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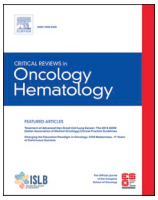

Primary neuroendocrine neoplasms of the vulva: A review of the MITO rare cancer group

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ABSTRACT

Gynecological neuroendocrine neoplasms are rare entities and can be divided into two groups: carcinoids and neuroendocrine carcinomas. Due to their rarity their management is not standardized. The aim of this work is to summarize and discuss the current literature evidence on this pathology. A scoping literature review was performed in multiple databases. Thirty-one studies were included: 30 case reports and one case series. Patients' age ranged between 28 and 92 years. Surgery was the most used treatment and the surgical approach included local excision (N = 16/31; 51.6%) with (N = 5/16; 31.25%) or without (N = 11/16; 68.75%) inguinal lymphadenectomy. Adjuvant radiotherapy was delivered in 12 (38.7%) cases; instead, platinum-based therapies were frequently used when chemotherapy was chosen for adjuvant treatment. The overall survival ranged between 20 days to 4 years. However, further research is needed; currently, multimodal approach including surgery, chemotherapy and radiotherapy appeared safe and feasible for the treatment of these rare and aggressive diseases.

1. Introduction

Primary neuroendocrine neoplasms (NENs) of the female genital tract are rare cancers accounting for 2% of all gynecological malignancies (Rouzbahman and Clarke, 2013a) and arising from the endocrine cells of the neuroectoderm, neural crest, and endoderm (Heller and Shah, 2011; Tempfer et al., 2018). They usually affect the cervix and ovary and only occasionally the vulva (Crane et al., 2020). In the gynecological tract, only Bartholin glands and the fallopian tube contain immunohistochemically-normal neuroendocrine cells (Chen et al., 2021; Grondin et al., 2019) that are instead normally identifiable in the gastrointestinal and respiratory tract, where NENs are a common diagnosis (Di Domenico et al., 2020). Synaptophysin and chromogranin A are co-stored and co-secreted by NENs and the cell surface expresses somatostatin receptors (Heller and Shah, 2011; Oronsky et al., 2017) of whom excessive secretion causes a typical paraneoplastic syndrome (Dias et al., 2015). NENs can be divided into two biologically and clinically different groups: well-differentiated NETs (WDNETs), or carcinoids, and poorly differentiated NETs (PDNETs), or NE carcinomas (NECs), which include small cell (SCNECs) and large cell (LCNECs), being the latter the rarest (Rindi et al., 2018). A subtype of SCNECs originating from sensory Merkel cells of the skin is represented by Merkel cell carcinomas (MCC), which typically interest the vulva (Patibandla et al., 2018a). In the most recent WHO classification, NECs seem the only type of NENs originating in the vulva (Rindi et al., 2018; Talia and Ganesan, 2022) even if sporadic vulvar carcinoids have been

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reported in the literature (Srivastava et al., 2012). Their histogenesis and pathogenesis are not clear yet. While most MCCs might be caused by monoclonal integration of Merkel cell polyomavirus or by exposure to ultraviolet light (Patibandla et al., 2018a), the role of high-risk HPV on the pathogenesis of non-MCC NENs can be only supposed based on the association described in squamous cell vulvar and vaginal carcinoma and cervical NECs (Castle et al., 2018). Due to their extreme rarity, optimal management is not standardized and prognosis data are lacking. Since there is currently no consensus nor guidelines regarding the management of NENs, the present work aims to summarize and discuss the state-of-the-art literature evidence on this rare disease, in particular: i) to update and synthesize the literature concerning primary vulvar NENs; ii) to report any information regarding clinic-pathological features, treatment strategies, and patients' outcomes.

2. Material and methods

2.1. Data sources and searches

A scoping literature review was performed according to the PRISMA guidelines from April 2022 to December 2022 (Page et al., 2021), searching in multiple databases (PubMed, Scopus and Web of Science) the following combination of the following keywords and MESH: "vulvar neuroendocrine tumor", "vulvar small cell cancer", "vulvar large cell cancer", "vulvar carcinoids", "vulvar Merkel cell carcinoma" with no limitations or additional filters. Relevant articles were obtained in full-text format and screened for additional references. The protocol has not been registered. We defined inclusion criteria for the literature search and data reporting according to the Population, Intervention, Comparison, and Outcomes (PICO) methodology (Methley et al., 2014) as follows:

- Population: patients with a diagnosis of primary vulvar NENs;
- Intervention: any type of treatment, including surgery, chemotherapy, radiotherapy, or observational treatment;
- Comparison: if available, any randomized controlled trials or matched case studies
- Outcomes: local control, survival rates and toxicities of the reported treatment delivered.
- Study design: any interventional, observational, prospective, case series/reports and retrospective studies

Manuscripts were included in the analysis if the following criteria were met: i) studies describing patients' diagnosis of vulvar NEN; ii) articles written in the English language; iii) interventional, observational, prospective, and retrospective studies can be considered; iv) considering the rarity of these cases, case reports were included. The exclusion criteria were: i) abstracts of medical conferences, editorials, and preliminary studies with animal models; ii) previous reviews and/or multimedia materials about vulvar NENs; iii) papers written in languages other than English; iv) manuscripts that reported primary vulvar tumor other than NENs (squamous cell carcinoma (SCC), melanomas, sarcomas, lymphomas, etc.); metastatic vulvar NENs, tumors not arising from the vulva; cases with uncertain diagnosis.

2.2. Study selection

Four independent reviewers (IC, MGV, RF and TGDA) selected the studies using a 2-steps screening method. In the first step, the screening of titles and abstracts was performed to verify eligibility/inclusion criteria and exclude irrelevant studies. In the 2nd step, full texts of relevant articles were screened by the 4 reviewers to: (1) verify study eligibility and inclusion criteria and (2) avoid duplications of the included cases. Two other authors (VDM and RM) independently searched reference lists of recognized manuscripts in order to integrate the literature search. AB and IP checked the data extracted. Discrepancies between the investigators were resolved through a consensus.

2.3. Statistical analysis

Before data analysis, we performed an exploration phase of the data. Categorical data were described by frequency and percentage, with continuous data by mean, median, and range. The percentages of patients or studies for whom the specific data were available were reported if required for the description of the endpoints.

3. Result

While the initial results led to 258 publications, after the screening process, only thirty-one studies met the inclusion criteria (Fig. 1). The manuscripts included in the analysis were published between 1985 and 2022. Overall, we found 30 case reports (Copeland et al., 1985; Husseinzadeh et al., 1988; Chandeying et al., 1989; Cliby et al., 1991; Chen, 1994; Loret de Mola et al., 1993; Scurry et al., 1996; Gil-Moreno et al., 1997; Hierro et al., 2000; Obermair et al., 2001; Nuciforo et al., 2004; Pawar et al., 2005; Khoury-Collado et al., 2005; Mohit et al., 2009; Sheikh et al., 2010; Iavazzo et al., 2011; Soni et al., 2011; Winer et al., 2012; Zhang et al., 2012; Liu and Yue, 2013; Fawzi et al., 1997; Aminimoghaddam et al., 2016; van Rosmalen et al., 2016; Correia et al., 2017; Gabrilovich et al., 2017; Kamian et al., 2018; Wu et al., 2018; Botha et al., 2020; Jamshidi et al., 2020; Yin et al., 2022) and one case series (Frumovitz et al., 2020). Key characteristics of the analyzed population and treatments are summarized in Tables 1 and 2 and the details are reported in **Supplemental** Tables 1 and 2 **respectively.**

3.1. Population

A total of 31 patients were eligible for the final analysis. Across all studies, the age of patients ranged between 28 and 92 years (median: 52.5 years). Tumor site was reported in 30/31 (96.8%) patients (Copeland et al., 1985; Husseinzadeh et al., 1988; Chandeying et al., 1989; Cliby et al., 1991; Chen, 1994; Loret de Mola et al., 1993; Scurry et al., 1996; Gil-Moreno et al., 1997; Hierro et al., 2000; Obermair et al., 2001; Nuciforo et al., 2004; Pawar et al., 2005; Khoury-Collado et al., 2005; Mohit et al., 2009; Sheikh et al., 2010; Iavazzo et al., 2011; Soni et al., 2011; Winer et al., 2012; Zhang et al., 2012; Liu and Yue, 2013; Fawzi et al., 1997; Aminimoghaddam et al., 2016; van Rosmalen et al., 2016; Correia et al., 2017; Gabrilovich et al., 2017; Kamian et al., 2018; Wu et al., 2018; Botha et al., 2020; Jamshidi et al., 2020; Yin et al., 2022) and was unknown for only 1 (3.2%) patient (Liu and Yue, 2013). NENs were located in a labium majus in 13 (41.9%) patients (Chandeying et al., 1989; Gil-Moreno et al., 1997; Nuciforo et al., 2004; Pawar et al., 2005; Mohit et al., 2009; Sheikh et al., 2010; Iavazzo et al., 2011; Soni et al., 2011; Aminimoghaddam et al., 2016; van Rosmalen et al., 2016; Gabrilovich et al., 2017; Botha et al., 2020; Yin et al., 2022), a labium minus in 3 (9.67%) (Husseinzadeh et al., 1988; Hierro et al., 2000; Kamian et al., 2018), both the lips in 1 (3.2%) (Correia et al., 2017), the Bartholin gland in 7 (22.5%) (Copeland et al., 1985; Chandeying et al., 1989; Obermair et al., 2001; Khoury-Collado et al., 2005; Soni et al., 2011; Wu et al., 2018; Jamshidi et al., 2020), the inguinal region in 1 (3.2%) (Winer et al., 2012) and other parts of the vulva in the remaining cases (Cliby et al., 1991; Chen, 1994; Loret de Mola et al., 1993; Scurry et al., 1996; Zhang et al., 2012; Fawzi et al., 1997). Available histotype subvariants were as follows: MCC in 16 (51.6%) (Chandeying et al., 1989; Chen, 1994; Loret de Mola et al., 1993; Scurry et al., 1996; Gil-Moreno et al., 1997; Hierro et al., 2000; Pawar et al., 2005; Khoury-Collado et al., 2005; Mohit et al., 2009; Sheikh et al., 2010; Iavazzo et al., 2011; Soni et al., 2011; Winer et al., 2012; Aminimoghaddam et al., 2016; Kamian et al., 2018; Botha et al., 2020), SCNECs in 7 (22.5%) (Copeland et al., 1985; Cliby et al., 1991; Obermair et al., 2001; Correia et al., 2017; Wu et al., 2018; Jamshidi et al., 2020;

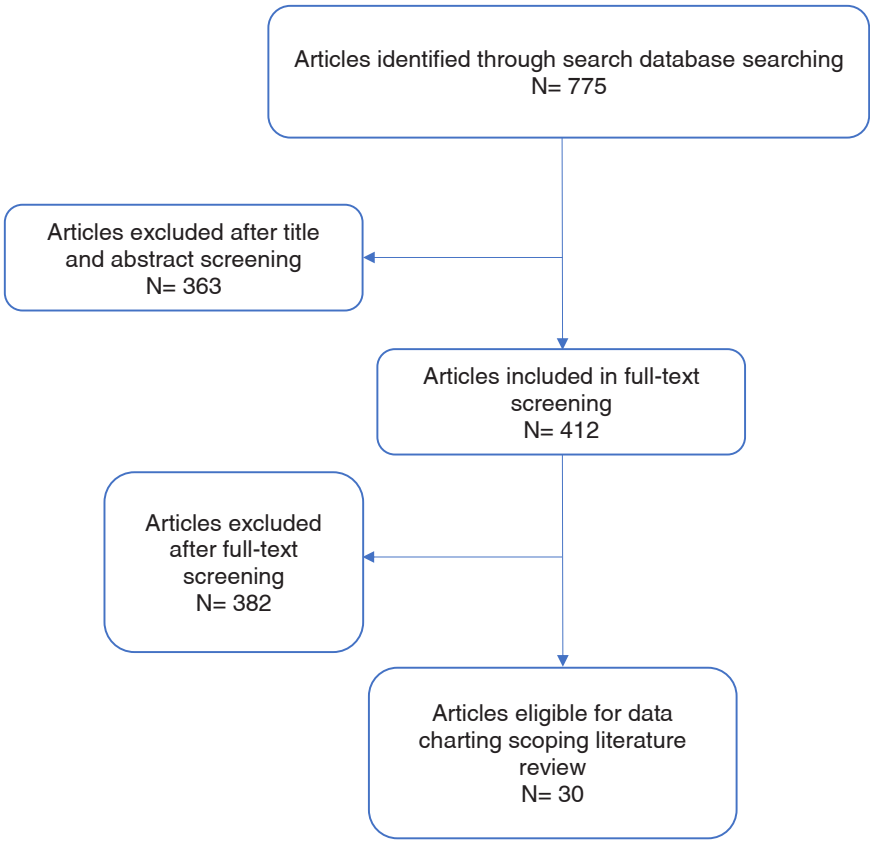

Fig. 1. Flowchart of the literature search process.

Table 1
Population's characteristics.

N pts	Age (years)	Histologic subtype	Primary site	Figo stage
31	Mean: 52.5 Range: 28–92	MCC: 16 SCNEC: 7 PDNET: 1 VC and AC with NE differentiation: 3 Paragangliomas: 2 Unclassified: 2	Labium majus: 13 Labium minus: 3 Both lips: 1 Bartholin gland: 7 Inguinal region: 1 Other vulvar sites: 5 Unknown: 1	I: 1 II: 2 III: 11 Unknown: 17

MCC: Merkel cell carcinomas; SCNECs: small cell neuroendocrine carcinoma; PDNET: poorly differentiated neuroendocrine carcinoma; VC: vulvar carcinoma; AC: adenocarcinoma; NE: neuroendocrine.

Table 2
Treatment and outcomes.

N pts	Surgery	Medical treatment	Radiotherapy
31	Local excision: 16 Radical vulvectomy: 11 Hemivulvectomy: 3	Adjuvant medical treatment: 9 Medical treatment at relapse: 2 Medical treatment for progression: 3	Neoadjuvant radiotherapy: 1 Adjuvant radiotherapy: 12

Frumovitz et al., 2020), PDNET in 1 (3.2%) (Fawzi et al., 1997), vulvar carcinoma and adenocarcinoma with neuroendocrine differentiation in 3 (9.4%) cases (Zhang et al., 2012; van Rosmalen et al., 2016; Gabrilovich et al., 2017) and paragangliomas features were described in 2 (6.25%) cases (Nuciforo et al., 2004; Liu and Yue, 2013). In 2 (9.67%) cases the tumor was not classified (Husseinzadeh et al., 1988; Yin et al., 2022). Tumor stage was reported in 45.1% (N = 14/31) of the entire cohort (Husseinzadeh et al., 1988; Chandeying et al., 1989; Gil-Moreno et al., 1997; Hierro et al., 2000; Obermair et al., 2001; Pawar et al., 2005; Khoury-Collado et al., 2005; Sheikh et al., 2010; Iavazzo et al., 2011; Soni et al., 2011; van Rosmalen et al., 2016; Correia et al., 2017; Gabrilovich et al., 2017 Apr; Kamian et al., 2018) ranging between I and IIIB. The tumor grading (G), reported only in 9 (29%) cases (Copeland et al., 1985 Nov; Gil-Moreno et al., 1997 Mar; Mohit et al., 2009 May; Fawzi et al., 1997 Jan; Aminimoghaddam et al., 2016; Correia et al., 2017; Gabrilovich et al., 2017; Kamian et al., 2018; Yin et al., 2022) was mainly G3 (N = 7/9; 77.78%) (Copeland et al., 1985; Mohit et al., 2009; Fawzi et al., 1997; Correia et al., 2017; Gabrilovich et al., 2017; Kamian et al., 2018) followed by G2 (N = 1/9; 11,11%) (Aminimoghaddam et al., 2016) and undifferentiated (N = 1/9; 11,11%) (Gil-Moreno et al., 1997). One (3.2%) woman was affected by HIV (Botha et al., 2020) and the HPV status was reported only in 1 (3.2%) case (Correia et al., 2017).

3.2. Intervention

Surgery was the first treatment choice in most studies and details were reported in Table 2. The main surgical approach consisted in a local excision (N = 16/31; 51.6%) with (N = 5/16; 31.25%) (Hierro et al., 2000; Khoury-Collado et al., 2005; Gabrilovich et al., 2017; Kamian et al., 2018; Wu et al., 2018) or without (N = 11/16; 68.75%) inguinal lymphadenectomy (Chen, 1994; Loret de Mola et al., 1993; Gil-Moreno et al., 1997; Obermair et al., 2001; Pawar et al., 2005; Mohit et al., 2009; Sheikh et al., 2010; Soni et al., 2011; Winer et al., 2012;

Zhang et al., 2012; Yin et al., 2022). Eleven (35.48%) patients underwent radical vulvectomy, mainly associated with mono or bilateral inguinal lymphadenectomy (Husseinzadeh et al., 1988; Chandeying et al., 1989; Scurry et al., 1996; Nuciforo et al., 2004; Mohit et al., 2009; Iavazzo et al., 2011; Fawzi et al., 1997; Correia et al., 2017; Kamian et al., 2018; Botha et al., 2020; Jamshidi et al., 2020). Hemivulvectomy with mono or bilateral inguinal lymphadenectomy was performed in 3 (9.67%) cases (Copeland et al., 1985; Cliby et al., 1991; Aminimoghaddam et al., 2016). Adjuvant radiotherapy (RT) was delivered in 12 (38.7%) cases and total doses ranged between 5000 and 6000 rad (Copeland et al., 1985; Husseinzadeh et al., 1988; Chandeying et al., 1989) in the oldest reports and 45–65 Gy in the newest (Scurry et al., 1996; Hierro et al., 2000; Khoury-Collado et al., 2005; Mohit et al., 2009; Kamian et al., 2018; Jamshidi et al., 2020). Mainly the RT followed a conventional fractionation schedule, except in Kamian et al. in which hyper-fractionation (for a total dose of 45 Gy/ over 30 fractions twice a day) was chosen (Kamian et al., 2018). The RT volumes mainly included the vulvar region, pelvis and inguinal node stations; Scurry et al. included the para-aortic for an MCC with squamous and glandular differentiation arising in the posterior fourchette and left labium (Scurry et al., 1996). Neoadjuvant RT up to a total dose of 30 Gy in 10 fractions was described in Mohit et al (Mohit et al., 2009). The most commonly reported medical treatment regimens included cisplatin/cyclophosphamide/methotrexate, cisplatin/paclitaxel; cisplatin/etoposide; cyclophosphamide/vincristine/doxorubicin. Pembrolizumab 200 mg intravenously every 3 weeks was reported by Frumovitz et al (Frumovitz et al., 2020).

3.3. Comparison

None of the studies included a control group for comparison.

3.4. Outcomes

When reported, the outcome measures varied widely across the included studies. The local control (LC) and the progression-free survival (PFS) ranged between 8 weeks to 4 years (Copeland et al., 1985; Husseinzadeh et al., 1988; Cliby et al., 1991; Chen, 1994; Loret de Mola et al., 1993; Scurry et al., 1996; Gil-Moreno et al., 1997; Obermair et al., 2001; Nuciforo et al., 2004; Khoury-Collado et al., 2005; Mohit et al., 2009; Sheikh et al., 2010; Soni et al., 2011; Zhang et al., 2012; Liu and Yue, 2013; Aminimoghaddam et al., 2016; van Rosmalen et al., 2016; Gabrilovich et al., 2017; Kamian et al., 2018; Wu et al., 2018; Botha et al., 2020; Jamshidi et al., 2020; Yin et al., 2022). The Overall survival (OS) ranged between 20 days after active treatment to 4 years (Copeland et al., 1985; Cliby et al., 1991; Chen, 1994; Loret de Mola et al., 1993; Scurry et al., 1996; Gil-Moreno et al., 1997; Hierro et al., 2000; Obermair et al., 2001; Nuciforo et al., 2004; Khoury-Collado et al., 2005; Mohit et al., 2009; Liu and Yue, 2013; Fawzi et al., 1997; Aminimoghaddam et al., 2016; van Rosmalen et al., 2016; Gabrilovich et al., 2017; Wu et al., 2018; Botha et al., 2020; Jamshidi et al., 2020; Yin et al., 2022). Where available, data on the type of treatment at recurrences are outlined in Supplemental Table 2. In cases of local recurrence, surgical excision remained the most frequent treatment (Loret de Mola et al., 1993; Nuciforo et al., 2004; Mohit et al., 2009; Soni et al., 2011; Yin et al., 2022). RT was chosen as a local approach in case of systemic progression. Systemic chemotherapy was mainly used in the case of distant progressive disease (Husseinzadeh et al., 1988; Chen, 1994; Loret de Mola et al., 1993; Soni et al., 2011; Jamshidi et al., 2020). Details on the outcomes of each study are shown in Supplemental Table 2. When reported, the toxicity rates were mild, except for Fawzi et al (Fawzi et al., 1997). and Hierro et al (Hierro et al., 2000). in which women died from bleeding of the right groin probably from the femoral artery and sepsis, respectively.

4. Discussion

The gynecological NENs, primary or secondary, are uncommon disease accounting for 2% of all gynecological tumors (Gadducci et al., 2017; Gardner et al., 2011; Patibandla et al., 2018b; Rouzbahman and Clarke, 2013b). Across the female genital tract NENs, vulvar NENs are the rarest forms (Caruso et al. (2021).

There are currently neither treatment guidelines nor consensus, based on prospective, well-designed clinical trials, because of the rarity of these tumors and, consequently, vulvar NENs represent a considerable therapeutic challenge for clinicians. To try to fill this knowledge gap, we reviewed the literature collecting the evidence of this uncommon tumor and analyzing the clinical management as well as outcomes.

We found only case report and a vulvar case in a little cohort of gynecological NENs for a total of 31 patients from 31 different studies (Copeland et al., 1985; Husseinzadeh et al., 1988; Chandeying et al., 1989; Cliby et al., 1991; Chen, 1994; Loret de Mola et al., 1993; Scurry et al., 1996; Gil-Moreno et al., 1997; Hierro et al., 2000; Obermair et al., 2001; Nuciforo et al., 2004; Pawar et al., 2005; Khoury-Collado et al., 2005; Mohit et al., 2009; Sheikh et al., 2010; Iavazzo et al., 2011; Soni et al., 2011; Winer et al., 2012; Zhang et al., 2012; Liu and Yue, 2013; Fawzi et al., 1997; Aminimoghaddam et al., 2016; van Rosmalen et al., 2016; Correia et al., 2017; Gabrilovich et al., 2017; Kamian et al., 2018; Wu et al., 2018; Botha et al., 2020; Jamshidi et al., 2020; Yin et al., 2022; Frumovitz et al., 2020). For this reason, a meta-analysis was not feasible. The current review showed that these neoplasms are generally diagnosed in younger women compared to most common vulvar cancers such as SCC, with a median age of 52.5 years (range: 28–92 years). The most common histological subtypes were MCCs presented in more than 50% of the analyzed cohort (Chandeying et al., 1989; Chen, 1994; Loret de Mola et al., 1993; Scurry et al., 1996; Gil-Moreno et al., 1997; Hierro et al., 2000; Pawar et al., 2005; Khoury-Collado et al., 2005; Mohit et al., 2009; Sheikh et al., 2010; Iavazzo et al., 2011; Soni et al., 2011; Winer et al., 2012; Aminimoghaddam et al., 2016; Kamian et al., 2018; Botha et al., 2020) followed by SCNECs (Copeland et al., 1985; Cliby et al., 1991; Obermair et al., 2001; Correia et al., 2017; Wu et al., 2018; Jamshidi et al., 2020; Frumovitz et al., 2020). This review confirmed that surgical excision is the first-line approach to vulvar NENs and that the final diagnosis was mostly achieved after previous local excisions performed in non-referral centers (Palaia et al., 2011). Considering the high tendency to develop local and distant relapse compared to the most common squamous cell carcinomas, we found that inguinal lymphadenectomy (mono or bilateral) was generally performed (Copeland et al., 1985; Husseinzadeh et al., 1988; Chandeying et al., 1989; Cliby et al., 1991; Scurry et al., 1996; Hierro et al., 2000; Nuciforo et al., 2004; Khoury-Collado et al., 2005; Mohit et al., 2009; Iavazzo et al., 2011; Fawzi et al., 1997; Aminimoghaddam et al., 2016; Correia et al., 2017; Gabrilovich et al., 2017; Kamian et al., 2018; Wu et al., 2018; Botha et al., 2020; Jamshidi et al., 2020). So far there is no agreement on which surgical technique reduces the risk of local relapses and, at the same time, improves patient quality of life minimizing long-term morbidity (Palaia et al., 2011). It should be stressed that in the analyzed cases, surgical complications were rarely reported and consisted mainly in wound breakdown or dehiscence (Husseinzadeh et al., 1988; Chandeying et al., 1989; Scurry et al., 1996; Hierro et al., 2000; Mohit et al., 2009; Yin et al., 2022) or severe adverse events (Hierro et al., 2000; Fawzi et al., 1997; Yin et al., 2022). However, considering that NENs might affect young and almost sexually active women, the surgical morbidity must be better known to suggest the appropriate medical strategy.

The most effective adjuvant approach remains controversial (Basile et al., 2006). The role of adjuvant RT in skin MCCs has been addressed in several previous works (Zeitoun et al., 2022; Savage et al., 1997; Meeuwissen et al., 1995) in which adjuvant RT has been proven to reduce local relapses compared to surgery alone. The radiosensitivity of NENs justifies the use of RT also in the other subtypes. The volume of RT

described in the analyzed cases included the tumor bed, the vulvar, and the pelvic region, with some cases delivering at inguinal or even para-aortic lymph nodes. For unresectable diseases or patients unfit for surgery, definitive RT could be an option (Howitt et al., 2017; Kefeli and Usubütün, 2015; Khan and Barnes, 2012) as well as for palliation in case of oligoprogression (Jamshidi et al., 2020). Across the selected studies, the technical RT details were seldom reported and differed substantially, underlining the need for standardization of the doses and volumes in the management of NENs. Moreover, considering the high radiosensitivity and the importance to avoid RT sequelae after RT often negatively impacts the urogynecological sphere and the well-being of the patients (Barcellini et al., 2022), particle RT (Helm et al., 2022) might be tested in the future.

Systemic therapy schemes, often used in a multimodal approach with surgery and RT, both in adjuvant and palliative settings, were mainly extrapolated from data published in neuroendocrine carcinoma of the lung. The most frequently used regimen included: cisplatin and etoposide (Husseinzadeh et al., 1988; Chen, 1994; Loret de Mola et al., 1993; Wu et al., 2018; Jamshidi et al., 2020) followed by carboplatin/cisplatin and paclitaxel (Gabrilovich et al., 2017; Kamian et al., 2018) cisplatin, methotrexate and cyclophosphamide (Soni et al., 2011), irinotecan (Jamshidi et al., 2020). Pembrolizumab was tested on one vulvar SCNEC in the open-label, investigator-initiated phase II basket trial by Frumovitz et al (Frumovitz et al., 2020). and demonstrated minimal activity in recurrent tumors. Considering the possibility to increase the efficacy of immunotherapy when it is combined with RT, further studies might be warranted (Durante and Formenti, 2020) also in this challenging scenario. There is an emerging enthusiasm for investigating the role of other molecular targeted agents in NENs (Bellati et al., 2007) of whom results will probably become available in the next future. In particular, Bellati et al. demonstrated that cancer testis tumor-associated antigens (C/T-TAAs) are frequently expressed in aggressive vulvar cancer and could be used, in future, as prognostic markers as well as targets for immunotherapy.

Considering medical treatments other than chemotherapy, tyrosine kinase inhibitors (TKI) and (ICI) could represent a future therapeutic approach for the treatment of neuroendocrine tumors of the vulva. Promising anti-tumor activity and safety have been demonstrated in other vulvar cancer and neuroendocrine tumor types, however, further studies are needed to demonstrate their effectiveness in vulvar NEN (Bogani et al., 2023; Raymond et al., 2011).

Overall, the clinical outcome of patients with vulvar NEN is very poor and worse than that of most frequent vulvar histotypes of the comparable stage, being the PFS and the OS less than 2 years in the majority of reported cases. Unfortunately, given the high heterogeneity of available data, it is difficult to provide an exhaustive summary and draw definitive conclusions about the prognostic/predictive factors impacting survival. Considering the dismal prognosis, future treatments should include the adoption of synergistic combination strategies with new drugs also combined with new RT techniques. Due to the rarity of this disease, it will be essential to centralize patients with vulvar NENs in referral centres highly specialized in the diagnosis and management of rare tumors and being part of network collaborative groups on rare diseases. In addition, neuroendocrine tumors can be difficult to diagnose and a second review at a specialized centre can help to ensure the correct diagnosis and offer patients the best possible care. Moreover, it should be mandatory to collaborate and share single-institution experiences worldwide in order to create evidence-based data. Last but not least, patients with advanced, recurrent or metastatic gynecological NENs should be strongly encouraged to participate in clinical trials.

5. Conclusions

We reviewed the available literature on vulvar NENs, focusing on the treatment option and outcomes. We summarized the state-of-the-art literature evidence on vulvar NENs, with a focus on available treatment approaches and outcomes. A multimodal approach including surgery, chemotherapy and RT appeared safe and feasible. However, the incidence of the disease, the low-quality evidence of the analyzed papers, which are mostly case reports, and the wide variability in treatment strategies mean that definitive recommendations regarding the best practice cannot be made.

It is urgently necessary to create international debates with experts in rare gynecological tumors also on single clinical cases as well as international databases in order to collect adequate data to make a step forward in the treatment of these rare and aggressive diseases.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2023.104201.

References

Aminimoghaddam, S., Maghsoudnia, A., Shafiee, S., 2016. Moderately differentiated neuroendocrine cell carcinoma of the vulva: a case report and review of the literature. Gulf J. Oncol. 1 (22), 72–75.

Barcellini, A., Dominoni, M., Dal Mas, F., Biancuzzi, H., Venturini, S.C., Gardella B, Orlandi, E., Bø, K., 2022. Sexual health dysfunction after radiotherapy for gynecological cancer: role of physical rehabilitation including pelvic floor muscle training. Front. Med. 8, 813352 https://doi.org/10.3389/fmed.2021.813352.

Basile, S., Angioli, R., Manci, N., Palaia, I., Plotti, F., Benedetti Panici, P., 2006. Gynecological cancers in developing countries: the challenge of chemotherapy in low-resources setting. Int J. Gynecol. Cancer 16 (4), 1491–1497. https://doi.org/10.1111/j.1525-1438.2006.00619.x.

Bellati, F., Napoletano, C., Tarquini, E., Palaia, I., Landi, R., Manci, N., Spagnoli, G., Rughetti, A., Panici, P.B., Nuti, M., 2007. Cancer testis antigen expression in primary and recurrent vulvar cancer: association with prognostic factors. Eur. J. Cancer 43 (17), 2621–2627. https://doi.org/10.1016/j.ejca.2007.08.031.

Bogani, G., Palaia, I., Perniola, G., Tomao, F., Giancotti, A., Di Mascio, D., Capalbo, G., Muzii, L., Benedetti Panici, P., Di Donato, V., 2023. An update on current pharmacotherapy for vulvar cancer. Expert Opin. Pharm. 24 (1), 95–103. https://doi.org/10.1080/14656566.2022.2117608.

Botha, Adam R., Mbodi, Langanani, Wadee, Reubina, 2020. Advanced neuroendocrine carcinoma (Merkel cell carcinoma) of the vulva: a case report and literature review. South. Afr. J. Gynaecol. Oncol. 12 (1), 1–5. https://doi.org/10.1080/20742835.2020.1740434.

Caruso, G., Sassu, C.M., Tomao, F., Di Donato, V., Perniola, G., Fischetti, M., Benedetti Panici, P., Palaia, I., 2021. The puzzle of gynecologic neuroendocrine carcinomas: state of the art and future directions. Crit. Rev. Oncol. Hematol. 162, 103344 https://doi.org/10.1016/j.critrevonc.2021.103344.

Castle, P.E., Pierz, A., Stoler, M.H., 2018. A systematic review and meta-analysis on the attribution of human papillomavirus (HPV) in neuroendocrine cancers of the cervix. Gynecol. Oncol. 148 (2), 422–429. https://doi.org/10.1016/j.ygyno.2017.12.001.

Chandeying, V., Sutthijumroon, S., Tungphaisal, S., 1989. Merkel cell carcinoma of the vulva: a case report. Asia Ocean. J. Obstet. Gynaecol. 15 (3), 261–265. https://doi.org/10.1111/j.1447-0756.1989.tb00186.x.

Chen, K.T., 1994. Merkel's cell (neuroendocrine) carcinoma of the vulva. Cancer 73 (8), 2186–2191. https://doi.org/10.1002/1097-0142(19940415)73:8<2186::aid-cncr2820730825>3.0.co;2-q.

Chen, P.P., Ramalingam, P., Alvarado-Cabrero, I., et al., 2021. High-grade neuroendocrine carcinomas of the vulva: a clinicopathologic study of 16 cases. Am. J. Surg. Pathol. 45 (3), 304–316. https://doi.org/10.1097/PAS.0000000000001558.

Cliby, W., Soisson, A.P., Berchuck, A., Clarke-Pearson, D.L., 1991. Stage I small cell carcinoma of the vulva treated with vulvectomy, lymphadenectomy, and adjuvant chemotherapy. Cancer 67 (9), 2415–2417. https://doi.org/10.1002/1097-0142(19910501)67:9<2415::aid-cncr2820670934>3.0.co;2-w.

Copeland, L.J., Cleary, K., Sneige, N., Edwards, C.L., 1985. Neuroendocrine (Merkel cell) carcinoma of the vulva: a case report and review of the literature. Gynecol. Oncol. 22 (3), 367–378. https://doi.org/10.1016/0090-8258(85)90053-8.
Correia, A., Branco, E.C., Correia, P., Guimarães, M., Sá, L., 2017. Small cell carcinoma of the vulva: case report. Clin. Pract. 7 (2), 918. https://doi.org/10.4081/cp.2017.918.
Crane, E.K., Ramos, P., Farley, J.H., Naumann, R.W., Tait, D.L., Higgins, R.V., Brown, J., 2020. Molecular profiling in a large cohort of gynecologic neuroendocrine tumors. Gynecol. Oncol. 159, 262. https://doi.org/10.1016/j.ygyno.2020.05.452.
Di Domenico, A., Pipinikas, C.P., Maire, R.S., et al., 2020. Epigenetic landscape of pancreatic neuroendocrine tumours reveals distinct cells of origin and means of tumour progression. Commun. Biol. 3 (1), 740 https://doi.org/10.1038/s42003-020-01479-y.
Dias, J.L., Cunha, T.M., Gomes, F.V., Callé, C., Félix, A., 2015. Neuroendocrine tumours of the female genital tract: a case-based imaging review with pathological correlation. Insights Imaging 6, 43–52. https://doi.org/10.1007/s13244-014-0378-5.
Durante, M., Formenti, S., 2020. Harnessing radiation to improve immunotherapy: better with particles. Br. J. Radiol. 93 (1107), 20190224. https://doi.org/10.1259/bjr.20190224.
Fawzi, H.W., Cross, P.A., Buckley, C.H., Monaghan, J.M., 1997. Neuroendocrine (Merkel cell) carcinoma of the vulva. J. Obstet. Gynaecol. 17 (1), 100–101. https://doi.org/10.1080/01443619750114310.
Frumovitz, M., Westin, S.N., Salvo, G., Zarifa, A., Xu, M., Yap, T.A., Rodon, A.J., Karp, D. D., Abonofal, A., Jazaeri, A.A., Naing, A., 2020. Phase II study of pembrolizumab efficacy and safety in women with recurrent small cell neuroendocrine carcinoma of the lower genital tract. Gynecol. Oncol. 158 (3), 570–575. https://doi.org/10.1016/j.ygyno.2020.05.682.
Gabrilovich, S., Cracchiolo, B., Heller, D.S., 2017. Vulvar adenocarcinoma with neuroendocrine differentiation: a case report. J. Low. Genit. Trac. Dis. 21 (2), e23–e25. https://doi.org/10.1097/LGT.0000000000000294.
Gadducci, A., Carinelli, S., Aletti, G., 2017. Neuroendrocrine tumors of the uterine cervix: a therapeutic challenge for gynecologic oncologists. Gynecol. Oncol. 144 (3), 637–646. https://doi.org/10.1016/j.ygyno.2016.12.003.
Gardner, G.J., Reidy-Lagunes, D., Gehrig, P.A., 2011. Neuroendocrine tumors of the gynecologic tract: a Society of Gynecologic Oncology (SGO) clinical document. Gynecol. Oncol. 122 (1), 190–198. https://doi.org/10.1016/j.ygyno.2011.04.011.
Gil-Moreno, A., Garcia-Jiménez, A., González-Bosquet, J., Esteller, M., Castellví-Vives, J., Martínez Palones, J.M., Xercavins, J., 1997. Merkel cell carcinoma of the vulva. Gynecol. Oncol. 64 (3), 526–532. https://doi.org/10.1006/gyno.1996.4575.
Grondin, K., Lidang, M., Boenelycke, M., et al., 2019. Neuroendocrine tumors of the fallopian tube: report of a case series and review of the literature. Int J. Gynecol. Pathol. 38 (1), 78–84. https://doi.org/10.1097/PGP.0000000000000458.
Heller, M.T., Shah, A.B., 2011. Imaging of neuroendocrine tumors. Radiol. Clin. 49, 529–548. https://doi.org/10.1016/j.rcl.2011.02.011.
Helm, A., Fournier, C., Durante, M., 2022. Particle radiotherapy and molecular therapies: mechanisms and strategies towards clinical applications. Expert Rev. Mol. Med 24, e8. https://doi.org/10.1017/erm.2022.2.
Hierro, I., Blanes, A., Matilla, A., Muñoz, S., Vicioso, L., Nogales, F.F., 2000. Merkel cell (neuroendocrine) carcinoma of the vulva. A case report with immunohistochemical and ultrastructural findings and review of the literature. Pathol. Res. Pract. 196 (7), 503–509. https://doi.org/10.1016/S0344-0338(00)80052-7.
Howitt, B.E., Kelly, P., McCluggage, W.G., 2017. Pathology of neuroendocrine tumours of the female genital tract. Curr. Oncol. Rep. 19, 59 https://doi.org/10.1007/s11912-017-0617-2.
Husseinzadeh, N., Wesseler, T., Newman, N., Shbaro, I., Ho, P., 1988. Neuroendocrine (Merkel cell) carcinoma of the vulva. Gynecol. Oncol. 29 (1), 105–112 doi: 10.1016/0090-8258(88)90154-0. doi: 10.1016/0090-8258(88)90154-0.
Iavazzo, C., Terzi, M., Arapantoni-Dadioti, P., Dertimas, V., Vorgias, G., 2011. Vulvar merkel carcinoma: a case report. Case Rep. Med. 2011, 546972 https://doi.org/10.1155/2011/546972.
Jamshidi, A.M., Eichberg, D.G., Gultekin, S., Komotar, R.J., 2020. Brain metastasis from Bartholin gland carcinoma. World Neurosurg. 143, 280–284. https://doi.org/10.1016/j.wneu.2020.07.122.
Kamian, Sh, Rafie Zadeh, M., Arab, M., Shafiei, M., 2018. Primary neuroendocrine tumor of vulva: a case report. Rev. Clin. Med 5 (1), 19–22.
Kefeli, M., Usubütün, A., 2015. An update of neuroendocrine tumors of the female reproductive system. Turk. Patoloji Derg. 31 Suppl 1, 128–144. https://doi.org/10.5146/tjpath.2015.01320.
Khan, L., Barnes, E.A., 2012. Radiotherapy for metastatic merkel cell carcinoma: a review of the literature. J. Skin Cancer 2012, 654981. https://doi.org/10.1155/2012/654981.
Khoury-Collado, F., Elliott, K.S., Lee, Y.C., Chen, P.C., Abulafia, O., 2005. Merkel cell carcinoma of the Bartholin's gland. Gynecol. Oncol. 97 (3), 928–931. https://doi.org/10.1016/j.ygyno.2004.12.064.
Liu, Y.Q., Yue, J.Q., 2013. Paraganglioma of the vulva: a case report and review of the literature. Int J. Clin. Exp. Pathol. 6 (10), 2247–2250.
Loret de Mola, J.R., Hudock, P.A., Steinetz, C., Jacobs, G., Macfee, M., Abdul-Karim, F. W., 1993. Merkel cell carcinoma of the vulva. Gynecol. Oncol. 51 (2), 272–276. https://doi.org/10.1006/gyno.1993.1286.
Meeuwissen, J.A., Bourne, R.G., Kearsley, J.H., 1995. The importance of postoperative radiation therapy in the treatment of Merkel cell carcinoma. Int J. Radiat. Oncol. Biol. Phys. 31 (2), 325–331. https://doi.org/10.1016/0360-3016(94)E0145-A.
Methley, A.M., Campbell, S., Chew-Graham, C., McNally, R., Cheraghi-Sohi, S., 2014. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. BMC Health Serv. Res. 14, 579 https://doi.org/10.1186/s12913-014-0579-0.
Mohit, M., Mosallai, A., Monabbati, A., Mortazavi, H., 2009. Merkel cell carcinoma of the vulva. Saudi Med. J. 30 (5), 717–718.
Nuciforo, P.G., Fraggetta, F., Fasani, R., Braidotti, P., Nuciforo, G., 2004. Neuroendocrine carcinoma of the vulva with paraganglioma-like features. Histopathology 44 (3), 304–306. https://doi.org/10.1111/j.1365-2559.2004.01783.x.
Obermair, A., Koller, S., Crandon, A.J., Perrin, L., Nicklin, J.L., 2001. Primary Bartholin gland carcinoma: a report of seven cases. Aust. N. Z. J. Obstet. Gynaecol. 41 (1), 78–81. https://doi.org/10.1111/j.1479-828x.2001.tb01299.x.
Oronsky, B., Ma, P.C., Morgensztern, D., Carter, C.A., 2017. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia 19, 991–1002. https://doi.org/10.1016/j.neo.2017.09.002.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71. https://doi.org/10.1136/bmj.n71.
Palaia, I., Bellati, F., Calcagno, M., Musella, A., Perniola, G., Panici, P.B., 2011. Invasive vulvar carcinoma and the question of the surgical margin. Int J. Gynaecol. Obstet. 114 (2), 120–123. https://doi.org/10.1016/j.ijgo.2011.02.012.
Patibandla, J.R., Fehniger, J.E., Levine, D.A., Jelinic, P., 2018a. Small cell cancers of the female genital tract: molecular and clinical aspects. Gynecol. Oncol. 149 (2), 420–427 doi: 10.1016/j.ygyno.2018.02.004. doi: 10.1016/j.ygyno.2018.02.004.
Patibandla, J.R., Fehniger, J.E., Levine, D.A., Jelinic, P., 2018b. Small cell cancers of the female genital tract: molecular and clinical aspects. Gynecol. Oncol. 149 (2), 420–427. https://doi.org/10.1016/j.ygyno.2018.02.004.
Pawar, R., Vijayalakshmy, A.R., Khan, S., al Lawati, F.A., 2005. Primary neuroendocrine carcinoma (Merkel's cell carcinoma) of the vulva mimicking as a Bartholin's gland abscess. Ann. Saudi Med 25 (2), 161–164. https://doi.org/10.5144/0256-4947.2005.161.
Raymond, E., Hobday, T., Castellano, D., Reidy-Lagunes, D., García-Carbonero, R., Carrato, A., 2011. Therapy innovations: tyrosine kinase inhibitors for the treatment of pancreatic neuroendocrine tumors. Cancer Metastasis Rev. 30 (Suppl 1), 19–26. https://doi.org/10.1007/s10555-011-9291-2.
Rindi, G., Klimstra, D.S., Abedi-Ardekani, B., Asa, S.L., Bosman, F.T., Brambilla, E., Busam, K.J., de Krijger, R.R., Dietel, M., El-Naggar, A.K., Fernandez-Cuesta, L., Klöppel, G., McCluggage, W.G., Moch, H., Ohgaki, H., Rakha, E.A., Reed, N.S., Rous, B.A., Sasano, H., Scarpa, A., Scoazec, J.Y., Travis, W.D., Tallini, G., Trouillas, J., van Krieken, J.H., Cree, I.A., 2018. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. In: Mod. Pathol., 31, pp. 1770–1786 doi: 10.1038/s41379-018-0110-y. doi: 10.1038/s41379-018-0110-y.
Rouzbahman, M., Clarke, B., 2013a. Neuroendocrine tumors of the gynecologic tract: select topics. Semin. Diagn. Pathol. 30 (3), 224–233. https://doi.org/10.1053/j.semdp.2013.06.007.
Rouzbahman, M., Clarke, B., 2013b. Neuroendocrine tumors of the gynecologic tract: select topics. Semin. Diagn. Pathol. 30 (3), 224–233. https://doi.org/10.1053/j.semdp.2013.06.007.
Savage, P., Constenla, D., Fisher, C., Thomas, J.M., Gore, M.E., 1997. The natural history and management of Merkel cell carcinoma of the skin: a review of 22 patients treated at the Royal Marsden Hospital. Clin. Oncol. 9 (3), 164–167. https://doi.org/10.1016/s0936-6555(97)80073-8.
Scurry, J., Brand, A., Planner, R., Dowling, J., Rode, J., 1996. Vulvar Merkel cell tumor with glandular and squamous differentiation. Gynecol. Oncol. 62 (2), 292–297. https://doi.org/10.1006/gyno.1996.0229.
Sheikh, Z.A., Nair, I., Vijaykumar, D.K., Jojo, A., Nandeesh, M., 2010. Neuroendocrine tumor of vulva: a case report and review of literature. J. Cancer Res. Ther. 6 (3), 365–366. https://doi.org/10.4103/0973-1482.73370.
Soni, M., Aggarwal, S., Soni, P., Gupta, P., Dadhich, S., Saini, S., 2011. Vulvar Merkel cell carcinoma: a rare entity. J. South Asian Feder. Obstet. Gynaecol. 3 (3), 145–146. https://doi.org/10.5005/jp-journals-10006-1153.
Srivastava, S.A., Wang, Y., Vallone, J., et al., 2012. Primary clear cell carcinoid tumors of the vulva. Am. J. Surg. Pathol. 36 (9), 1371–1375. https://doi.org/10.1097/PAS.0b013e3182631e22.
Talia, K.L., Ganesan, R., 2022. Neuroendocrine neoplasia of the female genital tract. Surg. Pathol. Clin. 15 (2), 407–420. https://doi.org/10.1016/j.path.2022.02.012.
Tempfer, C.B., Tischoff, I., Dogan, A., Hilal, Z., Schultheis, B., Kern, P., Rezniczek, G.A., 2018. Neuroendocrine carcinoma of the cervix: a systematic review of the literature. BMC Cancer 18, 530. https://doi.org/10.1186/s12885-018-4447-x.
van Rosmalen, M.H., Reijnen, C., Boll, D., Pijnenborg, J.M., van der Wurff, A.A., Piek, J. M., 2016. Vulvar mucinous adenocarcinoma with neuroendocrine differentiation: a case report and review of the literature. Pathol. Res. Pract. 212 (3), 234–237. https://doi.org/10.1016/j.prp.2016.01.005.
Winer, I.S., Lonardo, F., Johnson, S.C., Deppe, G., 2012. Merkel cell carcinoma in a patient with noninvasive vulvar Paget's disease. Am. J. Obstet. Gynecol. 207 (1), e9–e11. https://doi.org/10.1016/j.ajog.2012.03.028.
Wu, J.C., Xi, M.L., Wang, Y.Q., Tang, W.B., Zhang, Y.Q., 2018. Primary small cell neuroendocrine carcinoma of the Bartholin's gland: a case report. Oncol. Lett. 16 (4), 4434–4438. https://doi.org/10.3892/ol.2018.9231.

Yin, Y., Han, L., Chen, Y., Ruan, J., Zheng, A., 2022. Vulvar neuroendocrine carcinoma: a case report and literature review. Gynecol. Pelvic Med. 5, 30. https://doi.org/10.21037/gpm-21-62.

Zeitoun, J., Calvary, M., Bonneau, C., Rouzier, R., 2022. Impact of vulvar cancer surgery on quality of sex life: a review of literature. J. Low. Genit. Trac. Dis. 26 (1), 38–42. https://doi.org/10.1097/LGT.0000000000000633.

Zhang, C., Quddus, M.R., Sung, C.J., Moore, R.G., Lawrence, W.D., 2012. Vulvar encapsulated solid papillary carcinoma with neuroendocrine differentiation: a case report. Int J. Surg. Pathol. 20 (1), 97–100. https://doi.org/10.1177/1066896911401387.

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