Gynecologic Oncology 141 (2016) 247–254

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Natural history and outcome of neuroendocrine carcinoma of the cervix

Benjamin Margolis [a,f], Ana I. Tergas [a,c,d,f], Ling Chen [a], June Y. Hou [a,d,f], William M. Burke [a,d,f], Jim C. Hu [e,f], Cande V. Ananth [a,c], Alfred I. Neugut [b,c,d,f], Dawn L. Hershman [b,c,d,f], Jason D. Wright [a,d,f,*]

[a] Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, United States
[b] Department of Medicine, Columbia University College of Physicians and Surgeons, United States
[c] Department of Epidemiology, Mailman School of Public Health, Columbia University, United States
[d] Herbert Irving Comprehensive Cancer Center, Columbia University College of Physicians and Surgeons, United States
[e] Department of Urology, Weill Cornell Medical College, United States
[f] New York Presbyterian Hospital, United States

HIGHLIGHTS

- NECC are aggressive tumors associated with an increased risk of death.
- Survival is inferior for NECC compared to squamous cell tumors for women with both early and advanced stage disease.
- Further studies are needed to improve therapeutic options for NECC.

ARTICLE INFO

Article history:
Received 5 January 2016
Received in revised form 30 January 2016
Accepted 8 February 2016
Available online 9 February 2016

Keywords:
Cervical cancer
Neuroendocrine carcinoma
Squamous cell carcinoma
Cervical carcinoma
Cervix

ABSTRACT

Objective. Neuroendocrine carcinomas of the cervix (NECC) are rare and thought to be aggressive. We performed a population-based analysis to examine the natural history, treatment patterns and outcomes of women with NECC compared to squamous cell carcinoma (SCCC) and adenocarcinoma (AC) of the cervix.

Methods. The National Cancer Database (NCDB) was utilized to identify women with NECC, SCCC, and AC treated from 1998 to 2011. Clinical, demographic, and treatment characteristics were compared between the groups. The association between tumor histology and survival was examined using Kaplan-Meier analyses and multivariable Cox proportional hazards regression models.

Results. We identified 127,332 patients, including 1,896 (1.5%) with NECC and 101,240 (79.5%) with SCCC and 24,196 (19.0%) with AC. Patients with NECC were younger, more often white, commercially insured, and diagnosed with metastatic disease at presentation compared to women with SCCC. Patients with early-stage NECC were more likely to receive adjuvant chemotherapy and radiation after surgery ($P < 0.05$ for both). In multivariable models stratified by stage and adjusted for clinical and demographic characteristics, the risk of death was higher for patients with NECC compared to SCCC for all stages of disease: stages IB–IIA (HR = 2.96; 95% CI, 2.48–3.52), stages IIB–IVA (HR = 1.70; 95% CI, 1.45–1.99) and stage IVB (HR = 1.14; 95% CI, 0.91–1.43).

Conclusion. NECC are aggressive tumors associated with an increased risk of death. Survival is inferior for NECC compared to squamous cell tumors for women with both early and advanced stage disease.

1. Introduction

Neuroendocrine carcinomas of the cervix (NECC) are rare tumors that comprise 2–5% of cervical malignancies [1–4]. This category of tumors is comprised of small cell, large cell, carcinoid and atypical carcinoid histologic types. Small cell and large cell tumors are poorly differentiated and are characterized by a high mitotic rate, necrosis, frequent lymphovascular space involvement and a more aggressive clinical course. Carcinoid and atypical carcinoid tumors are well-differentiated, are thought to be derived from neural crest cells, and are extremely rare [1]. Atypical carcinoid tumors display significant nuclear atypia and are poorly studied.

In general, NECCs are characterized by early spread beyond the cervix and a poor prognosis. Five-year survival rates for NECC are reported at 0–30% [5]. Given that NECC is uncommon, data to guide clinical decision-making is limited and treatment regimens are often extrapolated from neuroendocrine tumors from other sites. Therapy for early stage disease involves radical surgery for tumors <4 cm, often in combination with adjuvant chemotherapy. Advanced

* Corresponding author at: Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, 161 Fort Washington Ave, 8th Floor, New York, NY 10032, United States.
E-mail address: jw2459@columbia.edu (J.D. Wright).

http://dx.doi.org/10.1016/j.ygyno.2016.02.008
0090-8258/

stage disease is treated with combination chemotherapy and radiation. The chemotherapy regimens most commonly utilized include cisplatin and etoposide (EP) or vincristine, doxorubicin, and cyclophosphamide (VAC). Prior work has shown that among women with NECC chemotherapy improves survival, particularly for locally advanced stage disease [6].

Table 1
Descriptive characteristics of the cohort stratified by histology.

	Squamous cell		Adenocarcinoma		Neuroendocrine		P-value
	N	(%)	N	(%)	N	(%)	
All	101,240	(79.5)	24,196	(19.0)	1896	(1.5)	
Year of diagnosis							<0.001
1998	8567	(8.5)	1752	(7.2)	130	(6.9)	
1999	8211	(8.1)	1653	(6.8)	112	(5.9)	
2000	8138	(8.0)	1695	(7.0)	126	(6.7)	
2001	7744	(7.7)	1623	(6.7)	118	(6.2)	
2002	7440	(7.4)	1626	(6.7)	138	(7.3)	
2003	6982	(6.9)	1529	(6.3)	141	(7.4)	
2004	6848	(6.8)	1585	(6.6)	118	(6.2)	
2005	6894	(6.8)	1633	(6.8)	133	(7.0)	
2006	6864	(6.8)	1732	(7.2)	135	(7.1)	
2007	6884	(6.8)	1746	(7.2)	129	(6.8)	
2008	6869	(6.8)	1820	(7.5)	162	(8.5)	
2009	6898	(6.8)	1985	(8.2)	142	(7.5)	
2010	6513	(6.4)	1922	(7.9)	144	(7.6)	
2011	6388	(6.3)	1895	(7.8)	168	(8.9)	
Age							<0.001
<30	5410	(5.3)	1291	(5.3)	213	(11.2)	
30–39	20,677	(20.4)	6055	(25.0)	377	(19.9)	
40–49	27,069	(26.7)	6926	(28.6)	409	(21.6)	
50–59	20,850	(20.6)	4343	(18.0)	377	(19.9)	
60–69	13,961	(13.8)	2754	(11.4)	259	(13.7)	
≥70	13,273	(13.1)	2827	(11.7)	261	(13.8)	
Race							<0.001
White	63,615	(62.8)	17,992	(74.4)	1296	(68.4)	
Black	18,444	(18.2)	2124	(8.8)	293	(15.5)	
Hispanic	13,237	(13.1)	2601	(10.8)	195	(10.3)	
Other	4642	(4.6)	1.141	(4.7)	102	(5.4)	
Unknown	1302	(1.3)	338	(1.4)	10	(0.5)	
Insurance status							<0.001
Commercial	45,845	(45.3)	15,057	(62.2)	1006	(53.1)	
Medicare	18,452	(18.2)	3746	(15.5)	366	(19.3)	
Medicaid	19,791	(19.6)	2598	(10.7)	270	(14.2)	
Uninsured	10,978	(10.8)	1542	(6.4)	152	(8.0)	
Other	1001	(1.0)	241	(1.0)	11	(0.6)	
Unknown	5173	(5.1)	1012	(4.2)	91	(4.8)	
Region							<0.001
Northeast	18,606	(18.4)	4624	(19.1)	361	(19.0)	
Midwest	22,946	(22.7)	5644	(23.3)	391	(20.6)	
South	42,071	(41.6)	9105	(37.6)	758	(40.0)	
West	17,617	(17.4)	4823	(19.9)	386	(20.4)	
Location							<0.001
Metropolitan	77,896	(76.9)	18,882	(78.0)	1512	(79.8)	
Urban	15,965	(15.8)	3439	(14.2)	265	(14.0)	
Rural	1924	(1.9)	384	(1.6)	35	(1.9)	
Unknown	5455	(5.4)	1491	(6.2)	84	(4.4)	
Hospital type							<0.001
Community cancer program	8222	(8.1)	1582	(6.5)	108	(5.7)	
Comprehensive community cancer program	46,489	(45.9)	11,890	(49.1)	901	(47.5)	
Academic	43,997	(43.5)	10,170	(42.0)	856	(45.2)	
Other	2532	(2.5)	554	(2.3)	31	(1.6)	
Stage							<0.001
IA (IA, IA1, IA2)	15,408	(15.2)	4185	(17.3)	49	(2.6)	
IB (IB, IB1, IB2, INOS)	29,461	(29.1)	10,592	(43.8)	519	(27.4)	
IIA (IIA, IIA1, IIA2)	929	(0.9)	245	(1.0)	14	(0.7)	
IIB (IIB, IINOS)	18,146	(17.9)	2500	(10.3)	187	(9.9)	
IIIA	1531	(1.5)	236	(1.0)	24	(1.3)	
IIIB	18,938	(18.7)	2248	(9.3)	380	(20.0)	
IVA	2924	(2.9)	337	(1.4)	55	(2.9)	
IVB	6017	(5.9)	1424	(5.9)	447	(23.6)	
IVNOS	1042	(1.0)	274	(1.1)	64	(3.4)	
Unknown	6844	(6.8)	2155	(8.9)	157	(8.3)	
Primary treatment							<0.001
Surgery	48,855	(48.3)	16,462	(68.0)	716	(37.8)	
Radiation	36,404	(36.0)	4949	(20.5)	710	(37.5)	
No surgery or radiation	6528	(6.5)	1493	(6.2)	347	(18.3)	
Unknown	9453	(9.3)	1292	(5.3)	123	(6.5)	