1-1-2020

Gynecologic Large Cell Neuroendocrine Carcinoma: A Review

Grant Burkeen
University of Kentucky

Aman Chauhan
University of Kentucky, amanchauhan@uky.edu

Rohitashva Agrawal
University of Kentucky

Riva Raiker
University of Kentucky

Jill M. Kolesar
University of Kentucky, Jill.Kolesar@uky.edu

See next page for additional authors

Gynecologic Large Cell Neuroendocrine Carcinoma: A Review

Digital Object Identifier (DOI)
https://doi.org/10.1177/2036361320968401

Notes/Citation Information
Published in *Rare Tumors*, v. 12.

Authors
Grant Burkeen, Aman Chauhan, Rohitashva Agrawal, Riva Raiker, Jill M. Kolesar, Lowell B. Anthony, B. Mark Evers, and Susanne Arnold

Review

rare tumors

Rare Tumors
Volume 12: 1–11

DOI: 10.1177/2036361320968401
journals.sagepub.com/home/rtu
SAGE

Gynecologic large cell neuroendocrine carcinoma: A review

Grant Burkeen[1], Aman Chauhan[2,3], Rohitashva Agrawal[2], Riva Raiker[1], Jill Kolesar[3,4], Lowell Anthony[2,3], B. Mark Evers[3,5] and Susanne Arnold[2,3]

Abstract

Large cell neuroendocrine carcinomas (LCNEC) are rare, aggressive high-grade neuroendocrine neoplasms within the neuroendocrine cell lineage spectrum. This manuscript provides a detailed review of published literature on LCNEC of gynecological origin. We performed a PubMed search for material available on gynecologic LCNEC. We analyzed 104 unique cases of gynecologic LCNECs, of which 45 were cervical primary, 45 were ovarian, 13 were uterine, and 1 was vaginal. A total of 45 cases of cervical LCNEC were identified with a median age of 36 years. Median overall survival was 16 months. We identified 45 ovarian LCNEC cases in the published literature with a median age of 54 years. Median overall survival was 8 months. 13 LCNEC cases of uterine origin were identified; 12 out of 13 were of endometrial origin and the median age was 71 years. The majority of patients presented with Stage III/IV disease (stages I–IV were 31%, 8%, 38%, and 23%, respectively). Gynecologic LCNEC is an aggressive malignancy. Our current understanding of the disease biology is very limited. Efforts are required to better understand the genomic and molecular characterizations of gynecological LCNEC. These efforts will elucidate the underlying oncogenic pathways and driver mutations as potential targets.

Keywords

Large cell neuroendocrine carcinoma, gynecologic LCNEC literature review, PubMed search

Date received: 3 May 2019; accepted: 30 September 2020

Introduction

Neuroendocrine tumors (NETs) are rare tumors that originate in cells of neuroendocrine lineage. NETs are classified pathologically by their grade as well as their differentiation; therefore, the tumor types within this lineage range from low to high grade but also from well differentiated to poorly differentiated.[1] High-grade neuroendocrine neoplasms, in particular, are a group of heterogeneous malignancies that can originate in any part of the body. Large cell neuroendocrine carcinoma (LCNEC) is an aggressive subtype of high-grade neuroendocrine neoplasm. The most common site of origin for LCNEC is the thorax; however,

[1]Department of Internal Medicine, University of Kentucky, Lexington, KY, USA
[2]Division of Medical Oncology, University of Kentucky, Lexington, KY, USA
[3]Markey Cancer Center, University of Kentucky, Lexington, KY, USA
[4]Department of Pharmacy Practice and Science, University of Kentucky, Lexington, KY, USA
[5]Department of Surgery, University of Kentucky, Lexington, KY, USA

Corresponding author:
Aman Chauhan, Assistant Professor of Medicine, Markey Cancer Center, University of Kentucky, 800 Rose Street, Roach Building, CC402, Lexington, KY 40536, USA.
Email: amanchauhan@uky.edu

it has been reported in the gastrointestinal tract, biliary tract, urogenital region, head, neck and the gynecologic tract among others. Diagnosis depends on a definite pathology because prognosis and treatment varies drastically between LCNEC and well-differentiated neuroendocrine tumors. LCNEC pathology is characterized by an organoid, trabecular, or cordlike growth pattern interspersed by peripheral palisading, rosette clusters, and geographic necrosis.[2] There is also a high mitotic rate with a predominance of large cells with large vesicular nuclei and prominent nucleoli.[2] The growth pattern for LCNEC follows peripheral palisading and necrosis to a variable extent. LCNEC is usually argyrophilic and normally shows positive reactivity for synaptophysin, CD56, or chromogranin.[3] Chromogranin is a sensitive and specific serum marker for low-grade neuroendocrine tumors, however its utility is limited in high-grade neuroendocrine carcinomas (NEC).[4] Anecdotal reports suggest that neuron-specific enolase is a sensitive tumor marker for LCNEC and other high-grade NEC, however NET/NEC serum tumor markers suffer from lack of specificity and high variability and cannot be considered diagnostic.[5] Furthermore, adenocarcinoma, squamous cell carcinoma or small cell carcinoma can coexist with LCNECs.[6] As there are many cell types in the female gynecologic tract, this large cell pathology is often misdiagnosed. Regarding the prevalence of human papilloma virus (HPV) in gynecologic LCNEC, the presence of HPV has been demonstrated in most reported cases of LCNEC, ranging from 53% to 100% with the most common strains of virus being HPV16 and HPV18.[7]

This manuscript provides a detailed review of published literature on LCNEC of gynecological origin. We discuss the results and provide a management strategy for these very rare malignancies.

Methods

We performed a PubMed search for material available on gynecologic LCNEC. Search words included: "management of large cell neuroendocrine carcinoma" and "large cell neuroendocrine carcinoma," which resulted in 181 and 1969 publications, respectively. After additional filtering using the terms "gynecologic," "cervix," "ovary" and "uterus," 53 publications were reviewed. Of these, 29 pertinent manuscripts were identified for detailed review after removal of manuscripts not discussing case reports or not including relevant information necessary for this review.

Results

Cervical LCNEC: A total of 45 cases of cervical LCNEC were identified, with a median age of 36 years (range 21–75 years). Our summary of cervical LCNEC is reported in Table 1. The median age at presentation was 36 years (range 21–75). Patients were staged I (51%), II (22%), III (9%), and IV (9%), therefore most were early stage. The remaining four patients (9%) did not have a stage identified. Of the 45 patients, 76% received surgery management, with most receiving either radical or total abdominal hysterectomy. In this cohort, 69% of patients received systemic platinum-based chemotherapy and 47% of patients received radiation therapy. Outcomes varied significantly. Mortality related to cervical LCNEC was reported as 47% at the time of publication. Survival ranged from 2 weeks post-operative to 44 months. Median overall survival (OS) was 16 months; per stage median survival was 18.5, 12, 21, and 1 month for stages I, II, III, and IV, respectively. For the stage III disease cohort, Tangjitgamol et al. reported a case with a 44-month survival, thus explaining the increased survival.[8] Survival ranged from 0.5 to 151 months (no survival data was available for 11% of patients).

Ovarian LCNEC: We identified 45 unique ovarian LCNEC cases in the published literature, and these are summarized in Table 2. The median age at presentation was 54 years. Epithelial components that were associated with these malignancies included mucinous borderline tumor, mucinous adenocarcinoma, mucinous adenoma/cystadenoma, endometrioid adenocarcinoma and those with mixed or otherwise unspecified features. The majority of ovarian LCNECs were unilateral. Most patients were diagnosed at an early stage with stages I, II, III, and IV at 33%, 7%, 22%, and 24%, respectively. The remaining six patients did not have a stage reported. Of significance, all patients received surgery and 87% also received chemotherapy. In this cohort, of the 39 patients that received some form of chemotherapy; 34 received platinum-based therapy and the remaining five did not specify the form of chemotherapy. At publication, 56% of patients had died of the disease. Median overall survival was 8 months; stratified OS for stages I to IV was 9.5, 22.5 ($n = 3$ for this group), 8 and 8 months, respectively. Outcome data was not available for two patients. Stage II disease represents 3 of the 45 cases; survival of one case was not available. Oshita et al. reported a survival of 40 months in one patient with stage II disease, thus explaining the increased median survival of this cohort.[9] Of all the patients, survival ranged from 0 to 68 months.

Uterine/Vaginal LCNEC: We found 13 LCNEC cases of uterine origin as described in Table 3; 12 of the 13 were endometrial in origin and the remaining one was of uterine corpus origin. Median age at presentation was 71 years. Unlike previous cohorts, the majority of patients presented with stage III/IV disease. The percentage among stages I-IV were 31%, 8%, 38%, and 23%, respectively. 12 patients (92%) received surgery and 6 (46%) received chemotherapy. For the patients that received chemotherapy, a platinum-based therapy was employed in all cases; three patients received carboplatin plus etoposide, two patients received cisplatin + irinotecan, and one patient received carboplatin + paclitaxel. In this cohort, 6 of 13 patients received radiation therapy. The percentage of patients with

Table 1. Cervical large cell neuroendocrine carcinomas reported in the literature.

Origin	Presentation	Age	Stage	Surgery	Treatment	Response (duration)	Authors (Reference)
Cervix	Post-fibroid myomectomy surgery	48	IV	None	RT, nivolumab + sandostatin	AWD (12 months)	Shahabi et al.[4]
Cervix	Routine screening	27	IA	Radical abdominal trachelectomy, PLD	Cisplatin + etoposide	NED (6 months)	Rajkumar[25]
Cervix	N/A	30	IIB	None	RT and brachytherapy; Etoposide + cisplatin	NED (23 months)	Li[26]
Cervix	Vaginal bleeding	31	IB	TAH, BSO	RT, chemo	AWD (151 months)	Sato et al.[17]
Cervix	Vaginal bleeding	34	IB	TAH, BSO	RT, chemo	DOD (19 months)	Sato et al.[17]
Cervix	Vaginal bleeding	27	IB	TAH, BSO	RT, chemo	DOD (16 months)	Sato et al.[17]
Cervix	Vaginal bleeding	51	IB	TAH, BSO	RT, chemo	DOD (16 months)	Sato et al.[17]
Cervix	Abnormal Pap	47	IB	TAH, BSO	RT, chemo	NED (12 months)	Sato et al.[17]
Cervix	Abnormal Pap	42	IIA	TAH, BSO	RT, chemo	DOD (6 months)	Sato et al.[17]
Cervix	N/A	31	IA	RH	NFT	NED (10 months)	Yun[27]
Cervix	Atypical vaginal bleeding	40	IB	TAH, BSO, PLD	NFT	NED (9 months)	Kawauchi[28]
Cervix	Vaginal spotting	47	IIA	RH, PPALD	RT and brachytherapy (patient could not afford chemo)	NED (6 months)	Cetiner et al.[12]
Cervix	Screening Pap	25	IB1	RH, PPALD	*INITIAL*: Etoposide + cisplatin; *RECURRENCE*: Vincristine, adriamycin + cytoxan; carboplatin + etoposide; *THEN*: Topotecan; *THEN*: Paclitaxel; *THEN*: Protein kinase C inhibitor	Initial partial response then DOD (35 months)	Krivak et al.[15]
Cervix	Post-coital bleeding	36	IIA	None	RT, concurrent etoposide + cisplatin	Progression, DOD (33 months)	Krivak et al.[15]
Cervix	Vaginal bleeding most common	55	IIB	None	NFT	AWD (1 months)	Rhemtula[29]
Cervix	N/A	75	IIIB	None	RT	DOD (3 months)	Rhemtula[29]
Cervix	N/A	51	IVB	None	NFT	DOD (0.5 months)	Rhemtula[29]
Cervix	N/A	65	IVB	None	RT	DOD (1 months)	Rhemtula[29]
Cervix	N/A	42	N/A	None	NFT	N/A	Rhemtula[29]
Cervix	Vaginal bleeding	51	IIA2	RH, BSO, bilateral PLD	Irinotecan + cisplatin prior to surgery cisplatin	NED (21 months)	Omori et al.[7]
Cervix	Post-coital bleeding	31	N/A	RH	Cisplatin + irinotecan	NED (15 months)	Tanimoto[30]
Cervix	6 week post-partum check	33	IB	RH, BSO, PPALD	Cisplatin + etoposide	NED (24 months)	Yoseph[31]
Cervix	N/A	37	IIIB	Unknown	Unknown	DOD (21 months)	Kajiwara et al.[18]
Cervix	N/A	55	IIA	Unknown	Unknown	DOD (12 months)	Kajiwara et al.[18]
Cervix	N/A	38	IB	TAH, BSO	Chemo + radio-chemo	AWD (21 months)	Baykal[32]
Cervix	Pelvic pain and vaginal bleeding	31	IIIB	TAH, BSO, PPALD	Chemo, RT	N/A	Powell[33]
Cervix	N/A	60	N/A	RH	Chemo, RT	DOD (18 months)	Markapoulos[34]
Cervix	N/A	40	IVB	None	Platinum based chemo	N/A	Brown[35]
Cervix	Abnormal Pap	24	IB2	TAH	Concurrent cisplatin + RT; *THEN*: Etoposide + cisplatin + doxorubicin; *THEN*: Oral etoposide; Brachytherapy also used	NED (47 months)	Embry et al.[14]

(Continued)

Table 1. (Continued)

Origin	Presentation	Age	Stage	Surgery	Treatment	Response (duration)	Authors (Reference)
Cervix	Abnormal Pap	36	IA2	RH	NFT	NED (36 months)	Gilks et al.[16]
Cervix	Abnormal Pap	35	IB	RH	Etoposide + cisplatin + RT	DOD (18 months)	Gilks et al.[16]
Cervix	Abnormal Pap	33	IB	RH	Chemo	DOD (8 months)	Gilks et al.[16]
Cervix	Vaginal bleeding	31	IB	RH	Chemo	NED (36 months)	Gilks et al.[16]
Cervix	Vaginal bleeding	62	IIA	RH	NFT	DOD (6 months)	Gilks et al.[16]
Cervix	Vaginal bleeding	38	IA2	RH	N/A	LFU	Gilks et al.[16]
Cervix	Vaginal bleeding	31	IB	RH	Adriamycin, vincristine, cyclophosphamide	DOD (12 months)	Gilks et al.[16]
Cervix	N/A	29	IB	RH	NFT	DOD (24 months)	Gilks et al.[16]
Cervix	N/A	36	IB	RH	Cisplatin, etoposide, RT	DOD (24 months)	Gilks et al.[16]
Cervix	N/A	21	IB	RH	Cisplatin, etoposide, adriamycin	DOD (10 months)	Gilks et al.[16]
Cervix	N/A	29	IB	RH	Cisplatin, etoposide, adriamycin	NED (30 months)	Gilks et al.[16]
Cervix	N/A	25	IB	RH	Carboplatin, etoposide	NED (6 months)	Gilks et al.[16]
Cervix	Vaginal bleeding	37	N/A	RH	Chemo, RT	N/A	Niwa[36]
Cervix	N/A	42	III	Extrafascial hysterectomy, BSO, and partial OMY	Paclitaxel + carboplatin (patient declined RT); *RECURRENCE*: Re-induction paclitaxel carboplatin, then cisplatin and etoposide	DOD (44 months)	Tangjitgamol et al.[8]
Cervix	Abnormal Pap	45	IIB	RH, BSO and PLD	RT, brachytherapy, and concurrent cisplatin	NED (unknown)	Dikmen[37]
Cervix	Post-coital vaginal bleeding	35	IIB	TAH, RSO	Cyclophosphamide, adriamycin, cytoxan, cisplatin, etoposide, RT adjuvant therapy with ifosfamide, cisplatin, and etoposide	DOD (19 months)	Tsou et al.[1]

AWD: alive with disease; BSO: bilateral salpingo-oophorectomy; Chemo: non-specified chemotherapy; DOD: dead of disease; LFU: lost to follow up; N/A: not available; NED: no evidence of disease; NFT: no further treatment; OMY: omenectomy; PLD: pelvic lymph node dissection; PPALD: pelvic and para-aortic lymph node dissection; RH: radical hysterectomy; RSO: right salpingo-oophorectomy; RT: radiation therapy; TAH: total abdominal hysterectomy.

uterine LCNEC that died of disease was 46%. Median OS was 7.5, 23 ($n = 1$), 10 and 1 month for stages I-IV, respectively, with survival ranging from 1 month to 23 months. Jin et al. reported one case of a 53-year-old female that was diagnosed with stage IV vaginal LCNEC. She was treated with palliative chemotherapy and radiation and was alive with disease at 12 months.[10]

Tables 1–3 summarize the individual case-based data for cervical, ovarian, uterine and vaginal LCNEC, respectively.

Discussion

Neuroendocrine neoplasms of the gynecologic tract are particularly uncommon with NETs of the uterus or cervix representing 0.9% to 1.5% of the tumors and accounting for 100 to 200 diagnoses yearly in the United States.[11] Furthermore, with the potential ambiguity surrounding the diagnostic criteria, some LCNEC cases may have been inaccurately classified as undifferentiated or poorly differentiated adenocarcinoma. Large cell carcinomas of the gynecologic tract are especially aggressive, tend to recur, and there is limited data regarding the natural history, progression, and management of the disease. Due to the rare nature of the disease, it is challenging to determine an optimal therapy by utilizing randomized controlled trials, but it has been proposed that these patients could be treated similar to those with small-cell neuroendocrine carcinoma because of similar malignant potential and platinum sensitivity.[12] For therapeutic intervention, a multi-modality approach should be undertaken.

For our review, the 104 unique cases of gynecologic LCNECs were positive for neuroendocrine markers, such as chromogranin A, CD56 and synaptophysin. Of the 45 cases of LCNEC of the cervix, an abnormal screening Papanicolaou smear and vaginal bleeding were the most common reasons for presentation. For the majority of ovarian LCNEC cases, abdominal pain and/or abdominal distention were the reasons for presentation, whereas post-menopausal bleeding was the most common reason for presentation for endometrial and uterine LCNEC. The

Table 2. Ovarian large cell neuroendocrine carcinomas reported in the literature.

Origin (and associated cells)	Presentation	Age	Stage	Surgery	Treatment	Response (Duration)	Authors [Reference]
Ovary	Abdominal pain and amenorrhea	35	IIIC	TAH, BSO	NFT	AWD (3 months)	Agarwal[38]
Ovary – AdCa	Abdominal distention and pain	68	IV	TAH, BSO, OMY, PPALD	Etoposide + cisplatin	DOD (7 months)	Cokmert[39]
Ovary – Undifferentiated Non-Small Cell	Abdominal distention	77	IV	Surgical debulking	Etoposide + carboplatin	Died (1.5 months)	Ki[40]
Ovary – Undifferentiated Non-Small Cell	Abdominal discomfort	58	IA	TAH, BSO, OMY, PLD	*INITIAL*: Cisplatin + paclitaxel; *RECURRENCE*: Docetaxel	DOD (17 months)	Ki[40]
Ovary	Urinary frequency	67	IIB	TAH, BSO, OMY, PPALD	Carboplatin + paclitaxel	AWD (5 months)	Ki[40]
Ovary – Mucinous Adenoma	Abdominal distention	50	IA	TAH, BSO, OMY + PLD	*INITIAL*: Cisplatin + etoposide; *RECURRENCE*: Paclitaxel + carboplatin	DOD (7 months)	Asada[41]
Ovary – Pure	Abdominal distention, pain, fever, itching	40	IIIC	BSO, OMY, PPALD 9 mo after laparoscopic type I hysterectomy, bilateral PLD	Etoposide + cisplatin	NED (6 months)	Shakuntala[42]
Ovary – Pure	Pelvic mass	27	IC	LSO, OMY	Chemo	NED (10 months)	Behnam[43]
Ovary	Abdominal pain	76	N/A	TAH, BSO, OMY	NFT	Died post-op	Aslam[44]
Ovary – Pure	Abdominal distention	46	IIIC	Subtotal abdominal hysterectomy, BSO, OMY	Paclitaxel + carboplatin	DOD (4 months)	Tsuji et al.[11]
Ovary	Abdominal distention	35	N/A	TAH, BSO, OMY	Chemo	DOD (4 months)	Kim
Ovary – Pure	Abdominal discomfort	64	IA	TAH, BSO + OMY	Bleomycin, cisplatin + etoposide; Bleomycin discontinued due to development of side effects	NED (9 months)	Lindboe[45]
Ovary – Serous AdCa	Abdominal pain and distention	71	IIIB	TAH, BSO	Taxol + carboplatin	NED (8 months)	Choi[46]
Ovary – Mucinous AdCa	N/A	58	IIIB	TAH, BSO, OMY	Chemo	DOD (8 months)	Eichorn[47]
Ovary – Endometroid AdCa	N/A	77	IA	RSO, prior TAH	RT	DOD (19 months) with Mets	Eichorn[47]
Ovary – Mucinous AdCa	N/A	36	IA	TAH, BSO	N/A	Unknown	Eichorn[47]
Ovary – Mucinous AdCa	N/A	45	IB	TAH, BSO, OMY	Chemo	DOD (36 months)	Eichorn[47]
Ovary – Mucinous AdCa	N/A	68	IIB	TAH, BSO, OMY	N/A	Unknown	Eichorn[47]
Ovary – Mucinous AdCa	N/A	73	IIIC	Prior TAH, BSO, OMY	Paclitaxel, cisplatin, adriamycin	DOD (8 months)	Chen[20]
Ovary – Mucinous Intraepithelial AdCa	N/A	44	IA	TAH, BSO, OMY	Paclitaxel, carboplatin	DOD (4 months)	Chen[20]
Ovary – Mucinous AdCa + Teratoma	Abdominal mass	53	IV	TAH, BSO, OMY, PLD	Carboplatin + paclitaxel	DOD (3 months)	Chenevert[48]
Ovary – Mucinous AdCa + Teratoma	Abdominal distention	53	I	TAH, BSO, OMY	Cisplatin + etoposide	DOD (7 months)	Chenevert[48]
Ovary – Serous AdCa	Abdominal distention and ascites	68	IV	TAH, BSO, OMY, debulking	Carboplatin + paclitaxel	DOD (7 months)	Draganova-Tacheva[49]
Ovary – Mucinous	Abdominal pain	39	IV	TAH, BSO	Cisplatinum-based chemo	AWD (8 months)	Veras et al.[23]
Ovary – Mucinous	Abdominal pain	55	I	TAH, BSO	Cisplatinum-based chemo	NED (68 months)	Veras et al.[23]

(Continued)

Table 2. (Continued)

Origin (and associated cells)	Presentation	Age	Stage	Surgery	Treatment	Response (Duration)	Authors [Reference]
Ovary – none	Pelvic pain	42	IV	TAH, BSO	Cisplatinum-based chemo	DOD (20 months)	Veras et al.[23]
Ovary – Endometroid Ca	Ascites	53	III	TAH, BSO	Cisplatinum-based chemo	NED (37 months)	Veras et al.[23]
Ovary – AdCa and Mature Teratoma	Abdominal bloating	47	III	TAH, BSO	Cisplatinum-based chemo	NED (11 months)	Veras et al.[23]
Ovary – Mature Cystic Teratoma	Abdominal pain	25	IV	BSO, OMY, APPY	Cisplatinum-based chemo	DOD (36 months)	Veras et al.[23]
Ovary – Mucinous LMP	Vaginal bleeding	55	III	TAH, BSO	Cisplatinum-based chemo	DOD (2 months)	Veras et al.[23]
Ovary – Mucinous and Endometroid Ca	Pelvic mass	54	I	TAH, BSO	Cisplatinum-based chemo	**NED (66 months)**	**Veras et al.**[23]
Ovary – Endometroid	Ascites	63	IV	TAH, RSO	Cisplatinum-based chemo	DOD (9 months)	Veras et al.[23]
Ovary – AdCa	Abdominal pain	59	I	BSO	Cisplatinum-based chemo	NED (28 months)	Veras et al.[23]
Ovary – Mucinous Ca	Abdominal pain	22	I	RSO, APPY	Cisplatinum-based chemo	DOD (3 months)	Veras et al.[23]
Ovary – Mucinous Intraepithelial Ca	Abdominal distention and weight loss	36	N/A	TAH, BSO, OMY, PLD	Chemo	NED (6 months)	Yasuoka[50]
Ovary – Mucinous Cystadenoma	Abdominal distention	65	N/A	TAH, BSO, OMY, PLD, APPY	NFT	DOD (10 months)	Jones[51]
Ovary – Mucinous Cystadenoma and Mucinous AdCa	Abdominal distention	34	IC	TAH, BSO, OMY	Cisplatinum + cyclophosphamide	DOD (8 months)	Collins et al.[21]
Ovary – Endometrioid Adca	Abdominal pain, fatigue	33	N/A	LSO, partial OMY; *THEN*: TAH, RSO, PPALD	Irinotecan + nedaplatin	DOD (4 months)	Ohira[52]
Ovary – Pure	Dysarthria	73	IV	TAH with bilateral adnexectomy, left-sided nephrectomy, OMY	Carboplatin + paclitaxel	NED (12 months)	Dundr et al.[22]
Ovary- Pure	Asymptomatic pelvic mass	66	IV	TAH, BSO, OMY	*INITIAL*: Carboplatin + paclitaxel *RECURRENCE*: Brain RT	NED (64 months)	Oshita et al.[9]
Ovary – Endometroid AdCa	Asymptomatic pelvic mass	80	IIC	TAH, BSO, PLD, OMY, APPY	Carboplatin + paclitaxel	NED (40 months)	Oshita et al.[9]
Ovary – Endometroid AdCa	Abdominal pain	65	IC	TAH, BSO, OMY	Carboplatin + paclitaxel	DOD (2 months)	Oshita et al.[9]
Ovary –Endometroid AdCa	Abdominal mass	42	IIIB	TAH, BSO, peritoneum resection of Douglas pouch, OMY, PLD	Carboplatin + paclitaxel	NED (32 months)	Oshita et al.[9]
Ovary – Pure	Abdominal pain and distention	40	N/A	BSO, OMY, sigmoid colon debulking	Etoposide + cisplatin	NED (6 months)	**Shakuntala**[42]
Ovary – Mature Cystic Teratoma	Unknown	69	IV	debulking	Paclitaxel + carboplatin	DOD (6 months)	Miyamoto[53]

AdCa: adenocarcinoma; APPY: appendectomy; AWD: alive with disease; BSO: bilateral salpingo-oophorectomy; Ca: carcinoma; Chemo: non-specified chemotherapy; DOD: dead of disease; LMP: low malignant potential; LSO: left salpingo-oophorectomy; Mets: metastases; N/A: not available; NED: no evidence of disease; NFT: no further treatment; OMY: omenectomy; PLD: pelvic lymph node dissection; PPALD: pelvic and para-aortic lymph node dissection; RSO: right salpingo-oophorectomy; RT: radiation therapy; TAH: total abdominal hysterectomy.

Table 3. Endometrial, uterine corpus and vaginal large cell neuroendocrine carcinoma reported in the literature.

Origin (plus associated cells)	Presentation	Age	Stage	Surgery	Treatment	Response (duration)	Authors (Reference)
Endometrium – Pure	Postmenopausal vaginal bleeding	71	IVB	RH, BSO, OMY, PPALD	NFT	DOD (1 months)	Nguyen et al.[5]
Endometrium – Sarcomatoid	Abnormal uterine bleeding	40	IB	TAH, BSO, OMY, PLD	NFT	AWD (16 months)	Terada[54]
Endometrium – Pure	N/A	50	IIIC	TAH, BSO, OMY	RT, cisplatin, etoposide	AWD (12 months)	Mulvany[55]
Endometrium – Endometroid	N/A	80	IC	TAH, BSO	NFT	DOD (5 months)	Mulvany[55]
Endometrium – Endometroid	N/A	77	IIB	TAH, BSO	RT	DOD (23 months)	Mulvany[55]
Endometrium – Endometroid	N/A	79	IIIA	TAH, BSO, Omental biopsy	RT	AWD (2 months)	Mulvany[55]
Endometrium – Endometroid	N/A	88	IIIC	TAH, BSO, LN biopsy	RT	AWD (1 months)	Mulvany[55]
Endometrium	Abdominal distention	73	IVB	None	Patient refused	DOD (1 months)	Makihara[34]
Endometrium	Vaginal bleeding	73	IIIC	TAH, BSO, OMY, PPALD	Cisplatin + irinotecan	AWD (13 months)	Makihara[34]
Endometrium	Postmenopausal bleeding	59	IV	TAH, BSO, OMY, PPALD	Carboplatin + paclitaxel with RT and brachytherapy; *THEN*: Pegylated doxorubicin followed by etoposide, cisplatin and LAR	DOD (12 months)	Shahabi et al.[4]
Endometrium – Pure	Post-menopausal bleeding	70	IB	TAH, BSO, OMY	Cisplatin + etoposide	NED (6 months)	Deodhar[56]
Endometrium – Pure	N/A	42	IC	RH	Cisplatin + etoposide	AWD (9 months)	Albores-Saavedra et al.[3]
Uterine Corpus – Pure	Lower abdominal pain	52	IIIC2	TAH, BSO, PPALD	*INITIAL*: Irinotecan + cisplatin with RT *PROGRESSION*: RT, paclitaxel + carboplatin	DOD (10 months)	Kobayashi et al[24]
Vagina	Pelvic pain and difficulty voiding	53	IV	None	Palliative radiation + chemo	AWD (12 months)	Jin et al.[10]

AWD: alive with disease; BSO: bilateral salpingo-oophorectomy; Chemo: chemotherapy; DOD: dead of disease; LAR: long acting-release octreotide; LN: lymph node; N/A: not available; NED: no evidence of disease; NFT: no further treatment; OMY: omenectomy; PLD: pelvic lymph node dissection; PPALD: pelvic and para-aortic lymph node dissection; RH: radical hysterectomy; RT: radiation therapy; TAH: total abdominal hysterectomy.

one case of LCNEC of the vagina reported by Jin et al. was of a 53-year-old female who presented with metastatic stage IV disease.[10]

LCNEC of the gynecologic tract has a poor prognosis, especially for patients that present in an advanced stage. A variety of therapeutic regimens exist with attention toward a multimodality approach, including combinations of surgery, chemotherapy and radiation. This multimodal approach is supported by both the Society of Gynecologic Oncology and the Gynecologic Cancer Intergroup.[13] Survival outcome is variable and dependent on both stage at diagnosis and response to the treatment. Embry et al. reported that earlier stage ($p < 0.00001$) and the addition of chemotherapy ($p = 0.04$) were associated with improved survival for cervical LCNECs.[14] They also reported platinum agents ($p = 0.034$) and platinum+etoposide ($p = 0.027$) were associated with improved survival.[14] Furthermore, for LCNECs with metastatic lesions, long-term survival is uncommon.[15] Because of the rarity of these malignancies, management is often extrapolated from small and large cell carcinomas of the lung. Adjuvant chemotherapy with cisplatin, carboplatin, etoposide or cyclophosphamide has been used in the management of LCNEC of the lung, and is very frequently used in LCNEC of the gynecologic tract as well.[4]

Cervix

Our 45 cases of cervical LCNEC summarized in Table 1 include patients with all stages of disease as well as a wide range of survival (0.5 months to 151 months). Treatment included surgery, chemotherapy, and/or radiation, with a majority (76%) receiving surgery. Of note, Embry et al. reported 62 cases of cervical LCNEC; importantly, the authors documented a similar median age to ours (37 years) with the identical age range of 21 to 75. Furthermore, a majority of their patients also had stage I disease. Of these cases, 73% underwent primary surgery, 4.7% underwent primary radiation, 4.7% underwent chemotherapy and 8% had chemoradiation. There were 9.6% with no primary treatment. Reported patient outcomes were as follows: 58% died of disease, 26% had no evidence of disease, 3% were alive with disease and 13% had no survival data. Multivariate analysis revealed that earlier stage ($p < 0.00001$) and the addition of chemotherapy ($p = 0.04$) particularly platinum agents ($p = 0.034$) and the platinum+etoposide combination ($p = 0.027$) were associated with improved survival.[14]

For early stage cervical LCNEC, therapy should begin with radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Gilks et al. reported a case of a 36-year-old patient with stage I disease who had no evidence of it 36 months after a radical hysterectomy.[16] However, the current recommendation is to follow surgery with chemoradiation, cisplatin (platinum-based therapy) and etoposide.[13] Of note, this therapy is based on regimens used in small cell lung cancer as there are no prospective phase II or phase III clinical trials evaluating anti-tumor efficacy in gynecologic LCNEC. However, prophylactic brain irradiation is not recommended in these patients as it is with small cell lung cancer.

For locally advanced disease in women with neuroendocrine carcinoma (stage IB2–IVA disease), concurrent chemradiation followed by additional chemotherapy with intent to cure should be the treatment plan. The ideal regimen is the same as that described above, with cisplatin and etoposide given on a 3-week cycle. Sato et al. implemented chemotherapy (specific therapy not identified) with concurrent radiation therapy after a total abdominal hysterectomy and bilateral oophorectomy in a 31 to year-old patient with stage 1B disease; this patient was reported to be alive with disease at 151 months.[17] For patients with no evidence of intraperitoneal spread and nodal metastatic burden, neoadjuvant chemotherapy with cisplatin and etoposide followed by consolidation radiation therapy may be of some benefit.[13] However, per our analysis, LCNEC remains a disease with poor prognosis, with a median OS of less than 2 years.

Hormone receptor and growth factor receptor expression could have a role in predicting survival in cervical LCNEC. Tangjitgamol et al. performed this evaluation for cervical LCNEC and identified a significantly shorter OS in patients with a HER-2 neu negative status as compared to those with positive HER-2 neu tumors (median OS: 14.2 vs 33.1 months), and a trend towards a worse OS in patients positive for epidermal growth factor receptor.[8] The group concluded that the combination of negative HER-2 neu status and positive epidermal growth factor receptor expression impaired OS.[8]

There is a potential role for targeted therapy in cervical LCNEC. Somatostatin receptors are profusely expressed in low-grade NETs, and some somatostatin receptor binding is generally observed in high-grade NEC. Hence targeted therapy with octreotide, a somatostatin analog, could be explored as suggested by Shahabi et al. Potential mechanisms by which octreotide could inhibit tumor growth include inhibition of growth hormone secretion, such as IGF-1, inhibition of angiogenesis, and through direct action on the tumor.[4] Kajiwara et al. also proposed using octreotide to treat neuroendocrine tumors, since 3 out of 7 cases (2 of 5 small cell carcinomas and 1 of 2 LCNEC) expressed somatostatin receptor type 2A.[18] However, a larger study is needed to validate these conclusions. Many clinicians are skeptical of the role for somatostatin analog in LCNEC management.

The role of radiation therapy should be strongly considered, especially with the addition of brachytherapy in the setting of LCNEC of the cervix. Robin et al. found a significant improvement in OS when brachytherapy and external beam radiation therapy were combined. They identified 100 patients with locally advanced non-metastatic neuroendocrine cervical cancer (included both large cell and small cell) that were treated with definitive chemoradiotherapy between 2004 and 2012. There was a substantial improvement in OS when brachytherapy was administered in addition to external beam radiotherapy. By multivariate analysis, an improved median survival of 48.6 versus 21.6 months (95% CI, 0.255–0.883; $p = 0.019$) was seen with the addition of brachytherapy compared to external beam radiotherapy alone. This study was performed in patients with locally advanced neuroendocrine carcinoma of the cervix, of both large and small cell etiology, treated with chemoradiotherapy.[19]

Ovary

As evidenced by our 45 cases of ovarian LCNEC summarized in Table 2, patients with this disease unfortunately have a poor prognosis; 8 month survival was noted for those patients with both stage III and stage IV disease. Reported survival for all stages ranged from 0 to 68 months. In the 33 cases reported by Oshita et al., the 5-year survival was only 34.9%.[9] One case exhibited rapid disease progression with pelvic mass formation, liver metastasis and pelvic lymphadenopathy within 2 weeks after primary surgery, with the tumor being unresponsive to Taxol and carboplatin chemotherapy.[9] Evidence that ovarian LCNEC is an

aggressive malignancy has also been reported in other cases outlined above.[20,21] However, it is worth noting that there is evidence of success with surgery followed by adjuvant platinum-based chemotherapy. Dundr et al. reported a case of a 73-year-old with stage IV ovarian LCNEC and no evidence of the disease 12 months after undergoing surgery and chemotherapy with carboplatin and paclitaxel.[22] An anecdotal case series from MD Anderson Cancer Center reported 22 to 68 months survival in three stage I cases with standard surgery followed by adjuvant platinum-based chemotherapy.[23] Based on the above-mentioned observations, therapeutic consideration similar to primary lung LCNEC can be applied toward those of ovarian origin. This includes utilizing such regimens as cisplatin/vinorelbine, cisplatin/etoposide, cisplatin/vinblastine, cisplatin/gemcitabine and cisplatin/docetaxel in tumors that are initially unresponsive to first line taxotere and cyclophosphamide therapy.[9] In one case reported by Oshita et al., radiation was utilized for brain metastasis and the patient had no evidence of the disease for 64 months, which adds support to employing radiation in situations of local recurrence or distant metastasis.[9]

Uterus

Limited data exists to guide therapy in cases of uterine LCNEC, however as mentioned above, a multi-modality approach is commonly applied. Similar to LCNEC of the cervix, tumors in the uterus, notably the endometrium, are managed initially with cytoreductive surgery. Based on prior published reports, a hysterectomy and bilateral salpingo-ophorectomy are recommended at minimum.[5] Unfortunately, a number of cases were reported with early-stage disease at the time of surgery that developed distant metastasis or rapid recurrence; therefore, omentectomy and pelvic and paraaortic lymphadenectomy should be considered for accurate staging. Of note, physicians may want to determine a patient's response to chemotherapy prior to initiating surgery, as surgery has often been shown to be of little benefit. Currently there is no consensus regarding optimal management of these tumors after surgery. In the case reports as described, adjuvant chemotherapy and/or radiation was either performed or planned in the majority of the cases. Chemotherapy, radiation or both is favored by most treating physicians. Occasionally, neoadjuvant therapy is considered in cases where LCNEC is diagnosed on a preoperative curettage, or when an endometrial biopsy specimen is done in advanced cases of ovarian cancer. Adjuvant chemotherapy generally consists of platinum and etoposide based chemotherapy as in cervical disease.[5] Shahabi et al. incorporated octreotide into their treatment regimen due to a single case report of its use for an endometrial small cell NET in which a partial response was reported; however, disease progression was observed.[4] In the one case of LCNEC of the uterine corpus, Kobayashi et al. reported a rapidly progressing stage III disease that did not respond to irinotecan/cisplatin initially but paclitaxel/carboplatin with concurrent radiation was helpful.[24]

Conclusion

As discussed above, LCNECs are high-grade neuroendocrine carcinomas and represent a rare diagnosis, especially in sites such as the gynecologic tract. Our current understanding of the biology of this pathology is limited. As inadequate data exists regarding the treatment of this pathology, it has been demonstrated in the aforementioned cases of LCNEC in the gynecologic tract that a multimodality treatment approach including surgery, chemotherapy and radiation should be undertaken. Further efforts are required to gain more knowledge on how best to treat these aggressive malignancies.

Acknowledgements

Donna Gilbreath and Elise Wright at the University of Kentucky Markey Cancer Center's Research Communications Office assisted with preparation of this manuscript.

Contributorship

Conceived the project: AC
Performed research: GB, RA, RR
Drafted the manuscript: AC, GB, RR
Edited the manuscript: LA, SA, AC, JK
Oversight: BME, LA, SA, AC, JK
AC = Aman Chauhan
GB = Grant Burkeen
BME = B. Mark Evers
JK = Jill Kolesar
LA = Lowell Anthony
RA = Rohitashva Agrawal
RR = Riva Raiker
SA = Susanne Arnold

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval (include full name of committee approving the research and if available mention reference number of that approval)

Not applicable

Informed Consent

Not applicable

Trial Registration *(where applicable)*

Not applicable

ORCID iD

Aman Chauhan https://orcid.org/0000-0002-4183-2116

References

1. Tsou MH, Tan TD, Cheng SH, et al. Small cell carcinoma of the uterine cervix with large cell neuroendocrine carcinoma component. *Gynecol Oncol* 1998; 68(1): 69–72.
2. Gardner GJ, Reidy-Lagunes D and Gehrig PA. Neuroendocrine tumors of the gynecologic tract: a Society of Gynecologic Oncology (SGO) clinical document. *Gynecol Oncol* 2011; 122(1): 190–198.
3. Albores-Saavedra J, Gersell D, Gilks CB, et al. Terminology of endocrine tumors of the uterine cervix: results of a workshop sponsored by the College of American Pathologists and the National Cancer Institute. *Arch Pathol Lab Med* 1997; 121(1): 34–39.
4. Shahabi S, Pellicciotta I, Hou J, et al. Clinical utility of chromogranin A and octreotide in large cell neuro endocrine carcinoma of the uterine corpus. *Rare Tumors* 2011; 3(4): e41.
5. Nguyen ML, Han L, Minors AM, et al. Rare large cell neuroendocrine tumor of the endometrium: a case report and review of the literature. *Int J Surg Case Rep* 2013; 4(8): 651–655.
6. Rekhi B, Patil B, Deodhar KK, et al. Spectrum of neuroendocrine carcinomas of the uterine cervix, including histopathologic features, terminology, immunohistochemical profile, and clinical outcomes in a series of 50 cases from a single institution in India. *Ann Diagn Pathol* 2013; 17(1): 1–9.
7. Omori M, Hashi A, Kondo T, et al. Successful neoadjuvant chemotherapy for large cell neuroendocrine carcinoma of the cervix: a case report. *Gynecol Oncol Case Rep* 2014; 8: 4–6.
8. Tangjitgamol S, Manusirivithaya S, Choomchuay N, et al. Paclitaxel and carboplatin for large cell neuroendocrine carcinoma of the uterine cervix. *J Obstet Gynaecol Res* 2007; 33(2): 218–224.
9. Oshita T, Yamazaki T, Akimoto Y, et al. Clinical features of ovarian large-cell neuroendocrine carcinoma: four case reports and review of the literature. *Exp Ther Med* 2011; 2(6): 1083–1090.
10. Jin B, Pickens A, Shah MB, et al. Primary large cell neuroendocrine carcinoma of the vagina: cytomorphology of previously unreported case. *Diagn Cytopathol* 2010; 38(12): 925–928.
11. Tsuji T, Togami S, Shintomo N, et al. Ovarian large cell neuroendocrine carcinoma. *J Obstet Gynaecol Res* 2008; 34(4): 726–730.
12. Cetiner H, Kir G, Akoz I, et al. Large-cell neuroendocrine carcinoma of the cervix associated with cervical-type invasive adenocarcinoma: a report of case and discussion of histogenesis. *Int J Gynecol Cancer* 2006; 16(1): 438–442.
13. Frumovitz M. Small- and large-cell neuroendocrine cervical cancer. *Oncology (Williston Park)* 2016; 30(1): 70, 77–78, 93.
14. Embry JR, Kelly MG, Post MD, et al. Large cell neuroendocrine carcinoma of the cervix: prognostic factors and survival advantage with platinum chemotherapy. *Gynecol Oncol* 2011; 120(3): 444–448.
15. Krivak TC, McBroom JW, Sundborg MJ, et al. Large cell neuroendocrine cervical carcinoma: a report of two cases and review of the literature. *Gynecol Oncol* 2001; 82(1): 187–191.
16. Gilks CB, Young RH, Gersell DJ, et al. Large cell neuroendocrine [corrected] carcinoma of the uterine cervix: a clinicopathologic study of 12 cases. *Am J Surg Pathol* 1997; 21(8): 905–914.
17. Sato Y, Shimamoto T, Amada S, et al. Large cell neuroendocrine carcinoma of the uterine cervix: a clinicopathological study of six cases. *Int J Gynecol Pathol* 2003; 22(3): 226–230.
18. Kajiwara H, Hirabayashi K, Miyazawa M, et al. Immunohistochemical expression of somatostatin type 2A receptor in neuroendocrine carcinoma of uterine cervix. *Arch Gynecol Obstet* 2009; 279(4): 521–525.
19. Robin TP, Amini A, Schefter TE, et al. Brachytherapy should not be omitted when treating locally advanced neuroendocrine cervical cancer with definitive chemoradiation therapy. *Brachytherapy* 2016; 15(6): 845–850.
20. Chen KT. Composite large-cell neuroendocrine carcinoma and surface epithelial-stromal neoplasm of the ovary. *Int J Surg Pathol* 2000; 8(2): 169–174.
21. Collins RJ, Cheung A, Ngan HY, et al. Primary mixed neuroendocrine and mucinous carcinoma of the ovary. *Arch Gynecol Obstet* 1991; 248(3): 139–143.
22. Dundr P, Fischerova D, Povysil C, et al. Primary pure large-cell neuroendocrine carcinoma of the ovary. *Pathol Res Pract* 2008; 204(2): 133–137.
23. Veras E, Deavers MT, Silva EG, et al. Ovarian nonsmall cell neuroendocrine carcinoma: a clinicopathologic and immunohistochemical study of 11 cases. *Am J Surg Pathol* 2007; 31(5): 774–782.
24. Kobayashi A, Yahata T, Nanjo S, et al. Rapidly progressing large-cell neuroendocrine carcinoma arising from the uterine corpus: a case report and review of the literature. *Mol Clin Oncol* 2017; 6(6): 881–885.
25. Rajkumar S, Iyer R, Culora G, et al. Fertility sparing management of large cell neuroendocrine tumour of cervix: a case report & review of literature. *Gynecol Oncol Rep* 2016; 18: 15–17.
26. Li WW, Yau TN, Leung CW, et al. Large-cell neuroendocrine carcinoma of the uterine cervix complicating pregnancy. *Hong Kong Med J* 2009; 15: 69–72.
27. Yun K, Cho NP and Glassford GN. Large cell neuroendocrine carcinoma of the uterine cervix: a report of a case with coexisting cervical intraepithelial neoplasia and human papillomavirus 16. *Pathology* 1999; 31: 158–161.
28. Kawauchi S, Okuda S, Morioka H, et al. Large cell neuroendocrine carcinoma of the uterine cervix with cytogenetic analysis by comparative genomic hybridization: a case study. *Hum Pathol* 2005; 36: 1096–1100.
29. Rhemtula H, Grayson W, van Iddekinge B, et al. Large-cell neuroendocrine carcinoma of the uterine cervix–a clinicopathological study of five cases. *S Afr Med J* 2001; 91: 525–528.
30. Tanimoto H, Hamasaki A, Akimoto Y, et al. A case of large cell neuroendocrine carcinoma (LCNEC) of the uterine cervix successfully treated by postoperative CPT-11+CDDP

chemotherapy after non-curative surgery. *Gan To Kagaku Ryoho* 2012; 39: 1439–1441.
31. Yoseph B, Chi M, Truskinovsky AM, et al. Large-cell neuroendocrine carcinoma of the cervix. *Rare Tumors* 2012; 4: e18.
32. Baykal C, Al A, Tulunay G, et al. High-grade neuroendocrine carcinoma of the cervix. A case report. *Gynecol Obstet Invest* 2005; 59: 207–211.
33. Powell JL and McKinney CD. Large cell neuroendocrine tumor of the cervix and human papillomavirus 16: a case report. *J Low Genit Tract Dis* 2008; 12: 242–244.
34. Makihara N, Maeda T, Nishimura M, et al. Large cell neuroendocrine carcinoma originating from the uterine endometrium: a report on magnetic resonance features of 2 cases with very rare and aggressive tumor. *Rare Tumors* 2012; 4: e37.
35. Brown KR and Leitao MM Jr. Cisplatin-induced syndrome of inappropriate antidiuretic hormone (SIADH) in a patient with neuroendocrine tumor of the cervix: a case report and review of the literature. *Eur J Gynaecol Oncol* 2010; 31: 107–108.
36. Niwa K, Nonaka-Shibata M, Satoh E, et al. Cervical large cell neuroendocrine carcinoma with cytologic presentation: a case report. *Acta Cytol* 2010; 54: 977–980.
37. Dikmen Y, Kazandi M, Zekioglu O, et al. Large cell neuroendocrine carcinoma of the uterine cervix: a report of a case and review of the literature. *Arch Gynecol Obstet* 2004; 270: 185–188.
38. Agarwal L, Gupta B and Jain A. Pure large cell neuroendocrine carcinoma of the ovary with metastasis to cervix: a rare case report and review of literature. *J Clin Diagn Res* 2016; 10: ED01–ED03.
39. Cokmert S, Demir L, Doganay L, et al. Large cell neuroendocrine carcinoma of the ovary and its skin metastases: a case report and review of the literature. *West Indian Med J* 2014; 63: 667–672.
40. Ki EY, Park JS, Lee KH, et al. Large cell neuroendocrine carcinoma of the ovary: a case report and a brief review of the literature. *World J Surg Oncol* 2014; 12: 314.
41. Asada K, Kawana K, Teshima S, et al. Poor prognosis of ovarian cancer with large cell neuroendocrine carcinoma: case report and review of published works. *J Obstet Gynaecol Res* 2014; 40: 869–872.
42. Shakuntala PN, Uma Devi K, Shobha K, et al. Pure large cell neuroendocrine carcinoma of ovary: a rare clinical entity and review of literature. *Case Rep Oncol Med* 2012; 2012: 120727.
43. Behnam K, Kabus D and Behnam M. Primary ovarian undifferentiated non-small cell carcinoma, neuroendocrine type. *Gynecol Oncol* 2004; 92: 372–375.
44. Aslam MF, Choi C and Khulpateea N. Neuroendocrine tumour of the ovary. *J Obstet Gynaecol* 2009; 29: 449–451.
45. Lindboe CF. Large cell neuroendocrine carcinoma of the ovary. *APMIS* 2007; 115: 169–176.
46. Choi YD, Lee JS, Choi C, et al. Ovarian neuroendocrine carcinoma, non-small cell type, associated with serous carcinoma. *Gynecol Oncol* 2007; 104: 747–752.
47. Eichhorn JH and Young RH. Neuroendocrine tumors of the genital tract. *Am J Clin Pathol* 2001; 115 Suppl: S94–112.
48. Chenevert J, Bessette P, Plante M, et al. Mixed ovarian large cell neuroendocrine carcinoma, mucinous adenocarcinoma, and teratoma: a report of two cases and review of the literature. *Pathol Res Pract* 2009; 205: 657–661.
49. Draganova-Tacheva RA, Khurana JS, Huang Y, et al. Large cell neuroendocrine carcinoma of the ovary associated with serous carcinoma with mucin production: a case report and literature review. *Int J Clin Exp Pathol* 2009; 2: 304–309.
50. Yasuoka H, Tsujimoto M, Fujita S, et al. Monoclonality of composite large cell neuroendocrine carcinoma and mucinous epithelial tumor of the ovary: a case study. *Int J Gynecol Pathol* 2009; 28: 55–58.
51. Jones K, Diaz JA and Donner LR. Neuroendocrine carcinoma arising in an ovarian mucinous cystadenoma. *Int J Gynecol Pathol* 1996; 15: 167–170.
52. Ohira S, Itoh K, Shiozawa T, et al. Ovarian non-small cell neuroendocrine carcinoma with paraneoplastic parathyroid hormone-related hypercalcemia. *Int J Gynecol Pathol* 2004; 23: 393–397.
53. Miyamoto M, Takano M, Goto T, et al. Large cell neuroendocrine carcinoma arising in mature cystic teratoma: a case report and review of the literature. *Eur J Gynaecol Oncol* 2012; 33: 414–418.
54. Terada T. Large cell neuroendocrine carcinoma with sarcomatous changes of the endometrium: a case report with immunohistochemical studies and molecular genetic study of KIT and PDGFRA. *Pathol Res Pract* 2010; 206: 420–425.
55. Mulvany NJ and Allen DG. Combined large cell neuroendocrine and endometrioid carcinoma of the endometrium. *Int J Gynecol Pathol* 2008; 27: 49–57.
56. Deodhar KK, Kerkar RA, Suryawanshi P, et al. Large cell neuroendocrine carcinoma of the endometrium: an extremely uncommon diagnosis, but worth the efforts. *J Cancer Res Ther* 2011; 7: 211–213.