# Neuroendocrine Neoplasms of the Ovary: A Retrospective Study of the North Eastern German Society of Gynecologic Oncology (NOGGO)*

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**Abstract.** *Background/Aim: Neuroendocrine neoplasms (NEN) of the female genital tract account for 2% of gynecological cancers. The aim of this study was to share our experience of 11 primary neuroendocrine neoplasms of the ovary. Patients and Methods: All patients who presented and/or were treated at our Institution with histologically-confirmed NEN of the ovary were included. Clinical data including tumor stage, diagnostic and therapeutic management and survival were assessed. Pathological specimens were critically reviewed. Results: We identified 11 patients with NEN of the ovary consisting of nine neuroendocrine cancers and two carcinoids. Median age was 55.9 years. NEN were mostly poorly differentiated (72.4%). Primary surgery was performed in all patients. Adjuvant chemotherapy was administered in five patients consisting of platinum-based regimens. Median overall survival was 20 months. Conclusion: We propose a diagnostic algorithm for NEN of the ovary and discuss possible treatments according to FIGO stages. Patients should be included in multicenter studies whenever possible.*

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Neuroendocrine neoplasms (NEN) are a rare tumor entity arising from the diffuse neuroendocrine cell system. Most NEN are located in the gastroenteropancreatic system. Prognosis of this tumor entity is mainly dependent on the histological differentiation and grading, as measured by proliferative activity. In a large study performed earlier 5-year survival was found to be 50.4% if all malignant tumors were included. The cornerstone of treatment is surgical resection. Systemic chemotherapy, use of radio-nuclides and palliative surgery are effective methods for certain types of advanced neuroendocrine tumors. Cisplatinum in combination with etoposide is a very common chemotherapy regimen in poorly differentiated neuroendocrine carcinoma (1, 2). Carcinoids are a sub-group of slowly-growing neuroendocrine tumors that may be associated with production of vasoactive substances such as serotonin, that can lead to flushing and diarrhea, the so-called carcinoid syndrome. Symptom control in symptomatic carcinoid patients and tumor growth control can be achieved by somatostatin analogues such as octreotide or lanreotide (3, 4).

NEN with the primary in the female genital tract are extremely rare and account for less than 2% of gynecological cancers (5, 6). Most gynecological NEN are located in the uterine cervix and classified as small-cell neuroendocrine cancer or in the ovary as carcinoids (5, 7). Symptoms observed at initial diagnosis in NEN of the female genital tract are vaginal bleeding, vaginal discharge, pain, weight loss, constipation, hirsutism, malignant ascites and sometimes ectopic hormone production such as serotonin and vasopressin. The diagnosis of NEN mostly relies on histology including immunohistochemistry. Most common markers are chromogranin A, synaptophysin and neuron-

Table I. *Patients' overview.*

| Patient | Age at diagnosis (years) | FIGO | N | M | Grading | Ki-67 | Histology | Surgery | Chemotherapy | OAS (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 23 | 2 | N0 | MX | III | n.k. | Large cell | BSO+HE+Omentectomy+pelvic/ paraortic lymphonodectomy+ partial colon resection+appendectomy | Carboplatin/ Taxol after surgery | Alive, 111 months follow-up |
| 2 | 86 | 4 | N1 | M1 | III | 90 | n.s. | BSO+HE+Omentectomy+pelvic/ appendectomy paraortic lymphonodectomy+ partial colon resection+appendectomy | none | 2.1 |
| 3 | 40 | 1 | N0 | M0 | III | 50 | Small cell | BSO+Omentectomy+appendectomy | Cisplatin after surgery | 20 |
| 4 | 32 | 1 | N0 | M0 | I | n.k. | Carcinoid | BSO+HE+Omentectomy+pelvic/ paraortic lymphonodectomy+ appendectomy | None | Alive, 19 months follow-up |
| 5 | 64 | 3 | N1 | M0 | III | 70 | Small cell | Previous BSO, at diagnosis HE+Omentectomy+pelvic/ paraortic lymphonodectomy+ partial colon resection | None | 8 |
| 6 | 75 | 4 | N0 | M1 | III | n.k. | n.s. | BSO+HE+Omentectomy+ partial colon resection | Carboplatin/ Taxol after surgery | 11 |
| 7 | 61 | 1 | N0 | M0 | I | 5-10 | Large cell | BSO+HE | None | Alive, 37 months follow-up |
| 8 | 34 | 1 | NX | M0 | III | 5 (30% in metastasis) | n.s. | Salpingectomy on the left side | Cisplatin/Etoposide (5 yrs after diagnosis, progressive disease) | 80 |
| 9 | 62 | 1 | N0 | M0 | I | n.k. | Carcinoid | BSO+HE+Omentectomy+pelvic/ paraortic lymphonodectomy | None | Alive, 213 months follow-up |
| 10 | 69 | 3 | N1 | M0 | III | 60 | n.s. | BSO+HE+Omentectomy+ partial colon resection | Carboplatin/ Taxol after surgery | 8 |
| 11 | 69 | 3 | N0 | M0 | III | 60 | n.s. | BSO+HE+Omentectomy+pelvic/ paraortic lymphonodectomy | Carboplatin after surgery | 24 |

n.s., Not significant.

specific enolase. Somatostatin receptor scintigraphy can help detect the primary in well-differentiated NEN (grade I and II). There exist no treatment guidelines for NEN of the female genital tract. Due to this, many patients are treated according to protocols used for epithelial cancer of the genital tract and not according to recommendations for NEN of *e.g.* the gastrointestinal system. Neuroendocrine neoplasms of the ovary, for example, are often treated with debulking surgery followed by adjuvant chemotherapy with carboplatinum and paclitaxel in line with treatment standards for epithelial ovarian cancer, while neuroendocrine neoplasms of the cervix receive treatment according to guidelines for cervical cancer. The absence of guidelines as well as the lack of detailed knowledge on this rare tumor entity of the female genital tract may very well contribute to the poor prognosis of this condition.

The aim of the present study was to share our experience of neuroendocrine neoplasms arising from the ovary. Eleven patients with NEN of the ovary were analyzed to further enrich clinical knowledge of this very rare disease to guide further therapeutic approaches.

## Patients and Methods

In order to identify patients with NEN in the female genital tract a retrospective chart review of all patients with histologically-confirmed NEN of the ovary, treated at the Charité – University Medicine Berlin during the period from 1996 to 2011, was performed. Also patients that were presented to our "second-opinion center" from other institutions were included. Ethical approval was given by the ethical committee of the Charité University Berlin (number assigned by ethics board: EA2/075/12). All histological analyses were made by pathologists specialized for both gynecological malignancies and neuroendocrine neoplasms. The diagnosis "neuroendocrine neoplasm" was made if immunhistochemical markers for neuroendocrine differentiation, such as chromogranin A, synaptophysin and/or neurone-speficic enolase, were positive.

Diagnostics included a thorough history taking, clinical and gynecological examination, vaginal ultrasound, CT scan and/or somatostatin receptor imaging (Octreotide scintigraphy).

Table II. *Details of immunohistochemistry.*

| Immunohistochemistry | | |
|---|---|---|
| Chromogranin A (n=8) | Positive | 5 (62.5%) |
| | Negative | 3 (37.5%) |
| Synaptophysin (n=7) | Positive | 5 (71.4%) |
| | Negative | 2 (28.6%) |
| CD56 (n=6) | Positive | 5 (83.3%) |
| | Negative | 1 (16.7%) |
| CK7 (n=8) | Positive | 7 (87.5%) |
| | Negative | 1 (12.5%) |
| CK20 (n=3) | Positive | 2 (66.7%) |
| | Negative | 1 (33.3%) |
| Neuron-specific enolase (n=3) | Positive | 2 (66.7%) |
| | Negative | 1 (33.3%) |

Surgery was always performed by gynecological oncologists. Primary aims were a complete tumor resection and adequate staging according to FIGO guidelines. Standard procedures included midline laparotomy, peritoneal cytology, extrafascial hysterectomy, adnectomy and omentectomy. When necessary for complete tumor debulking, additional procedures like pelvic and para-aortic lymph node dissection, appendectomy and bowel resection were performed.

Medical charts were reviewed systematically regarding to demographic and clinical characteristics, including age at primary diagnosis, risk factors, medical history, diagnosis, stage, histological sub-type and grading according to ovarian cancer, surgical procedures and chemotherapy. Follow-up was updated if the last contact was more than 3 months ago. Patients have been regularly evaluated every 3 months for any evidence for tumor progression or recurrent disease by clinical examination and ultrasound.

Data were analyzed with the software program PASW 21 (SPSS Inc., Chicago, IL, USA). All results are presented in raw numbers, rates, medians or ranges depending on the underlying distribution. Correlations were performed with the Chi-square test or the Kendall's tau-b. Survival curves were estimated according to the method of Kaplan-Meier.

## Results

Eleven patients with NEN of the ovary were included in the study: 9 neuroendocrine cancers and 2 carcinoids. Two patients with neuroendocrine cancers had a focal neuroendocrine differentiation only within an ovarian cancer. Median age at diagnosis was 55.9 years (range=23-86 years). More than half of the patients were diagnosed in FIGO stages I/II (6 patients, 54.6%). Two patients already had distant metastasis at initial diagnosis – one patient with lung metastasis and the other one with infiltrates inside the urothelium of the urinary bladder. Most NEN were poorly differentiated (8 NEN, 72.4%) according to the grading classification of ovarian cancer. Ascites was present in 6 patients (54.5%). Table I shows a summary of all patients.

*Histology and immunohistochemistry.* Two patients were diagnosed with small-cell and two with large-cell neuroendocrine cancer of the ovary. Two patients (patient 4 and 9 in Table I) were diagnosed with carcinoids. Ki-67 was positive in seven patients: In five cases it was higher than 20% describing G3 tumors according to neuroendocrine classification. Most common markers in immunohistochemistry were chromogranin A being positive in 62.5%, synaptophysin being positive in 71.4% and CD56 being positive in 83.3%. Immunohistochemistry details are illustrated in Table II. An example of immunohistochemistry can be seen in Figure 1.

*Surgery.* Primary surgery was performed in all cases. Except for one case, all patients received bilateral salpingooophorectomy and hysterectomy. Fertility was preserved in one patient (patient 8) (Table I) by performing unilateral salpingooophorectomy only. However, when she developed recurrent disease two years after her initial diagnosis salpingooophorectomy of the other side and hysterectomy were then performed. Systematic pelvic and paraaortic lymphonodectomy was performed in six patients (54.5%). Bowel resection was necessary in five patients (45.5%) and omentectomy in nine patients (81.8%) in order to achieve optimal tumor debulking. Eight patients had no macroscopic tumor residuals left after the operation.

*Adjuvant chemotherapy.* Adjuvant chemotherapy was administered in five patients after surgery: Carboplatin and paclitaxel was applied in three patients, single-agent carboplatin and single-agent cisplatin in one patient each. Another five patients including the two carcinoid patients did not receive any chemotherapy at all. Patient 8 received cisplatin and etoposide five years after initial diagnosis due to progressive disease. Second-line chemotherapy was necessary in three patients: Patient 3 developed recurrent disease one year after initial diagnosis in the pelvis, bone and pulmonary metastasis so that it was decided to administer carboplatin in combination with etoposide. She further received six cycles of FOLFOX as third-line chemotherapy four month after completion of second-line chemotherapy. She died within nine months after FOLFOX therapy. Patient 11 was treated with six cycles of paclitaxel as second-line and two cycles of topotecan as third-line chemotherapy. She died one month after the second cycle of topotecan. Patient 1 developed recurrent disease within six month after adjuvant chemotherapy with carboplatin and paclitaxel so that a second-line chemotherapy with six cycles of topotecan was administered. Since then she has not suffered from progressive disease.

*Survival.* Median overall survival was 20 months (range=2-213 months) and median progression-free survival was 12 months. Table I shows overall survival for each patient.

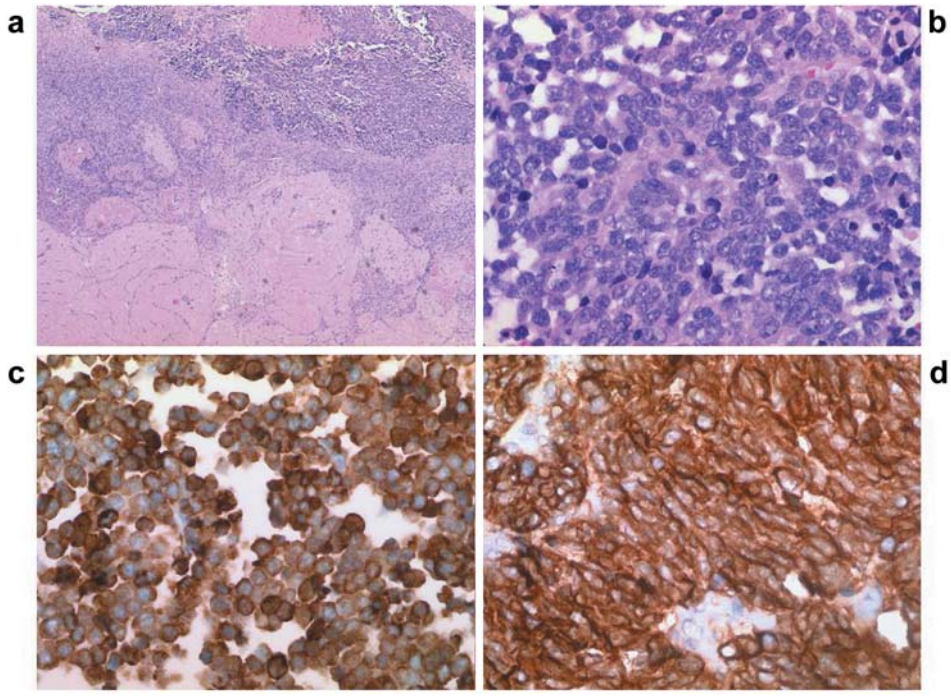


Figure 1. *Example of a neuroendocrine cancer. (a): Tumor below a corpus albicans. (b): Morphology of the tumor. Magnification ×400. Tumor cells have enlarged basophilic nuclei with granular to vesicular chromatin. Mitoses are easily detectable (arrows). (c): Neuroendocrine marker synaptophysin shows strong immunohistochemical cytoplasmatic reactivity. Magnification ×400. (d): Neuroendocrine marker CD56 shows strong immunohistochemical cytoplasmatic reactivity. Magnification ×400.*

Patients who were diagnosed with advanced stages had a significant shorter overall survival ($p$=0.003) and a significant shorter progression-free survival ($p$=0.006). When comparing the overall survival of patients with distant metastasis (M1) *versus* patients without distant metastasis overall survival was significantly better in patients without metastasis ($p$=0.027). However, there was no significant difference regarding the progression-free survival of patients with M1 and M0 ($p$=0.066).

## Discussion

In the present article we summarized 11 cases of NEN of the ovary. Most NEN of the ovary are associated with an epithelial ovarian cancer in terms of a focal neuroendocrine differentiation. Pure ovarian NEN are extremely rare (8). In our analyses there were seven pure NEN - the largest amount reported so far.

Due to the rarity of the disease no diagnostic and no treatment guidelines exist. So far 36 cases with ovarian non-small cell neuroendocrine carcinoma (LCNEC) have been reported in the literature (9-12). Most ovarian NEN are treated according to ovarian cancer treatment guidelines. However, ovarian NEN are – despite their often early diagnosis – more aggressive with a median OS of 20 months in our study. Median OS for all poorly-differentiated tumors was 10.9 months. The 5-year survival rate in the study of Oshita *et al*. who summarizes all 33 reported LCNEC, was 34.9% (9).

The most important pathological tool for the diagnosis of neuroendocrine neoplasms is immunohistochemistry. In order to diagnose a neuroendocrine neoplasm of the female gynecological tract there should be at least two positive neuroendocrine markers. Rekhi *et al*. reported that 88% of their collective with cervical NEN being positive for at least one neuroendocrine marker (13). The marker most frequently used in the analysis of Rekhi *et al*. was synaptophysin. They proposed an immunohistochemistry panel of synaptophysin, chromogranin and CD56. In our collective these three markers were positive in 71.4%, 62.5% and 83.3% respectively. The most common markers in our study were CK7 with a positivity in 87.5%, followed by CD56 with a positivity in 83.3%.

The protein Ki-67 is a marker for the aggressiveness of a tumor and strictly associated with cell proliferation. It is the essential component in the WHO classification of gastro-entero-pancreatic neuroendocrine neoplasms, and should be evaluated when diagnosing a neuroendocrine neoplasm. The grading of neuroendocrine tumors of the gastroenteropancreatic

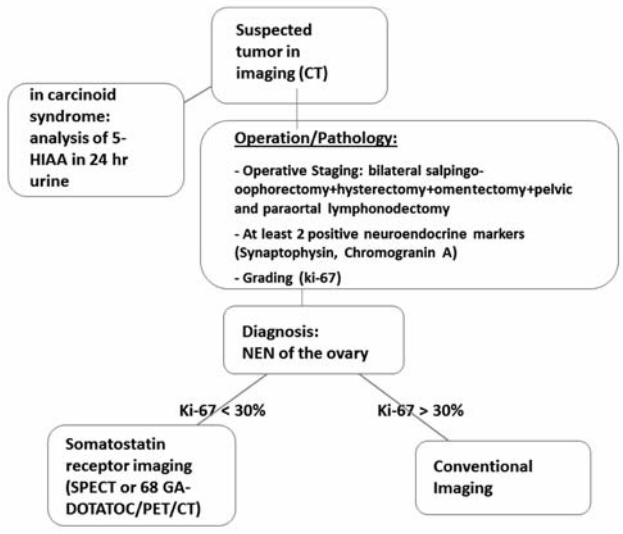


Figure 2. *Proposed diagnostic algorithm.*

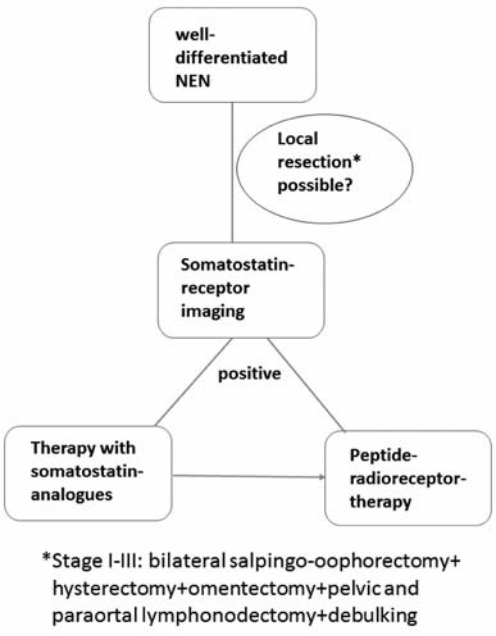


Figure 3. *Proposed therapy for well-differentiated neuroendocrine neoplasms.*

system is based on the percentage of Ki-67. In contrast to this fact, it is often not evaluated in neuroendocrine tumors of the gynecological tract. However, it is not only helpful in guiding us with regard to treatment but it also determines the use of diagnostic tools. That is because if Ki-67 is below 30% a somatostatin receptor imaging (either as octreotide scintrgraphy or 68Ga-DOTATOC.PET/CT) can provide additional information to a conventional CT scan for staging and therapy selection. Tumors expressing somatostatin receptors can be detected with the somatostatin receptor scintigraphy (14). In Figure 2 we propose a potential diagnostic algorithm for ovarian NEN.

In most patients ovarian NEN surgery was performed with the aim of complete macroscopic tumor resection. Bilateral salpingo-oophorectomy and total abdominal hysterectomy are the most common procedures in the literature, which was also the case in our study. In early-stage carcinoid tumors confined to one ovary unilateral salpingo-oophorectomy with a fertility-sparing approach with thorough follow-ups is possible (15). Oshita *et al*. reported that 29 out of 33 patients received adjuvant chemotherapy that was platinum-based in all reported cases by Veras *et al*. (8, 9). Platinum-based chemotherapy seems to be the adjuvant treatment-of-choice in poorly-differentiated NEC, and should always be administered in stages III and IV (Figure 4). In small cell NEC cisplatin and etoposide - according to the treatment of neuroendocrine cancers of the gastroenteropancreatic system and small cell lung cancer - is an adequate option. In large cell NEC the therapeutic choice might be different although sufficient clinical data are lacking to support an alternative approach to small cell NEC. We propose a platinum-based

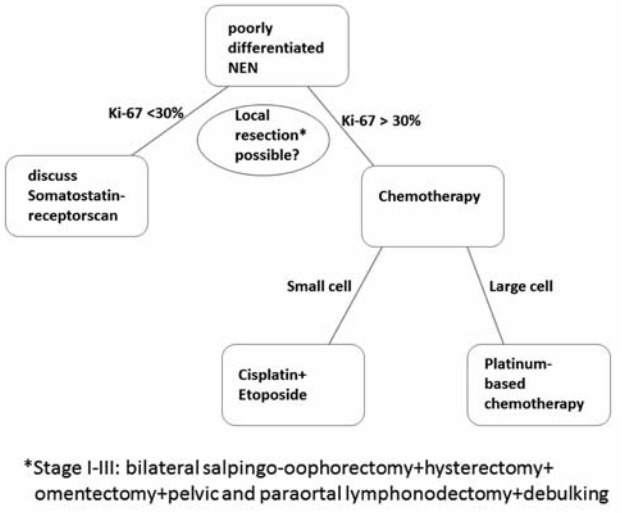


Figure 4. *Proposed therapy for poorly-differentiated neuroendocrine neoplasms.*

chemotherapy *e.g*. with cisplatin. It should be emphasized that all patients should be treated within a clinical study setting whenever possible and treatment should be discussed in interdisciplinary tumor conferences.

However, it is unclear if adjuvant chemotherapy should be always administered in early stages. There are two patients (patient 7 and 8) in our collective who were diagnosed with

an ovarian NEC FIGO stage I N0 M0 with a Ki-67 of 5-10%. They both did not receive adjuvant chemotherapy after their surgery. Patient 7 is still free of disease 37 months after initial diagnosis while patient 8 developed progressive disease five years after initial diagnosis and then chemotherapy was administered. In our opinion it is feasible to perform debulking surgery alone in patients with Ki-67 ≤5% and FIGO Ia. This should be especially taken into account in younger patients with unfulfilled wish for a child, FIGO Ia and Ki-67 ≤5%, where a unilateral salpingo-oophorectomy might be sufficient. In general, there is limited evidence to use systemic chemotherapy in slowly growing low proliferative NET, and alternative approaches such as somatostatin receptor targeted therapies should be considered.

In few cases in the literature somatostatin analogues such as octreotide were administered to slow tumor growth and to improve carcinoid symptoms (16-18). Octreotide was even shown to induce a remission in a patient with an endometrial NEN refractory to chemotherapy (17). We have not administered these substances, as there is not enough evidence of their efficacy in neuroendocrine neoplasms of the female genital tract. This therapeutic management is in contrast to neuroendocrine neoplasms in the gastroenteropancreatic system where octreotide and lanreotide are established and approved therapies and thus frequently used in order to improve symptoms and to slow tumor growth (2). In Figures 2 and 3 we propose treatment algorithms for well and poorly differentiated NEN.

*Pros and cons of current therapy*. The existing therapy options for ovarian NEN remain on a foundation of little evidence. Surgical resection is unquestionable the cornerstone of therapy, with undoubted benefit for the patient (15). Whether radical surgery including prophylactic omentectomy and hysterectomie provides an added benefit is unclear at this point. It is routinely performed, as an adaption from ovarian cancer surgery, but might very well be unnecessary. Systemic therapy options are likewise associated with pros and cons. Somatostatin analogues or peptide-radioreceptor therapy represent a therapy option with a rather indolent side effect profile. But since they are bound to the existence of somatostatin receptors, a positive receptor scan prior the therapy is obligatory. Also the efficacy of this option seems to be limited to well-differentiated neoplasms and should only be discussed in poorly differentiated tumors, when the Ki-67 index remains below 30%. In cases of poorly differentiated neoplasms with high proliferation index (Ki-67 >30%) chemotherapy remains the only option. The major point of controversy with chemotherapy remains the fact, that the benefit of adjuvant chemotherapy after surgical resection is not proven due to the rarity of this entity and the lack of study data. The con for this therapy option, could be the hypothesis, that it brings no benefit to the patient while being associated to substantial side effects like nausea, hair-loss and hemotoxicity

Neuroendocrine neoplasms of the ovary are a very rare tumor entity in gynecological oncology. Treatment guidelines do not exist and it remains unclear if this tumor entity should be treated according to treatment guidelines of NEN of the gastroenteropancreatic system or according to the guidelines of ovarian cancer. It is known, however, that surgery is the cornerstone of therapy and should be performed in any case. Larger, multicenter studies are warranted to shed more light on this rare tumor entity and to optimize treatment.

## Conflicts of Interest

The Authors declare that they have no competing interests.

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## References

1 Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen D-T, Helm J and Kvols L: First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer *117*: 268-275, 2011.

2 Oberg KE: The management of neuroendocrine tumours: current and future medical therapy options. Clin Oncol R Coll Radiol G B *24*: 282-293, 2012.

3 Modlin IM, Pavel M, Kidd M and Gustafsson BI: Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. Aliment Pharmacol Ther *31*: 169-188, 2010.

4 Rinke A, Müller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, Mayer C, Aminossadati B, Pape U-F, Bläker M, Harder J, Arnold C, Gress T, Arnold R and PROMID Study Group: Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol Off J Am Soc Clin Oncol *27*: 4656-4663, 2009.

5 Crowder S and Tuller E: Small cell carcinoma of the female genital tract. Semin Oncol *34*: 57-63, 2007.

6 Vora M, Lacour RA, Black DR, Turbat-Herrera EA and Gu X: Neuroendocrine tumors in the ovary: histogenesis, pathologic differentiation, and clinical presentation. Arch Gynecol Obstet, 2015.

7 Eichhorn JH and Young RH: Neuroendocrine tumors of the genital tract. Am J Clin Pathol *115 Suppl*: S94-112, 2001.

8 Veras E, Deavers MT, Silva EG and Malpica A: Ovarian nonsmall cell neuroendocrine carcinoma: a clinicopathologic and immunohistochemical study of 11 cases. Am J Surg Pathol *31*: 774-782, 2007.

9 Oshita T, Yamazaki T, Akimoto Y, Tanimoto H, Nagai N, Mitao M, Sakatani A and Kaneko M: Clinical features of ovarian large-cell neuroendocrine carcinoma: Four case reports and review of the literature. Exp Ther Med *2*: 1083-1090, 2011.

10 Asada K, Kawana K, Teshima S, Saito A, Kawabata M and Fujii T: Poor prognosis of ovarian cancer with large cell neuroendocrine carcinoma: case report and review of published works. J Obstet Gynaecol Res *40*: 869-872, 2014.
11 Shakuntala PN, Uma Devi K, Shobha K, Bafna UD and Geetashree M: Pure large cell neuroendocrine carcinoma of ovary: a rare clinical entity and review of literature. Case Rep Oncol Med *2012*: 120727, 2012.
12 Miyamoto M, Takano M, Goto T, Kato M, Sasaki N and Furuya K: Large cell neuroendocrine carcinoma arising in mature cystic teratoma: a case report and review of the literature. Eur J Gynaecol Oncol *33*: 414-418, 2012.
13 Rekhi B, Patil B, Deodhar KK, Maheshwari A, A Kerkar R, Gupta S, Tongaonkar HB and Shrivastava SK: 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 *17*: 1-9, 2013.
14 Oberg K and Castellano D: Current knowledge on diagnosis and staging of neuroendocrine tumors. Cancer Metastasis Rev 30 Suppl *1*: 3-7, 2011.
15 Reed NS, Gomez-Garcia E, Gallardo-Rincon D, Barrette B, Baumann K, Friedlander M, Kichenadasse G, Kim J-W, Lorusso D, Mirza MR and Ray-Coquard I: Gynecologic Cancer InterGroup (GCIG) consensus review for carcinoid tumors of the ovary. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc *24*: S35-41, 2014.
16 Pistilli B, Grana C, Fazio N, Cavaliere A, Ferrari M, Bodei L, Baio S, Scambia G, Paganelli G and Peccatori F: Pregnant with metastatic neuroendocrine tumour of the ovary: what now? Ecancermedicalscience *6*: 240, 2012.
17 Verschraegen CF, Matei C, Loyer E, Malpica A, Tornos C, Kudelka AP and Kavanagh JJ: Octreotide induced remission of a refractory small cell carcinoma of the endometrium. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc *9*: 80-85, 1999.
18 Grozinsky-Glasberg S, Grossman AB and Korbonits M: The role of somatostatin analogues in the treatment of neuroendocrine tumours. Mol Cell Endocrinol *286*: 238-250, 2008.

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