions.
FIGO, International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; OS, overall survival.

had an *RB1* alteration (0/3) were found to be HPV negative. Although HPV data was limited, women with *KIT* alterations were more frequently found to have an HPV positive test (5/6), other frequently altered genes with HPV positivity included *PIK3CA* (8/10), *MET* (4/5), *KRAS* (3/4), *MYC* (4/6), *TP53* (8/14), *GNAS* (2/4), *PTEN* (2/4), and *CTNNB1* (1/3).

DISCUSSION

In this study, we identified a number of targetable alterations among the women in our cohort, which highlights opportunities for targeted therapy. We also found that among patients with high-grade NECC, the presence of *RB1* alterations in primary or metastatic tumors was associated with significantly worse OS. At this time, *RB1* targeted therapy does not exist. Originally *CDK4/6* inhibitors were thought to target the *RB1* pathway but unfortunately *RB1* mutations were ultimately determined to bestow resistance to these drugs [9]. Up and downstream *RB1* pathway targeted therapies are currently being studied and hopefully may become available soon. The commonly altered genes in our cohort (*PIK3CA*, *TP53*, and *MYC*) were previously described in the literature for NECC, except for *KIT*.

Some non-treatment-related factors that have been formerly found to be associated with decreased survival and worse prognosis in patients with NECC are advanced-stage disease, older age at diagnosis, stromal invasion, small cell or unclassified NECC, immunohistochemical expression of HER-2/neu, and alterations in the *TP53* pathway [1,3-5,10].

Table 5. Incidence of common gene alterations in high-grade neuroendocrine cervical carcinoma

Gene	Eskander et al. (2020) [11] (n=97)	Cimic et al. (2021) [12] (n=62)	Pei et al. (2021) [10] (n=49)	Current study (n=109)	Total	Potential targeted therapies
PIK3CA	19.6	17.7	10.2	18.5	17.4	*PI3K*, *mTOR*, and *AKT* inhibitors
TP53	15.5	17.7	12.2	17.4	16.4	*WEE-1* and exportin inhibitors
MYC	15.5	3.2	14.3	14.5	13.4	None
PTEN	14.4	9.7	6.1	7.3	9.8	*PI3K*, *mTOR*, and *AKT* inhibitors
KRAS	8.2	11.3	10.2	7.3	8.8	*MEK* inhibitors
IRS2	3.1	NR	14.3	NR	6.9	None
ARID1A	9.3	NR	4.1	2.1	6.2	None
RB1	8.3	3.2	4.1	6.4	6.0	None
RICTOR	4.1	NR	10.2	4.4	5.7	None
SOX2	5.2	NR	6.1	NR	5.5	None
BRCA2	6.2	NR	4.1	3.7	5.0	*PARP1* and *PARP2* inhibitors
CTNNB1	4.1	4.8	NR	5.0	4.6	None
GNAS	4.1	NR	NR	4.6	4.4	None
KIT	1.0	NR	NR	7.3	4.4	Kinase inhibitors
ERBB2	4.1	1.6	4.1	8.3	3.6	*EGFR*, *ERBB2*, *ERBB4*, *BTK*, and *KDR* inhibitors, and *ERBB2* monoclonal antibodies

Values are presented as percentages. Total percentages represent weighted averages based on number of alterations in each study.
NR, not reported.

Our finding that *PIK3CA* and *TP53* were the most frequently altered genes in high-grade NECC (**Table 5**) is in line with findings from our previous, smaller study [7], which showed that the most common hotspot alterations in women with small cell NECC were alterations in *PIK3CA*, *KRAS,* and *TP53*. In contrast, the high rate of alteration of *MYC* in the current study was not noted in our earlier study. Our results are generally in line with the results of 3 recently published analyses of molecular alterations in high-grade NECC [10-12], as summarized in **Table 5**. Eskander et al. [11] reported results of molecular sequencing in 97 patients with high-grade NECC and found that the most frequently altered genes were *PIK3CA* (19.6%), *TP53* (16.5%), *MYC* (15.5%), and *PTEN* (14.4%), with a total of 294 genomic alterations identified in 109 genes. Cimic et al. [12] reported alterations in *PIK3CA* (17.7%), *TP53* (17.7%), *KRAS* (11.3%), *PTEN* (9.7%), *CTNNB1* (4.8%), *MYC* (3.2%), *RB1* (3.2%), *FGFR2* (3.2%), and *HNF1A* (3.2%) in 62 high-grade NECC tumor specimens. Similarly, Pei et al. [10] ran a next-generation sequencing analysis in 51 women with small cell NECC and found that the most frequently altered genes were *MYC* (14.3%), *IRS2* (14.2%), *TP53* (12.2%), *KRAS* (10.2%), *PIK3CA* (10.2%), *RICTOR* (10.2%), *KTM2D* (8.16%), *PTEN* (6.1%), *ATM* (6.12%), *ATRX* (6.12%), and *PRKDC* (6.12%). After clustering of genes by gene family and pathway, the 3-year OS was lower in women who had alterations in the *TP53* pathway (*TP53*, *ATM*, *MDM4*) than in those with wild-type genes in the same pathway (33.5% vs. 59.9%). A study involving whole exome sequencing of NECC specimens also confirmed that the most frequently altered genes were *PIK3CA* (27%), *KRAS/GNAS* (13%), and *TP53* (13%) [13].

In addition to providing information about rates of gene alterations, our current study showed that *RB1* alterations, but not alterations in other genes, may adversely affect OS in women with high-grade NECC. *RB1* encodes for a tumor suppressor protein that prevents G1-to-S-phase progression in cell division. HPV infection in cervical cells produces an oncoprotein that is known to inactivate *RB1*. HPV infection has been documented in around 85% of cases of NECC, and HPV16 and HPV18 are the types most commonly found [14,15].

RB1 alterations are also found in patients without HPV infection and in non-neuroendocrine carcinomas. Harms et al. [16] found that although neuroendocrine carcinoma of the skin, also known as Merkel cell carcinoma, is associated with *RB1* alterations, *RB1* alterations in

this disease are mostly seen in non-Merkel cell polyomavirus–infected skin cells. Rickman et al. [17] found that *RB1* loss was associated with poor OS in multiple non-neuroendocrine cancers, including osteosarcoma, glioblastoma, and lung cancer, and can predict therapy resistance in small cell lung cancer, pancreatic cancer, and breast cancer. They also reported that *RB1* bi-allelic loss was associated with decreased progression-free survival in 33 types of cancer and decreased OS in metastatic prostate cancer.

Neuroendocrine carcinomas are most frequently found in the gastrointestinal tract, pancreas, and lungs, and is not uncommon to see NECC treatment therapies to be based on their regimens. Yachida et al. [18] found that gastrointestinal neuroendocrine carcinomas frequently showed alterations in both *TP53* and *RB1*, with *RB1* alterations being more prevalent in small cell than in large cell NEC, suggesting different oncogenic mechanisms between these 2 subtypes. Rickman et al. [17] found that co-alteration of *RB1* and *TP53* is a hallmark finding in poorly differentiated NEC, present in up to 80% of cases, but is uncommon in well-differentiated NECs. Although scarce data, both in the literature and in our cohort, limit our ability to compare our results with those previously described in the literature, we also observed frequent co-alteration of *RB1* and *TP53*.

Limitations of our study include the large variety of panels tests performed and the fact that each included different genes and alteration locations within each gene. In addition, we were not able to conduct sub analyses according to the source of tumor tissue (primary tumor or metastasis) or the patient's treatment status (treatment-naïve or treated), and thus we were not able to determine whether there were any differences in alteration status between tumor sites or between different points in patients' clinical course.

ACKNOWLEDGEMENTS

We thank Stephanie Deming, Research Medical Library, MD Anderson Cancer Center, for editing the manuscript.

REFERENCES

1. Chen J, Macdonald OK, Gaffney DK. Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix. Obstet Gynecol 2008;111:1394-402.
PUBMED | CROSSREF
2. Margolis B, Tergas AI, Chen L, Hou JY, Burke WM, Hu JC, et al. Natural history and outcome of neuroendocrine carcinoma of the cervix. Gynecol Oncol 2016;141:247-54.
PUBMED | CROSSREF
3. Salvo G, Gonzalez Martin A, Gonzales NR, Frumovitz M. Updates and management algorithm for neuroendocrine tumors of the uterine cervix. Int J Gynecol Cancer 2019;29:986-95.
PUBMED | CROSSREF
4. Tempfer CB, Tischoff I, Dogan A, Hilal Z, Schultheis B, Kern P, et al. Neuroendocrine carcinoma of the cervix: a systematic review of the literature. BMC Cancer 2018;18:530.
PUBMED | CROSSREF
5. Stecklein SR, Jhingran A, Burzawa J, Ramalingam P, Klopp AH, Eifel PJ, et al. Patterns of recurrence and survival in neuroendocrine cervical cancer. Gynecol Oncol 2016;143:552-7.
PUBMED | CROSSREF
6. Tangjitgamol S, Ramirez PT, Sun CC, See HT, Jhingran A, Kavanagh JJ, et al. Expression of HER-2/neu, epidermal growth factor receptor, vascular endothelial growth factor, cyclooxygenase-2, estrogen

receptor, and progesterone receptor in small cell and large cell neuroendocrine carcinoma of the uterine cervix: a clinicopathologic and prognostic study. Int J Gynecol Cancer 2005;15:646-56.
PUBMED | CROSSREF

7. Frumovitz M, Burzawa JK, Byers LA, Lyons YA, Ramalingam P, Coleman RL, et al. Sequencing of mutational hotspots in cancer-related genes in small cell neuroendocrine cervical cancer. Gynecol Oncol 2016;141:588-91.
PUBMED | CROSSREF
8. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16:219-42.
PUBMED | CROSSREF
9. Knudsen ES, Pruitt SC, Hershberger PA, Witkiewicz AK, Goodrich DW. Cell cycle and beyond: exploiting new RB1 controlled mechanisms for cancer therapy. Trends Cancer 2019;5:308-24.
PUBMED | CROSSREF
10. Pei X, Xiang L, Chen W, Jiang W, Yin L, Shen X, et al. The next generation sequencing of cancer-related genes in small cell neuroendocrine carcinoma of the cervix. Gynecol Oncol 2021;161:779-86.
PUBMED | CROSSREF
11. Eskander RN, Elvin J, Gay L, Ross JS, Miller VA, Kurzrock R. Unique genomic landscape of high-grade neuroendocrine cervical carcinoma: implications for rethinking current treatment paradigms. JCO Precis Oncol 2020;4:PO.19.00248.
PUBMED | CROSSREF
12. Cimic A, Vranic S, Arguello D, Contreras E, Gatalica Z, Swensen J. Molecular profiling reveals limited targetable biomarkers in neuroendocrine carcinoma of the cervix. Appl Immunohistochem Mol Morphol 2021;29:299-304.
PUBMED | CROSSREF
13. Hillman RT, Cardnell R, Fujimoto J, Lee WC, Zhang J, Byers LA, et al. Comparative genomics of high grade neuroendocrine carcinoma of the cervix. PLoS One 2020;15:e0234505.
PUBMED | CROSSREF
14. Alejo M, Alemany L, Clavero O, Quiros B, Vighi S, Seoud M, et al. Contribution of human papillomavirus in neuroendocrine tumors from a series of 10,575 invasive cervical cancer cases. Papillomavirus Res 2018;5:134-42.
PUBMED | CROSSREF
15. Castle PE, Pierz A, Stoler MH. A systematic review and meta-analysis on the attribution of human papillomavirus (HPV) in neuroendocrine cancers of the cervix. Gynecol Oncol 2018;148:422-9.
PUBMED | CROSSREF
16. Harms PW, Harms KL, Moore PS, DeCaprio JA, Nghiem P, Wong MK, et al. The biology and treatment of Merkel cell carcinoma: current understanding and research priorities. Nat Rev Clin Oncol 2018;15:763-76.
PUBMED | CROSSREF
17. Rickman DS, Beltran H, Demichelis F, Rubin MA. Biology and evolution of poorly differentiated neuroendocrine tumors. Nat Med 2017;23:1-10.
PUBMED | CROSSREF
18. Yachida S, Totoki Y, Noë M, Nakatani Y, Horie M, Kawasaki K, et al. Comprehensive genomic profiling of neuroendocrine carcinomas of the gastrointestinal system. Cancer Discov 2022;12:692-711.
PUBMED | CROSSREF