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A Society of Gynecologic Oncology Evidence-based Review (and Recommendations)

Neuroendocrine tumors of the gynecologic tract update

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HIGHLIGHTS

- WHO has updated NET classifications in order to simplify terminology across NETs.
- Treatment recommendations for cervical NEC have been updated and outlined.
- Hypercalcemic type ovarian NECs are no longer considered true NENs.
- Treatment for most gynecologic NECs/NENs is derived from experience with other NETs.
- Clinical trials are needed to improve outcomes in patients with NETs.

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1. Introduction

Neuroendocrine tumors of the gynecologic tract are rare and therefore limited guidelines for treatment exist. Current treatment recommendations are often extrapolated from histologically similar tumors from other sites or are based on retrospective studies. In 2011, the Society of Gynecologic Oncology published a clinical document outlining treatment recommendations for women with neuroendocrine tumors of the gynecologic tract [1]. Since the first document, there have been changes to the classification system of these tumors, advancements in the understanding of the underlying molecular genetics, and new and novel treatment recommendations. This evidence-based review is an update to the 2011 document.

2. Methods

To identify all new relevant studies, a Medline search was conducted using the phrases "neuroendocrine, carcinoid, non-small cell" which were combined with cervix, endometrial, uterine, ovarian, vulva, and vagina. Only studies published between 2011 and 2020 were considered for inclusion as the prior manuscript covered studies before that period. For sections in which there was no new data available, this is stated.

3. Terminology

What is the latest terminology for describing neuroendocrine tumors (NETs) of the female reproductive system? What is the grading system for NETs?

The terminology has historically been confusing for gynecologic neuroendocrine tumors. In 2014, the World Health Organization (WHO) classification of tumors (4th edition) classified neuroendocrine tumors (neuroendocrine neoplasms or NEN) by organ system and tumor type and clearly divided them into low-grade and high-grade [2]. At that time, cervix, corpus and vulva/vagina were updated to low-grade neuro-endocrine tumor (NET) and high-grade neuroendocrine carcinoma (NEC) categories, along with an additional Merkel cell carcinoma (MCC) designation for the vulva. The older terminology of "carcinoid" and "atypical carcinoid" were considered equivalent to NET (low grade), while "small cell" and "large cell" were equivalent with NEC (high grade). Ovarian tumors did not receive separate identification of NENs. The following subtypes of ovarian tumors were included in the classification system but not officially identified as NEN at this anatomic site: carcinoid tumor, small cell carcinoma, and paraganglioma. Large cell terminology did not exist for ovarian tumors. Of note, small cell carcinoma was divided into pulmonary type and hypercalcemic type.

In 2017–18, the WHO and International Agency for Research on Cancer (IARC) convened a consensus task force to introduce new terminology that would, ultimately, be incorporated into the 5th edition of WHO classification of tumors [2–5]. While recognizing that there may be some differences based on anatomic site of origin, this system was meant to allow both pathologists and clinicians to manage all NENs in a consistent fashion to allow further research and for prognostic purposes. The recommended classification distinguishes between differentiated neuroendocrine tumor (NET, grades 1–2) and poorly differentiated (grade 3) neuroendocrine carcinoma (NEC) for all sites. Grading would only be performed for NETs (Grades 1–2) under strict guidance, as provided within the consensus document, utilizing Ki-67 labeling index performed by IHC on the regions of most intense labeling (0.4 mm^2), mitotic count and other specific tumor characteristics (such as necrosis). The specific anatomic site of tumor should be specified for treatment purposes, but is technically no longer a component of the classification system across ALL disease sites.

The terms carcinoid and atypical carcinoid were removed from the terminology. The only exception to this is the ovarian carcinoid tumor due to its excellent prognosis as compared to other NET's. Additionally, there is no further grading of Grade 1 vs. 2 tumors in ovary. Rather, of the various histologic subtypes, the only two entities that are classified are the ovarian carcinoids (Grade 1) and the ovarian NEC (grade 3). NEC itself is further subdivided into small cell, large cell and combined (or mixed) carcinoma of small cell or large cell type given that the NEC is often not a pure neuroendocrine tumor and is admixed with other high-grade carcinomas. Table 1 summarizes the WHO classification as provided in the 5th addition.

4. Epidemiology

Specifically, with regard to gynecologic NENs, the actual incidence is difficult to ascertain given that the definitions and classifications have changed dramatically over the last 30 years and especially within the last 10–15 years. Generally, NENs are thought to account for ≤2% of all gynecologic malignancies [6–8] and as such are quite rare when compared to other gynecologic malignancies. Using the Surveillance, Epidemiology and End Results (SEER) cancer registry data, Gibbs et al. identified 559 cases of gynecologic neuroendocrine tumors of which 242 were cervical, 160 were ovarian, 118 were uterine and 39 were vulvar/vaginal [5].

The low-grade NETs are typically indolent and benign in nature. These tend to occur more commonly in the ovary than in any other gynecologic site, hence they have been reclassified in the 5th edition [8–10]. The NECs, however, are extremely aggressive and the majority tend to present with advanced disease. In a recent study that divided patients into two time points (1987–1999 and 2000–2012), there was no significant change in overall survival across all gynecologic NET subtypes. As the authors grouped both low grade and high-grade tumors together, the survival outcomes cannot be separated for the two groups. However, a contemporary SEER database study separated out for high grade neuroendocrine carcinomas and identified 832 cases [11]. Patients with stage I disease had a 61% survival as compared to 33% for patients with stage III disease.

The importance of continued research and targeted therapies is highlighted given the poor clinical outcomes. For the purposes of this manuscript, gynecologic neuroendocrine tumors will be described as

Table 1
Current classification system for neuroendocrine neoplasms of the gynecologic tract. Modified from the 5th edition WHO terminology [5].

Category/Family	Grade	Site
NET	1, 2	Uterus, Cervix, Vulva, Vagina
NEC:	3	Ovary, Uterus, Cervix, Vulva, Vagina
Small Cell		
Large Cell		
Combined Small Cell NEC		
Combined Large Cell NEC		
Carcinoid	1	Ovary Only

NENs for the entire group and differentiated for treatment purposes (where these data exist) between NET and NEC.

5. Cervical NENs

How are cervical NENs different from other cervical cancers?

There are two different classifications of cervical NENs: NET and NEC. NETs (primarily low grade) encompass carcinoid and atypical carcinoid, which are extremely rare variants and will not be addressed in the current manuscript as only case reports exist with mostly unconfirmed pathology. The most common subtype of NEC is small cell (~80%) followed by large cell carcinoma (12–15%) and others (~7.6%) [10]. Patient outcomes have been evaluated utilizing prior FIGO staging (2009 and earlier) with only one group using the updated 2018 staging system which includes nodal evaluation [10]. In general, based on the older staging systems, patients present with similar stage distribution to typical squamous cervical cancer. Ultimately, comparison of stage for stage outcomes when incorporating lymph node involvement will need to be performed.

The most significant difference related to NEC as compared to typical cervical cancer (squamous and adenocarcinoma) is response to therapy, risk of recurrence and overall survival (OS). The five-year OS for these tumors when diagnosed at Stage I-II is ~20–50% (some studies suggest as high as 85% in early and microscopic Stage IA disease); however, this decreases to ~2–15% for patients with Stage III-IV disease. Prognostic factors for worse outcomes identified in the literature include lympho-vascular space invasion (LVSI), locally advanced disease, lymph node involvement and distant disease [7,12–16]. However, these data are primarily based on small retrospective studies.

What is the difference between low-grade and high-grade cervical NETs?

As stated previously, low-grade cervical NETs are very rare and encompass Grade 1 (typical carcinoid) and Grade 2 (atypical carcinoid). Using the 5th edition WHO terminology, the poorly differentiated (high grade) include small and large cell variants. The difference in grading of cervical NETs is based on mitotic index and Ki-67. Low grade NETs have a mitotic index of <2/10 hpf and Ki-67 index of ≤2 and the high-grade NETs have a mitotic index >20/10 hpf and a Ki-67 index of >20 [10].

What is the role of HPV in the etiology of high-grade cervical NENs?

Since the last publication, the role of HPV in the development of cervical NENs has been evaluated and an association between these tumors and HPV 16 and 18 has been described. In a study of 49 tumors with neuroendocrine features, which included carcinoid, atypical carcinoid, large cell and small cell carcinoma. The authors identified HPV in 42 of the samples (86%); HPV 16 was found in 55% and HPV 18 in 41% [17]. The authors also performed p16 staining and in the 44 cases in which it could be completed, 86% showed over-expression. Overall, concordant findings of p16 and HPV detection was noted in 89% of cases. These data suggest an association between HPV and NEN. A large systematic review and meta-analysis drew similar conclusions [18]. The authors included a total of 448 cases of small cell neuroendocrine carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC) from 41 studies and found that 85% of SCNEC and 88% of LCNEC were HPV positive of which HPV 16 and HPV 18 were primarily involved. There was a predominantly higher proportion of HPV 18 than HPV 16 in SCNEC as compared to other cervical cancer histologies, including LCNEC.

What is the Immunohistochemical (IHC) and molecular profile of cervical NECs?

5.1. IHC characterization

Pathologic diagnosis of LCNEC requires both morphologic characteristics and identification of neuroendocrine markers by IHC while SCNEC can be diagnosed based on morphology alone. Specifically, the neuroendocrine markers typically utilized include chromogranin, CD56, synaptophysin and PGP9.5. The most sensitive markers are CD56 and synaptophysin, while chromogranin is the most specific. Most of these tumors will also be positive for p16 given the association with HPV. P63 can also be used to differentiate between a non-NEN variant of squamous cell carcinoma, as the vast majority of NEN tumors are negative for p63. Ki67 is also used in the newer classification [8,9,12,19]. In addition, newer markers are also under evaluation. For example, insulinoma-associated protein 1 (INSM1) may ultimately be more specific than the above noted markers. Kuji et al., in a study of 37 NECs of the cervix, noted positive INSM1 staining in >95% of cases [20].

5.2. Molecular characterization of Cervical NEC

A small number of studies have examined mutational hotspots in these neoplasms and attempted to characterize them from a molecular/somatic mutation standpoint. Frumovitz et al., studied 44 patients with SCNEC and found mutations in *PIK3CA* (18%), *KRAS* (14%) and *TP53* (11%) as the most common somatic mutations. At least 55% of these patients had ≥1 mutation present, many of which were targetable [21]. The authors suggested that these molecular changes were different from other HPV-mediated pure squamous cell tumors. However, other studies have found profiles that corroborate both these findings but also HPV specific mediated changes in the MAPK, PI3K/AKT/mTOR, and p53 pathway [22–24]. Prior to next-generation sequencing, loss of heterozygosity (LOH) studies were used to identify "hotspots." Mixed results were seen but specifically identified in the short arm of Chromosome 3 in up to 44% of patients studied and on Chromosome 17 (p53 locus) in 0–40% of patients [25,26]. A recent comprehensive genomic profiling of 97 patients with high-grade cervical NEC reported that 73% of these tumors had potentially actionable alterations with the most common being PIK3CA, MYC, TP53 and PTEN. In addition, homologous recombination and high tumor mutation burden were identified [27]. In general, molecular analysis via proteomic and transcriptomic approaches will continue to provide potential targetable pathways in these cancers.

Limited data are available regarding typical immunotherapy markers that can be used to identify patients that may benefit from immuno-oncology (IO) agents. Eskander et al. reported that 2% of tumors had a high tumor mutation burden. In a small study of ten patients, Morgan et al. demonstrated PD-L1 expression in 70% of tumors and mismatch repair deficiency (dMMR) in 33%. They examined the concordance of dMMR and PD-L1 positivity in >10% of tumor cells and this occurred in 3/10 (30%) of the patient samples [28]. This is in contrast to a recently published manuscript by Carroll et al. in which 40 patient samples were tested for PD-L1, mismatch repair proteins, and Poly (ADP-ribose) polymerase (PARP). All 28 (100%) samples tested showed intact expression for mismatch repair proteins. Of the 31 samples tested for PD-L1 expression, 5 (16%) were positive. Interestingly, of the 11 small cell specimens tested for PARP-1, 10 (91%) showed PARP protein expression by IHC [29].

An additional whole genomic characterization by Hillman et al. on 15 patients with cervical NECs demonstrated a higher percentage of PI3K/MAPK mutations as compared to SCLC or bladder neuroendocrine tumors. This suggests that cervical NECs may behave more like typical squamous cell carcinoma or adenocarcinoma where these specific mutations are more common [30]. Ultimately, consideration of somatic profiling for these patients to determine utilization of IO and targeted agents should be strongly considered.

How are cervical NENs staged and what is the recommended imaging?

Cervical NENs are staged using the same FIGO system as for other cervical cancer histologies. The 2018 FIGO staging system allows for both pathologic and imaging findings to be included. SGO and NCCN guidelines currently recommend initial imaging evaluation with CT of chest, abdomen and pelvis and/or FDG-PET/CT. ^{68}Ga-dotatate PET/CT was FDA approved in 2016 and might be preferred in the future for cervical NEC although currently it is still utilized in trial protocols only. MRI of the abdomen and pelvis is not currently recommended, however many providers utilize this modality for treatment planning in other cervical histologies and this could be extended to NEC treatment planning as well. Brain imaging is not routinely performed unless distant metastasis (i.e. lung or liver) are identified or neurologic symptoms are present.

What is the recommended treatment for newly diagnosed SCNEC?

5.3. Early stage: IA1-IA2, IB1, IB2 and IIA1

5.3.1. Surgery

Many retrospective studies of early stage SCNEC include radical hysterectomy with lymph node assessment followed by either chemotherapy alone, chemoradiation or another sequence of radiation and chemotherapy. Ishikawa et al. reviewed 93 patients with Stage I-II NEC. Eighty-eight women (94.6%) underwent surgery, with the majority undergoing radical hysterectomy with pelvic lymphadenectomy and adjuvant chemotherapy +/− radiation therapy (60%). Only 5 patients underwent definitive radiation therapy, however these patients did worse with hazard ratio for recurrence (compared to surgery) 4.74 (95% CI 1.01–15.9) [27]. In another large retrospective analysis, Cohen et al. [31] reported on 135 patients with Stage I-IIA disease. Those that underwent radical hysterectomy ($n = 89$) had improved outcomes as compared to those who did not undergo surgery with 5 year OS (38.2% vs. 23.8 respectively $p < 0.001$). In their multivariable analysis, stage (OR 2.52; 95% CI 1.76–3.62, $p < 0.001$), radical hysterectomy (OR 0.62; 95% CI 0.41–0.94, $p < 0.026$) and chemotherapy (OR 0.62; 95% CI 0.41–0.92, $p < 0.19$) were independent predictors of survival.

Contrary to these studies, Wang et al. [14] found in a cohort of 146 women, that patients with stage IA– IIB disease who underwent any combination of surgery +/− adjuvant therapy at primary treatment had a trend of worse PFS (41.2% versus 60.5%, $p = 0.086$) and OS (47.9% versus 61.9%, $p = 0.122$) at 5 years compared to those who underwent primary chemotherapy and RT. While these were not statistically significant results, it suggests that there may be subsets of patients who might benefit more from surgery or from primary chemoradiation. The issue is being able to accurately predict these cohorts and triage them appropriately.

Two large database studies from the National Cancer Database (NCDB) and the SEER database comparing surgery vs. RT +/− brachytherapy were recently completed. Huo et al. did not find a significant difference in 5 yr. OS based on treatment for women with stage I (61% vs. 53% $p = 0.27$) or II (48% vs. 28% $p = 0.308$) NEC [11]. Margolis et al. also found that primary radiation and surgery were not significantly different in early stage disease (HR 1.59 95% CI 0.97–2.6) [6]. Chemotherapy was not directly addressed in either of these studies. Hence, if surgery is considered, preoperative imaging is important to determine presence of distant metastasis, which as with other cervical cancer histologies, would preclude a primary surgical treatment modality.

Of note, no current studies have specifically examined the use of sentinel lymph node (SLN) mapping in cervical NEC. Salvo et al. (see below extended discussion) reported on 10 patients that had both SLN and full lymphadenectomy and found a false negative rate of zero. More studies are needed to definitely decide this question. Fertility sparing surgery in this patient population is limited to only case reports. As these are self-selected patients, recommendations from available data cannot be made [32–34].

5.3.2. Chemotherapy

The majority of studies recommend an etoposide and platinum (EP) containing regimen based on data gleaned from small cell carcinoma of the lung (SCLC). This is the "base regimen" and other regimens examined have typically consisted of two-drug regimens [7,10,35,36]. Studies often combine both cisplatin and carboplatin within the "platinum" group. Ishikawa et al. [12] demonstrated that adjuvant chemotherapy with etoposide-platinum or irinotecan-platinum decreased recurrences with a HR of 0.27 (95% CI, 0.10–0.69; $p = 0.006$). Adjuvant chemotherapy also showed a trend for improved OS (HR = 0.39, 95% CI, 0.15–1.01; $p = 0.053$). Cohen et al. [31] reported improved outcomes in those who received any chemotherapy in the adjuvant setting as compared to no additional therapy with 5 year overall survivals of 47.3% vs. 38.7%, respectively, but this was not statistically significant ($p = 0.9$); the authors argued that their numbers may have been too small to note a statistical difference. As noted above, Wang et al. [14,15] demonstrated worse outcomes in the surgical arm of their study and reported that 7/9 patients who received chemotherapy with a platinum and etoposide regimen of 5 or more (5+) cycles along with chemoradiation were alive without evidence of disease at 5 years. While they made no definitive conclusions in early stage disease, the use of this chemotherapy regimen demonstrated significant efficacy in their cohort. Lee et al. [37] analyzed 58 patients with early cervical NEC. While they did not identify the various chemotherapy regimens utilized in their retrospective analysis, they noted that patients who did not receive adjuvant chemotherapy had worse outcomes with a median PFS of ~12 months vs. >40 months, and median OS ~18 months vs. not reached ($p = 0.025$ and 0.020, respectively).

Other platinum containing regimens including carboplatin and paclitaxel (CT) used in early stage disease might be efficacious, although data are limited. Yaun et al. examined postoperative chemotherapy and found that the 5-year OS for CT was 65.3% with no patients surviving in the non-CT cohort [38]. Hoskins et al. [39] utilized alternating CT and EP along with radiation in 14 patients and compared this to 17 patients who received EP along with radiation. Outcomes in terms of recurrence (29% vs. 35%), 3 yr. PFS and OS were similar (57% and 60% respectively), but the toxicity from the alternating protocol was significantly less, suggesting that this might be a viable alternative regimen.

In addition to the type of chemotherapy, the number of required cycles in early stage disease has been investigated in a limited fashion. Yaun et al. [38] demonstrated improved outcomes in all patients receiving >4 cycles of chemotherapy regardless of chemotherapy type. Pei et al. [40] reported that 5 or more cycles of EP (EP5+) improved 5-year PFS compared with other treatments (67.6% vs. 20.9%, $p < 0.001$). This finding was confirmed on multivariate analysis with fewer than 5 cycles of non-EP or EP regimens increasing the risk of recurrence at 5 years (HR 3.42; 95% CI, 1.64–7.12; $p = 0.001$) and no adjuvant chemotherapy worsening outcomes even more (HR, 5.40; 95% CI 1.71–17.08, p = 0.001). As noted above, Wang et al. also demonstrated improved outcomes in all patients receiving EP5+ [14].

5.3.3. Radiation

The use of radiation as compared to surgery and chemotherapy in early stage disease is more controversial. Multiple studies have ascertained no additional benefit to radiation in univariate and multivariate analyses when surgery and adjuvant chemotherapy are completed in early stage disease [7,12–14,37,40]. Ishikawa et al. [11] examined the use of radiation for the prevention of pelvic recurrence and did not identify a statistically significant difference in patients with high-risk features. Specifically, 4/25 patients (16%) who received adjuvant radiation recurred in the pelvis and 15/62 (25%) who had

not received therapy recurred which was not statistically significant. Pei et al. [40] reported on their cohort of 92 patients and noted >70% of the patients had distant recurrences and did appear to benefit from radiation. They also examined patients with high-risk features, such as positive parametrium or lymph nodes, and found that EP alone vs. EP/concurrent cisplatin with radiation or RT had similar outcomes ($p = 0.496$).

An additional retrospective analysis by Salvo et al. was recently published [41]. They studied 100 patients with presumed early stage cervical NEC from a single institution and examined outcomes following radical hysterectomy. In this cohort, 95% of patients were referred for adjuvant therapy and 89 patients received therapy; 43 patients had radiation therapy (+/− concurrent chemotherapy) followed by additional adjuvant chemotherapy, 26 patients received adjuvant chemotherapy alone and 16% radiation alone. The authors attempted to correlate the type of adjuvant therapy with recurrence sites and subsequently reported on 40 patients. Of these patients, 12 did not have radiation and 28 had some type of adjuvant radiation therapy. Those who received radiation were 62% less likely to have a local recurrence. They recommend giving all patients some form of adjuvant therapy, and suggested that some patients might be able to undergo simple hysterectomy and adjuvant chemotherapy and radiation with similar outcomes to those undergoing radical surgery. A significant critique of the study, however, is the unknown number of patients in this analysis that received no additional therapy (versus chemotherapy alone) and the type and number of cycles of chemotherapy given. Additionally, there was no difference in PFS or OS in the radiation vs. non-radiation groups suggesting that local recurrence could potentially be salvaged with later radiation. Finally, as many patients will receive post-operative radiation, it is important to note that no contemporary data suggesting worse outcomes for patients undergoing radical hysterectomy followed by intensity modulated radiation therapy (IMRT) has been presented.

External beam radiation +/− vaginal cuff radiation remains a component of most institutional lexicons for early stage NEC of the cervix, but this should be examined within the context of each individual patient given the above conflicting data.

Prophylactic brain/cranial Irradiation (PCI): There are no updates from the prior SGO publication, nor from NCCN. Routine use of PCI is not recommended. Brain metastases were seen only in patients who had lung metastases (10%), suggesting that prophylactic brain irradiation would be of little benefit [42]. Currently this remains controversial even in SCLC where rate of brain metastasis is significantly higher. Consideration regarding PCI should be individualized with shared decision-making.

5.3.4. Final recommendations

For early stage disease (<IB3) in which imaging has been completed, the recommended surgical approach is radical hysterectomy, pelvic lymphadenectomy with or without BSO. There is insufficient data to recommend performing routine sentinel lymph node mapping in patients with this disease. While full staging should be strongly considered in accordance with NCCN guidelines, the limited data available suggests that SLN dissection will likely be sufficient and could be considered in patients that have been adequately counselled. Adjuvant therapy using a platinum-etoposide regimen for a minimum of 5 cycles should be administered. Alternative regimens can also be considered; however, the data are insufficient to offer a specific alternative regimen recommendation, although platinum and paclitaxel can be considered.

The addition of radiation therapy in this select group of patients is controversial. There are retrospective studies that support both administering and withholding adjuvant radiation therapy. If choosing between chemotherapy and adjuvant radiation in this patient population, the preponderance of data suggests that chemotherapy is the more important factor. However, if patients are to receive radiation therapy, EP x 2 cycles should be utilized during radiation in place of single agent cisplatin followed by additional EP chemotherapy. See Fig. 1 for proposed treatment algorithm [33].

5.4. Advanced stage: IB3, IIA2-IVB

Although there is no standard chemotherapy regimen for NEC of cervix, treatment options are extrapolated from SCLC and limited retrospective data with EP being the most common regimen utilized. Tempfer et al. reviewed 112 studies that showed etoposide and cisplatin (EP) to be the most commonly used treatment regimen (24/40 studies). Radiotherapy-based primary treatment schemes in the form of radiotherapy, radio-chemotherapy or radiotherapy with concomitant or followed by chemotherapy were also commonly used (15/48 studies) [10].

For platinum containing regimens, carboplatin may be substituted for cisplatin in patients with underlying renal disease or peripheral neuropathy. Other regimens such as cisplatin, vinblastine and bleomycin (PVB) or vincristine, doxorubicin, cyclophosphamide, alternating with cisplatin and etoposide (VAC/PE) have been studied. Chang et al. reported a 5-year survival of 33% for those who received PVB compared to 68% for those were treated with VAC/PE. Due to significant toxicity, EP regimens are generally preferred over VAC-containing regimens [43].

In stages IIB-IVB, primary treatment regimens containing etoposide and platinum for at least 5 cycles (EP5+) was associated with a significantly better 5-year disease free survival (42.9% versus 11.8%, $p = 0.041$) and overall survival (45.6% versus 17.1%, $p = 0.035$) compared to treatments with fewer cycles. Furthermore, concurrent chemoradiation with EP5+ was associated with improved 5-year disease free survival (62.5% versus 13.1%, $p = 0.025$) and overall survival (75.0% versus 16.9%, $p = 0.016$) [14].

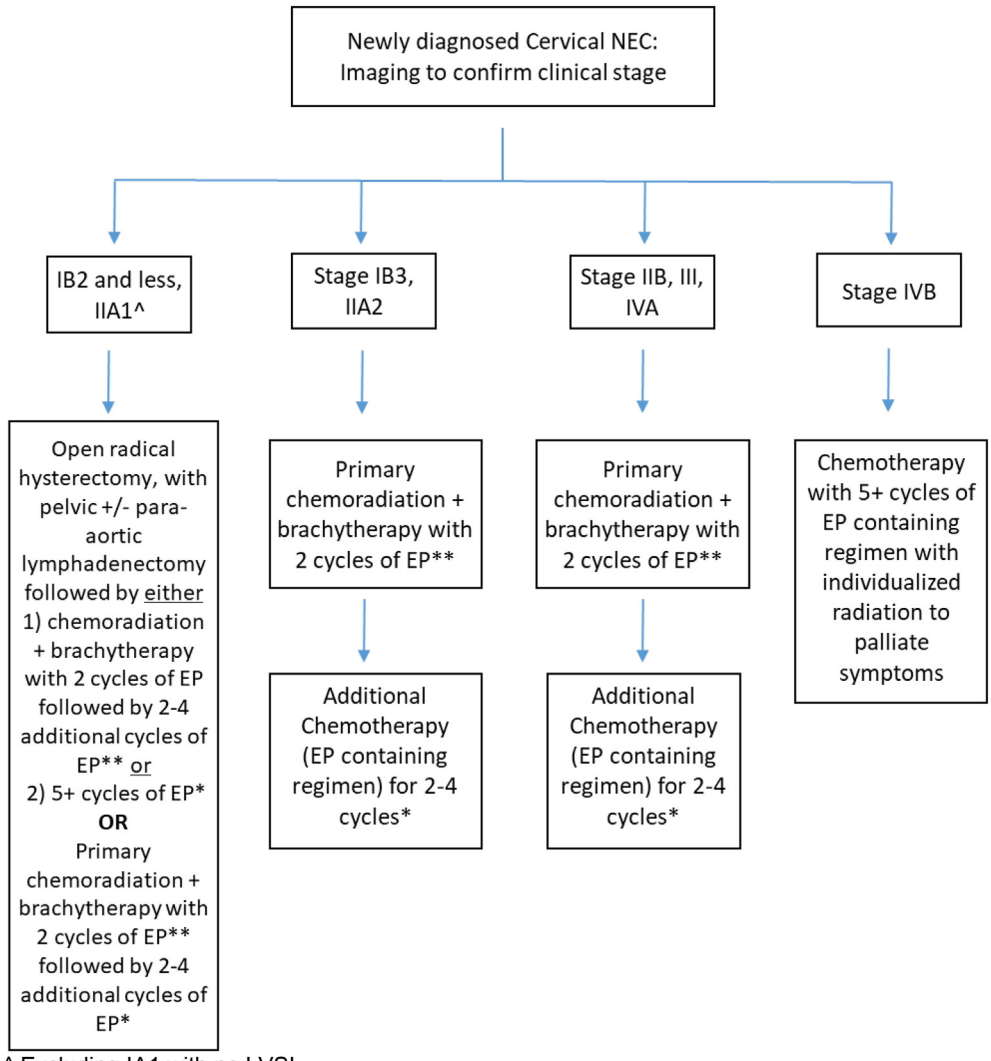
Bajaj et al. presented at the ASTRO 2018 meeting that patients with locally advanced small cell carcinoma of the cervix treated with definitive chemoradiation demonstrated improved outcomes when treated with concurrent and adjuvant chemotherapy, especially with an EP regimen, > 75 Gy and brachytherapy. Recurrence was associated with current smoking (HR 3.32, $p < 0.01$), pelvic/PA node disease (HR 3.3, $p = 0.01$), with <50 Gy vs. 71–80 Gy (HR 3.3, $p = 0.07$), HPV negativity (HR 2.4, $p = 0.16$) and no brachytherapy (HR 0.05, $p < 0.01$). In this study, 15.1% of patients recurred in the brain. Decreased HR of brain recurrence was associated with brachytherapy (HR 0.05, $p < 0.1$), > 75 Gy (HR 0.11, $p = 0.04$) and receipt of EP vs. cisplatin alone (HR 0.35, $p = 0.23$) [44].

In general, as with other cervical cancer subtypes, an improvement in median OS has been shown with the addition of brachytherapy to external beam radiation. Specifically, compared with external beam radiotherapy alone, brachytherapy was associated with an improved median survival of 49 vs. 22 months (HR 0.48) in locally advanced disease [44].

A proposed treatment algorithm is outlined below (adapted from Salvo et al. [36] and NCCN guidelines [45] and overall literature review):

What are the treatment options for patients with recurrent disease?

Given the rarity of the disease, there is limited consensus for optimal treatment in the recurrent setting for NEC. Clinical trials and targeted treatment based on molecular profiling must be considered and treatment will need to be individualized due to the paucity of data. Currently, treatment choices are similar to those for recurrent SCLC. In relapsed disease **≥6 months** after completion of therapy, the NCCN guidelines for SCLC recommends consideration of re-treatment with EP. In metastatic SCLC, addition of atezolizumab or durvalumab to EP is FDA approved for first line regardless of PD-L1 or TMB status and can be considered in this recurrent setting. In relapsed disease **<6 months** in SCLC, NCCN recommendations are to consider agents such as topotecan or lurbinectedin (see below) or clinical trials. Alternative NCCN recommended regimens include: irinotecan, paclitaxel, docetaxel,



^ Excluding IA1 with no LVSI

*Chemotherapy EP:
Cisplatin 50-60 mg/m^2 on day 1 every 3 weeks
Etoposide 100-120 mg/m^2 on days 1-3 every 3 weeks
(with growth factor support)

** The combination of these regimens are chemotherapy with EP plus radiation therapy. The optimal combinatorial regimen is expert opinion although the first regimen is recommended:

1. 2 cycles of EP q3 weeks (Cisplatin 60 mg/m^2 and Etoposide 100 mg/m^2 given day 1 of each 21 day cycle) during RT followed by an additional 2-4 cycles of EP as above

2. Carboplatin AUC 5-6 and Paclitaxel 175 mg/m^2 on day 1 of 21 day cycle for total of 6 cycles.If Carboplatin and Paclitaxel are chosen, single agent cisplatin would typically be given throughout the radiation.
3. Sandwich: Cisplatin/Etoposide alternating with Carboplatin and Paclitaxel (2-3 cycles chemotherapy) followed by concurrent single agent cisplatin with RT followed by an additional 3-4 cycles of alternating chemotherapy.

Fig. 1. Treatment algorithm for NEC of cervix.

temozolomide, oral etoposide, vinorelbine, gemcitabine as well as the triplet combination of cyclophosphamide, doxorubicin and vincristine (CAV).

Lurbinectedin, an alkylating drug and analog of trabectedin, received accelerated FDA approval in June 2020 for metastatic SCLC refractory to platinum and is an alternative in the NCCN guidelines. This agent is of interest in small cell cervical cancer. Alternately, a phase II trial by Frumovitz et al. combined a triplet regimen of topotecan 0.75 mg/m^2 on days 1 to 3, paclitaxel 175 mg/m^2 on day 1 and bevacizumab 15 mg/kg on day 1 of a 21-day cycle (TPB). TPB is an active FDA approved regimen for recurrent cervical cancer. Median progression free survival was 8 months for the TPB regimen vs. 4 months for all other regimens. Median OS unfortunately was not significantly improved; it was 9.7 months for TPB regimen vs. 9.4 months for other regimens [46].

Nivolumab +/− ipilimumab is an option in SCLC for those who have not received checkpoint inhibitors in prior line(s) of therapy [47].

Nivolumab monotherapy is approved for third line or later metastatic SCLC. Combination of nivolumab and ipilimumab had ORR 21.9% vs. 11.6% for nivolumab alone in SCLC. However, median OS was similar between the groups. Not surprisingly, toxicities were more common with combination therapy vs. nivolumab alone. Given some similarities between cervical NEC and SCLC, this type of combination therapy could be considered. As noted above in the molecular characterization section, single agent IO therapy in cervical small cell cancer may not be beneficial, however additional trials are sorely needed. One small Phase II trial examined single agent pembrolizumab in 6 patients with progressive small cell neuroendocrine cervical carcinoma. Frumovitz et al. [48] found minimal response with median progression-free interval of 2.1 months. However, a case report by Paraghamian et al. of recurrent metastatic NEC treated with nivolumab demonstrated a complete and durable response 4 months after treatment discontinuation for adverse drug effects [49].

In the setting of multiple recurrences or progressive disease, the data are even more limited with only a few case reports or basket trials. Therefore, the recommendation is to consider a clinical trial or individualized targeted therapy based on somatic profiling. For example, a case report by Lyons et al. [50] described a patient with isolated recurrence limited to the vagina. A KRAS mutation was identified and she received the MEK inhibitor trametinib. After 8 cycles of therapy, she was noted to have complete radiographic response. Given high numbers of patients with MAPK/PI3K mutations noted to date, this type of targeted therapy remains promising. Farago et al. [51] utilized olaparib and temozolomide combination in relapsed SCLC with substantial clinical activity (ORR 41.7%, PFS 4.2 and OS 8.5 months).

Additional agents from other disease sites should also be considered although they may not have been tested in this setting. Agnostic tumor type approvals have also been seen in the last two years. For example, larotrectinib and entrectinib have both been approved for NTRK gene fusion-positive tumors, and pembrolizumab is FDA approved for TMB-high solid tumors.

6. Ovarian NENs

What is the classification for ovarian NENs?

In the 2014 WHO classification of tumors, there is no separate classification for NENs of the ovary. The broad categorization of primary (rather than metastatic) NENs consisted of carcinoid tumor (at least four subtypes), small cell NEC of the ovary pulmonary type (SCCOPT), large cell NEC and rare tumors such as paragangliomas and pheochromocytomas [9]. In the new 2020 WHO classification as noted above, the only NET of the ovary that remains is the carcinoid tumor and therefore these are truly synonymous ONLY within the ovarian classification. SCCOPT is no longer classified as a separate entity but rather is incorporated in the small cell NEC category for ovarian tumors [5].

Prior to any further discussion, an important issue must also be addressed. While small cell carcinoma of the hypercalcemic type (SCCOHT) is often included in the grouping with NECs, the pathologic markers and molecular sub-classification suggest that this type of ovarian carcinoma is, in actuality, not an NEN at all. Rather, this subtype is associated with *SMARCA4* mutations which encode the protein, BRG-1, and is more closely related to a rhabdoid-like tumor than one of NEN differentiation [52–56]. Given this, the discussion of SCCOHT is beyond the scope of the current manuscript.

7. Ovarian carcinoids

There are four described types of ovarian carcinoid tumors identified as primary ovarian neoplasms. These include insular, trabecular, strumal and mucinous. These are the most common of the ovarian NENs and generally arise within the background of mature cystic teratomas. Foci of these tumors can also be identified within other germ cell tumors as well. Of note, most NETs of this type occur unilaterally rather than bilaterally (more common with metastatic disease). Insular carcinoids are the most common (~50%) of the carcinoid tumors of the ovary and appear with GI or respiratory epithelium. Strumal carcinoids are now thought to be more common (~40% of carcinoid tumors) than previously identified and is actually a combination of any of the carcinoids and thyroid tissue. Trabecular carcinoids are less common and most consistent with hindgut or foregut carcinoids. Mucinous carcinoids are the rarest and also called goblet cell carcinoids and must be differentiated from Krukenberg tumors. [5,9,57].

8. NECs

The two "true" NECs of the ovary are now considered the small cell (previously SCCOPT) and large cell NEC/non-small cell carcinoma of the ovary. Typically, both of these types of NEC arise in association with other histologic types. To date, approximately 40 true primary small cell NEC cases have been described in the literature [58]. These patients have a median age at diagnosis of ~45 years old and ~ 50% presented with bilateral disease. The pathologic features are similar to those of the SCLC and have IHC characteristics similar to cervical cancer. Prognosis tends to be very poor with overall survival median of ~24 months for all stages. High recurrence rates, even in the setting of stage I disease, appears to be more common than in typical epithelial histologies [8,9,58].

Large Cell NEC is also an extremely rare entity. As of 2019, fewer than 60 cases of this tumor type have been described in the literature. This aggressive subtype metastasizes early and is generally associated with other epithelial or germ cell tumors. Fifty percent of the patients in one review died within 12 months of their diagnosis. Even patients diagnosed with stage I disease had an average overall survival of only 42 months [59,60].

What is the treatment for ovarian NENs?

8.1. Surgery

Since the publication of the last document, there have been several studies published evaluating small cell carcinoma of the ovary (SCCO) using the NCDB, SEER and institutional databases [61,62]. *However, these studies primarily include the more common hypercalcemic type (SCCOHT). Based on the new WHO classification, this tumor is no longer considered a NEN.* The majority of true small cell NEC of the ovary that have been reported are in peri- or post-menopausal women and hysterectomy with bilateral salpingo-oophorectomy along with debulking is recommended.

Other than providing prognostic information as stage is associated with survival [63], there does not appear to be a benefit from routine lymphadenectomy. In a multivariable analysis of women ($n = 469$) with small cell carcinoma of the ovary (SCCOHT included), performance of lymphadenectomy was not associated with lower mortality [61]. However, as with other ovarian malignancies, the authors recommend resection of any enlarged lymph nodes.

8.2. Chemotherapy

8.2.1. Carcinoid tumors

There is no role for adjuvant therapy in well-differentiated NET carcinoid tumors if localized. Unfortunately, NCCN guidelines do not include therapy for these tumors for advanced disease. However, one can extrapolate from more common gastrointestinal NET (GINET). The main principles of selection of appropriate therapy for advanced disease are the indolent biology and prolonged natural history of most well

Table 2
Therapy extrapolated from GI NET.

Preferred Regimen: Octreotide or Lanreotide	Cytotoxic Chemotherapy Options:
Advanced Disease and/or Distant Metastases (if progression on octreotide or lanreotide): Everolimus or 177Lu-dotatate (if SSR-positive imaging)	Fluorouracil (5-FU) Capecitabine Dacarbazine Oxaliplatin Streptozosin Temozolomide Doxorubicin

differentiated NETs. This should be weighed against the risk-benefit ratio and toxicity of available therapeutic options.

For asymptomatic patients with a low tumor burden and stable disease, observation should be considered until clinically significant progressive disease. Other options include the use of somatostatin analogs. Analogs such as octreotide or lanreotide are highly effective in controlling the symptoms associated with carcinoid syndrome. In addition, somatostatin analogs have also been shown to stabilize disease and control tumor growth. Rinke et al. [64,65] demonstrated that long acting octreotide showed a significantly longer PFS compared with placebo (14.3 vs. 6 months). Dose escalation is an option at the time of initial disease progression on long-acting somatostatin analogs. Somatostatin analogs can also be continued after progression to control symptoms related to hormone hypersecretion.

At the time of disease progression in patients with advanced NETs, the mTOR inhibitor everolimus may be considered. mTOR mediates downstream signaling in a number of pathways that are implicated in NET growth including VEGF and insulin-like growth factor signaling pathways. In addition, mTOR regulates angiogenesis by controlling the production of hypoxia inducible factor. Combined everolimus and octreotide was associated with significant improvement of median PFS compared to placebo and supportive care (11 vs. 3.9 months, HR 0.48) [66]. Multiple tyrosine kinase inhibitors have been evaluated in advanced GINET. These include sunitinib, sorafenib, pazopanib, lenvatinib and cabozantinib. Response rates were low although all studies report a high rate of disease stabilization. Bevacizumab and pegylated interferon alpha showed some activity. During the first 18 weeks of therapy, 18% of the bevacizumab-treated cohort had a radiographic partial response while about 77% had stable disease. After 18 weeks, 95% treated with octreotide and bevacizumab remained progression-free compared with 68% of those who received octreotide and interferon-alpha [67].

Peptide receptor radio-ligand therapy with Lutetium Lu-177 dotatate plus octreotide has demonstrated in the NETTER-1 trial a significantly higher objective response rate compared to octreotide alone (18 vs. 3%) [64]. Patients in this study had advanced, progressive, and somatostatin-receptor-positive midgut NET. Nearly half of the patients had undergone a previous form of systemic therapy other than somatostatin analogue therapy. Lu-177 dotatate was well tolerated overall with the most common side effects being nausea, vomiting, and fatigue. Hematologic toxicities were mostly mild degrees of thrombocytopenia (25%), lymphopenia (9% for grade 3 or 4), and anemia (14%). Long-term toxicity included a 2% risk of myelodysplastic syndrome and 0.5% rate of acute leukemia [68,69].

Cytotoxic chemotherapy for advanced carcinoid tumors (GINETs) is not considered a standard treatment and the clinical benefit remains controversial, hence extrapolation to ovarian carcinoids is also limited. NCCN guideline suggests cytotoxic chemotherapy can be considered in patients with disease progression and no other treatment options. Single-agent therapy with capecitabine, fluorouracil, streptozosin, dacarbazine, and doxorubicin among others showed modest response rates [70,71] (See Table 2).

8.2.2. NEC

Small cell NEC of the ovary is rare (<1% of all ovarian cancer) and aggressive. These tumors are typically admixed with other histologic subtypes and are generally associated with poor outcomes. They occur in an older age group and are not associated with hypercalcemia [57]. Optimal treatment of this type of cancer is unclear given the paucity of data. There is currently no standard regimen. As reviewed in the data above, surgery followed by chemotherapy and radiation therapy is the main treatment strategy even in stage one disease. The evidence for chemotherapy is generally extrapolated from its use in SCLC. Aggressive multi-agent chemotherapy and potentially adjuvant radiotherapy may improve survival. The role of consolidative radiotherapy in small cell NEC is unknown.

At this time, the data are too limited to make any conclusive recommendations. Expert pathologic review, international tumor registry and clinical trials for treatment approaches to improve the outcomes are sorely needed.

8.2.3. Genetics

While SCCOHT is NOT an ovarian NEC, many readers will continue to consider it as such and will recommend genetic testing for their patients with true NENs of the ovary. Inactivating mutations of *SMARCA4* are felt to be the driver mutations in the vast majority of SCCOHT. There is no current indication that true ovarian NEN's are associated with germline (i.e. inheritable) mutations.

9. Endometrial NENs

What is the evaluation for endometrial NEN?

Neuroendocrine tumors of the uterus are rare and account for approximately 1% of all endometrial carcinomas [1,72]. The majority of women will present with abnormal bleeding or symptomatic metastatic disease. As with other endometrial cancer histologies, the diagnosis can be made with an endometrial biopsy or dilatation and curettage. Women with endometrial NENs typically present with advanced disease (Stage III and Stage IV) in 55.7% of cases [72]. Therefore, imaging should be performed to rule out metastatic disease. Tumor markers such as CA-125 may be elevated as with other advanced endometrial cancer histologies.

What is the recommended treatment for newly diagnosed NEC of the endometrium?

Based on an NCDB study from 2019 and other case series and reports, there are no standard treatments that can be recommended for women with this disease. There are no large series or prospective data to guide therapy. In one series, the risk of death was increased based on age (> 80 years) and stage II disease or higher. Women who were treated with chemotherapy had a HR for death of 0.36 (95% CI, 0.23–0.56) compared to women who did not receive chemotherapy; however, no decreased risk of death was identified for those receiving radiation therapy. In this series, there was no difference in outcome for those women with small cell or large cell endometrial NEC and chemotherapy regimens were not standardized [72].

In one recent review of the literature of LCNEC [73], the authors state that the small cell regimen of etoposide and cisplatin should be considered, while some other authors favor a platinum-based regimen with gemcitabine. Independent of the regimen specifics, overall survival is poor with a 5-year survival of 38.3% and median survival of 17 months.

Given the paucity of data, the combination of surgery, chemotherapy with a platinum-based regimen and targeted radiation should be considered.

What are the treatment options for recurrent disease?

In a clinicopathologic study of endometrial NEC, the authors identified abnormal MMR expression by IHC in 44% of cases tested [74]. This

may provide the opportunity for treatment with IO agents alone and in combination with other agents, which was not specifically done in this study. Other targets such as those identified for SCNEC (MEK inhibitors) or those being investigated for SCLC may be opportunities for women with this disease. Molecular profiling for potential targeted agents should be performed in all patients at diagnosis. If this had not yet been completed it should be performed in the recurrent setting as it may help guide treatment decisions.

10. Vulvar/vaginal NENs

Other than additional new case reports and reclassification as reviewed above, there is no new additional information since the last SGO update in 2011.

11. Conclusion

NEN's are a diverse collection of rare gynecologic tumors. Given this, patients should be managed with a multi-disciplinary team and collaborative approach. Expert pathology review, tumor registries and referrals to academic gynecologic cancer programs specializing in rare tumors may be considered. Treatment options are often based on extrapolation from other gynecologic and non-gynecologic malignancies and tumor genomic profiling may identify beneficial targeted therapies. Clinical trials are key components of treatment as well to improve outcomes in this patient population.

Declaration of Competing Interest

All authors have nothing to disclose.

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