VAGINAL and VULVAR CANCERS

CHI Formulary Indication Review

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Council of Health Insurance

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Abbreviations

5-FU	5-Fluorouracil
AFP	Alpha-Fetoprotein
AJCC	American Joint Committee on Cancer
BGCS	British Gynecological Cancer Society
BSC	Best Supportive Care
CADTH	Canadian Agency for Drugs and Technologies in Health
CCRT	Concurrent Chemoradiotherapy
CHI	Council of Health Insurance
CT	Computed Tomography
DES	Diethylstilbesterol
DGGG	German Society of Gynecology and Obstetrics
DKG	German Cancer Society
dMMR	Deficient Mismatch Repair
dVIN	Differentiated Vulvar Intraepithelial Neoplasia
EBRT	External Beam Radiotherapy
ECE	Extracapsular Extension
EMA	European Medicines Agency
ESGO	European Society of Gynecological Oncology
ESTRO	European Society for Radiotherapy & Oncology
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
GCT	Germ Cell Tumor
HAS	Haute Autorité de Santé
HGSIL	High-Grade Intraepithelial Neoplasia
HPV	Human Papillomavirus
HSIL	High-grade Squamous Intraepithelial Lesion
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IFLN	Inguinofemoral Lymph Node
IGABT	Image-Guided Adaptive Brachytherapy

IMRT	Intensity-Modulated Radiation Therapy
IQWIG	Institute for Quality and Efficiency in Health Care
IRS	Intergroup Rhabdomyosarcoma Study
JSGO	Japan Society of Gynecologic Oncology
KSA	Kingdom of Saudi Arabia
LEEP	Loop Electrosurgical Excision Procedure
LGSIL	Low-Grade Intraepithelial Neoplasia
LSIL	Low-grade Squamous Intraepithelial Lesion
MRI	Magnetic Resonance Imaging
MSI-H	Microsatellite Instability – High
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NOS	Not Otherwise Specified
NTRK	Neurotrophic Tyrosine Receptor Kinase
PBAC	Pharmaceutical Benefits Advisory Committee
PD-L1	Programmed Death – Ligand 1
PET	Positron Emission Topography
RMS	Rhabdomyosarcoma
RT	Radiation Therapy
SCC	Squamous Cell Carcinoma
SFDA	Saudi Food and Drug Authority
SIOPe	International Society of Pediatric Oncology - Europe
SLN	Sentinel Lymph Node
TMB-H	Tumor Mutational Burden – High
TNM	Tumor, Node, Metastasis
VaIN	Vaginal Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
VSCC	Vulval Squamous Cell Carcinoma
WHO	World Health Organization

Executive Summary

Vaginal and vulvar cancers are rare types of gynecologic malignancies with a significant impact on patients life. Primary vaginal cancer originates from the vagina and is defined as a disease without evidence of cervical or vulvar cancer or a history of either within the past five years. Vulvar cancer originates from the outer surface area of the female genitalia. Both vaginal and vulvar lesions have precursors and display levels of dysplasia before progression to invasive disease. Similar to cervical cancer, human papillomavirus (HPV) is one of the risk factors linked to both diseases. In vaginal cancer, the most common clinical presentation is unscheduled vaginal bleeding or/and the presence of vaginal mass. Other potential symptoms are related to the local extension of disease, urinary symptoms (e.g., frequency, dysuria, hematuria), gastrointestinal complaints (e.g., tenesmus, constipation, melena), and pelvic pain from the extension of disease beyond the vagina.

According to the recent Saudi cancer registry executed in 2020, primary vaginal and vulvar cancers were reported in only 5 and 16 patients, respectively, comprising 0.1% and 0.2% of all Saudi female nationals.[1]

This report compiles all clinical evidence related to vaginal and vulvar cancers according to the relevant sources. The ultimate objective of issuing vaginal and vulvar cancer guidelines by the Council of Health Insurance (CHI) is to update the IDF (CHI Drug Formulary) with the best available clinical evidence related to drug therapies, ensuring timely and safe access to vaginal and vulvar cancer patients in Saudi Arabia. The review's main focus was on Saudi, North American, European, and international guidelines issued within the last ten years, in addition to recent systematic reviews and meta-analyses.

The management of vaginal and vulvar cancers. The therapeutic options for involves a multidisciplinary approach and differs based on the stage of the disease the management of Vaginal cancer are extrapolated from cervical cancer, while vulvar cancer therapeutic options are extrapolated from both cervical and anal cancer. Most of the treatment regimen options for the management of vaginal and vulvar cancers on the global market are available in KSA and registered by the Saudi Food and Drug Authority (SFDA). Section 3 provides a full description of each with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of vaginal and vulvar cancers. Section 4 lists the key recommendations synthesis for vaginal and vulvar cancer treatment.

Major recommendations for suggested drug therapies are summarized in the table below:

Table 1. SFDA-Registered Drugs for the Management of Vulvar and Vaginal Cancer

Management of vulvar and vaginal cancer				
Medication/ Protocol	**Indication**	**Line of Therapy**	**Recommendation**	**Evidence**
Cisplatin	Concurrent chemoradiation (vaginal and vulvar tumors)	**1st (preferred)**	B	II
Carboplatin		**1st Alternative to cisplatin**	B	II
Cisplatin/Fluorouracil		**2nd**	B	II
Gemcitabine		**2nd**	B	II
Paclitaxel		**2nd**	B	II
Cisplatin/paclitaxel/bevacizumab	Management of advanced or recurrent/metastatic disease (vulvar tumors)	**1st (preferred)**	B	II
Cisplatin/paclitaxel		**1st (preferred)**	B	II
Carboplatin/paclitaxel		**1st (preferred)**	B	II
Carboplatin/paclitaxel/bevacizumab		**1st (preferred)**	B	II
Paclitaxel	Second-line or subsequent therapy in	**2nd**	B	II
Erlotinib		**2nd**	B	II
Cisplatin/gemcitabine		**2nd**		

	recurrent/metastatic disease (vulvar tumors)			
Pembrolizumab	Second-line or subsequent therapy in recurrent/metastatic disease (biomarker directed therapy) (vulvar tumors)	**2nd**	Useful in certain circumstance for TMB-high [TMB-H], PD-L1–positive, or MSI-high [MSI-H]/MMR deficient [dMMR] tumors	
Nivolumab		**2nd**	Useful in certain circumstance HPV-related tumors	
Larotrectinib		**2nd**	Useful in certain circumstance *NTRK* gene fusion-positive tumors	
Entrectinib		**2nd**		

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence (Vaginal Cancer)

1.1 KSA Guidelines

To date, there are no guidelines published by Saudi medical bodies on the management of vaginal cancers.

1.2 World Health Organization (WHO) Classification (2021)

Histopathological diagnosis of vaginal cancer is important in the selection process of proper treatment regimen, especially in advanced disease. The World Health Organization (WHO) published its fifth edition of the Classification of Female Genital Tumors in 2021 including benign and malignant tumors. The different histopathology of malignant vaginal tumors is detailed in table 2.[2]

Table 2. World Health Organization (WHO) Classification of the Malignant Tumors of the Vagina (Fifth Edition)

WHO Classification of malignant Vaginal Tumors, Fifth Edition		
Epithelial tumors	Low-grade squamous intraepithelial lesion	Vaginal intraepithelial neoplasia, grade 1
	High-grade squamous intraepithelial lesion	Vaginal intraepithelial neoplasia, grade 2
		Vaginal intraepithelial neoplasia, grade 3
	Squamous cell carcinoma, HPV-associated	
	Squamous cell carcinoma, HPV-independent	
	Squamous cell carcinoma not otherwise specified (NOS)	
	Adenocarcinoma NOS	
	Adenocarcinoma, HPV-associated	
	Endometrioid adenocarcinoma NOS	
	Clear cell adenocarcinoma NOS	
	Mucinous carcinoma, gastric type	
	Mucinous carcinoma, intestinal type	
	Mucinous adenocarcinoma	
	Mesonephric adenocarcinoma	

	Carcinosarcoma NOS	
	Carcinoma of Skene, Cowper, and Littre glands	
	Adenosquamous carcinoma	
	Adenoid basal carcinoma	
Mixed epithelial and mesenchymal tumours	Adenosarcoma	
Miscellaneous tumours	Germ cell tumour NOS	Yolk sac tumour, pre-pubertal type
		Mature teratoma NOS
		Dermoid cyst NOS

1.3 International Federation of Gynecology and Obstetrics (FIGO) Staging System (2021)

The most recent FIGO classification system published in 2021 is detailed in table 3 in comparison to other staging systems such as the tumor/node/metastasis (TNM) and the American Joint Committee on Cancer (AJCC) systems.

Table 3. Staging of Vaginal Cancer Using FIGO, TNM, and AJCC Systems

AJCC Stage	Stage grouping (TNM)	FIGO Stage	Stage description
IA	T1a N0 M0	I	The cancer is only in the vagina and is no larger than 2.0 cm (4/5 inch) (T1a) It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
IB	T1b N0 M0	I	The cancer is only in the vagina and is larger than 2.0 cm (4/5 inch) (T1b) It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
IIA	T2a N0 M0	II	The cancer has grown through the vaginal wall, but not as far as the pelvic wall and is no larger than 2.0 cm (4/5 inch) (T2a) It has not spread to nearby lymph nodes (N0) or to distant sites (M0)

IIB	T2b N0 M0	II	The cancer has grown through the vaginal wall, but not as far as the pelvic wall and is larger than 2.0 cm (4/5 inch) (T2b) It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
III	T1 to T3 N1 M0	III	The cancer can be any size and might be growing into the pelvic wall, and/or growing into the lower one-third of the vagina and/or has blocked the flow of urine (hydronephrosis), which is causing kidney problems (T1 to T3). It has also spread to nearby lymph nodes in the pelvis or groin (inguinal) area (N1) but not distant sites (M0)
	OR		
	T3 N0 M0	III	The cancer is growing into the pelvic wall, and/or growing into the lower one-third of the vagina and/or has blocked the flow of urine (hydronephrosis), which is causing kidney problems (T3) It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
IVA	T4 Any N M0	IVA	The cancer is growing into the bladder or rectum or is growing out of the pelvis (T4) It might or might not have spread to lymph nodes in the pelvis or groin (inguinal area) (Any N). It has not spread to distant sites (M0)
IVB	Any T Any N M1	IVB	The cancer has spread to distant organs such as the lungs or bones (M1). It can be any size and might or might not have grown into nearby structures or organs (Any T) It might or might not have spread to nearby lymph nodes (Any N)

1.4 Northern American Guidelines

In the past 10 years, no clinical guidelines have been published by northern American bodies on the pharmacological management of vaginal cancers.

1.5 European Guidelines

1.5.1 The European Society of Gynaecological Oncology (ESGO)/The European Society for Radiotherapy & Oncology (ESTRO)/The European Society of Pediatric Oncology (SIOPe) Guidelines for the Management of Patients with Vaginal Cancer (2023)

In May 2023, the European Society of Gynaecological Oncology (ESGO) jointly with the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of Pediatric Oncology (SIOPe) developed evidence-based guidelines in order to improve the management of patients with vaginal cancer within a multidisciplinary setting.[3]

Table 4. Summary of Recommendations for the Treatment of Vaginal Cancer in Adults

Squamous cell carcinoma
<u>Management of stage 1 (T1N0M0):</u>
A histological diagnosis should be made before undertaking any treatment [V, A].
The combination of radical surgery and radiotherapy should be as principle avoided in any treatment planning due to the increased risk of complications and side-effects after combined treatment [IV, A].
Surgery
The surgical route should be considered only for small size lesions (maximum size up to 2cm) that are not in close relation to critical structures (urethra, anal canal) to ensure free margins with acceptable morbidity [IV, A].
The surgical treatment consists of (partial) colpectomy and lymph node assessment depending on the location of the primary lesion [IV, A].
In patients with a tumor in the upper vagina, with a uterus in situ, a combination of hysterectomy and parametrial/paracolpia resection may berequired together with the (partial) colpectomy to ensure free margins [IV, C].
A fertility sparing approach may be considered in selected patients with adequate distance of the tumor to the cervix, but at any resection highest care should be undertaken not to result in obstructive symptoms such as haematometra or inability to access the cervix for cytology and HPV screening [IV, C].
In patients undergoing surgery for tumors involving the upper two thirds of the vagina pelvic lymph node assessment is recommended [IV, A].
In patients undergoing surgery with tumors involving the lower third of the vagina, surgical inguinal lymph node assessment is recommended [IV, A].

The use of sentinel lymph node (SLN) principle alone is not yet established in vaginal cancers [V, D].
In selected patients after initial incomplete excision on referral, surgical treatment may be considered when free margins can be ensured with acceptable morbidty [IV, C].
Radiotherapy and Brachytherapy - Adjuvant (Chemo-)radiotherapy
Adjuvant radiotherapy is recommended in patients with tumor positive resection margins, or lymph node metastasis [IV, A].
The addition of concomitant cisplatin-based chemotherapy is recommended in case of histologically confirmed lymph node metastasis [IV, A]. This addition can be considered in case of positive surgical margins [IV, B].
Radiotherapy and Brachytherapy - Primary (Chemo-)radiotherapy
A combination of external beam radiotherapy (EBRT) and brachytherapy is recommended in stage I [IV, A].
Concomitant cisplatin-based chemotherapy is recommended [IV, A].
Ovarian transposition should be discussed up front in premenopausal women undergoing radiotherapy [IV, B].
Management of stage T2-T3-T4 or any T-stage, N1M0:
Definitive platinum-based chemoradiotherapy and brachytherapy is the preferred treatment [IV, A].
In patients with T4a tumors and fistulation, GI and GU diversion should be considered before chemoradiotherapy [IV, A].
There is no valid evidence to support (neo-)adjuvant systemic therapy in vaginal cancer outside of clinical trials [V, C].
Distant metastatic disease at presentation and recurrent disease:
Distant Metastatic Disease
Patients with oligo-metastatic disease at presentation may be treated with definitive chemoradiotherapy including brachytherapy, in combination with systemic therapy [IV, C].
Referal to a palliative care specialist is recommended early on [V,A].
In medically fit patients with widespread distant metastatic disease at presentation, platinum-based systemic combination therapy, equivalent to cervical cancer regimens, is recommended [IV, A].
In rare histological types, the preferred systemic therapy regimen should be adapted accordingly [IV, A].

Selection of cytotoxic agents depends on the previous oncologic treatment, performance status and associated co-morbidities [IV, B].
Treatment of oligometastatic sites depends on the site of disease and symptoms and may consist of (stereotactic)radiotherapy, or surgical resection and radiofrequency ablation in selected cases [IV, C].
Palliative radiotherapy (single fraction/short course) to control bleeding, discharge, and pain due to pelvic disease or bone metastases should be considered [IV, A].
Surgical interventions including diversion stoma and/or stenting should be considered as appropriate, for example, in case of obstructive symptomatic disease [IV, A].
Local Recurrent Disease
Treatment of recurrent disease with curative intent requires centralization and involvement of a broad dedicated multidisciplinary team. A structured program for multidisciplinary diagnostic work-up, treatment, and follow-up must be present in centers responsible for the treatment [V, A].
Each center involved in the primary treatment of vaginal cancer should have an established network for discussion of difficult cases and willingness for referring patients with recurrence for treatment to highly specialized units [V, A].
Relevant imaging including positron emission tomography-computed tomography (PET-CT) is recommended to establish the status of the disease locally, regionally, and systemically [IV, A].
The recurrence should be confirmed by histological examination, also to rule out any metastasis from another primary site [IV,A].
In selected cases of central pelvic recurrence where clear margins can be achieved, a pelvic exenteration should be considered [IV, B].
Reirradiation with image-guided adaptive brachytherapy (IGABT) for central recurrences may be considered in experienced centers [IV, B].
In radiotherapy naïve patients, chemoradiation and brachytherapy is recommended [IV, A].
If active local therapy is not an option, palliative treatments as described in the section on distant metastatic disease should be considered [IV, A].
Adenocarcinomas
Recommendations for women exposed to diethylstilbesterol (DES) in utero are to have their first gynecologic examination at menarche with a careful colposcopic and cytological assessment of the cervix and vagina that should continue annually [V, A].
In general, treatment recommendations for vaginal adenocarcinomas are aligned

with the recommendations for vaginal squamous cell carcinoma (SCC) [V,B].
Sarcomas
These very rare forms of vaginal cancer should be jointly managed within a multidisciplinary setting together with a dedicated sarcoma team [V, A].
Registration in rare cancer networks is strongly encouraged [V, A].
Melanomas
These patients should be jointly managed within a multidisciplinary setting together with a dedicated melanoma team [V, A].
Registration in rare cancer networks is strongly encouraged [V, A].
Other Rare Subtypes
Other rare subtypes such as neuroendocrine and haematopoietic neoplasms of the vagina should be treated as per the guidelines of the respective tumor entity [V, A].
Registry in centralized databases for rare cancers is strongly encouraged [V, A].

Vaginal cancer in pediatrics:

1. Pediatric Rhabdomyosarcoma (RMS)

Vaginal RMS - Chemotherapy Schedule

- The chemotherapy schedule should be adapted to risk factors (Intergroup Rhabdomyosarcoma Study [IRS] stage, age, tumor size, nodal or distant spread, molecular and pathology findings) [IV, A].
- Neoadjuvant and adjuvant combination chemotherapy, including an alkylating (cyclophosphamide, ifosfamide) agent, is recommended [IV, A].
- In rare cases with regionally involved lymph nodes and/or with a fusion positive RMS subtype additional maintenance strategies, after adjuvant therapy, should be considered [IV, A].

Vaginal RMS - Local Therapy

- Highest consideration of any local therapy should be the organ preservation. After neoadjuvant therapy, local treatment should be discussed at a multidisciplinary team that includes different specialists who are experienced in treatment of pediatric patients (including a radiation oncologist specialized in brachytherapy). Radical, potentially mutilating surgical procedures during first line treatment should be avoided [IV, A].
- Local therapy is adapted to the tumor response and histological type, assessed by pelvic magnetic resonance imaging (MRI) and vaginoscopy after 3 and 6 courses of neoadjuvant chemotherapy. Any suspicious residual

vaginal lesions should be biopsied during this exam. In case of stable or progressive disease after three courses, second line chemotherapy should be proposed [IV, A].

- EBRT is recommended in rare cases with lymph node metastasis, preferably using proton therapy [IV, A].
- In case of complete remission of an embryonal RMS after 6 courses of neoadjuvant chemotherapy confirmed by a negative pelvic MRI and a negative vaginoscopy (including biopsies of any suspicious areas), no local treatment is indicated. A strict follow-up schedule is recommended [IV, A].
- A strict follow-up schedule should consist of pelvic MRI (grade A) with or without vaginoscopy every 3 months during the first 2 years, and MRI every 4 months during the third year, and every 6 months up to 5 years follow-up [IV, A].
- Omission of any local treatment, including radiotherapy, can only be considered in case of complete remission and if at least a certain amount of alkylating agents (i.e., cyclophosphamide > 8 gr/m2) was part of the neoadjuvant chemotherapy [IV, B].

<u>Surgery</u>

- At initial diagnosis, surgery is limited to a diagnostic biopsy for histological confirmation that may or may not include resection of any exoplytic/polypoid lesions but without any associated vaginal wall resections [IV, B].
- In case of residual tumor after neoadjuvant therapy:
    - Unifocal small residue: partial vaginectomy (resection of the vaginal wall recommended/biopsy not sufficient)/ partial excision of the cervix [IV, A]
    - If the residual tumouris located in the fornix/cervix: trachelectomy (or brachytherapy with cervix catheter) is recommended [IV, A]
    - If the tumor involves more than half of the vagina or is multifocal: brachytherapy should be preferred over total vaginectomy depending on the patients risk profile and available options [IV, C].
- A minority of patients may undergo a limited, but complete tumor resection with organ preservation. For tumors of the upper part of the vagina, partial vaginectomy, partial or total excision of the uterine cervix or trachelectomy (removal of the cervix, surrounding tissue, and the upper part of the vagina) are considered organ-salvaging procedures [IV, B]. In rare tumors not responding to chemotherapy, radical surgical procedures, such as total vaginectomy with or without hysterectomy, may be discussed [IV, C].

- Regional nodal spread: in the case of initial widespread nodal metastasis, systematic removal of lymph nodes is not recommended [IV, D]. However, in the rare case of initial isolated nodal metastasis in very young patients (<3 years), removal of this lymph node may be considered with the aim to tailor the extent of the EBRT target volume [IV, C].
- Ovarian transposition is recommended in situations where relevant radiation dose to the ovaries is anticipated [IV, B].

Radiotherapy

Radiotherapy is generally recommended for [IV, B]:

- Embryonal RMS, if no complete response is reached after induction chemotherapy and if conservative surgery with free margins is not possible.
- In rare case of alveolar RMS with fusion transcript.
- In cases of histologically, cytologically or radiologically confirmed regional nodal involvement.
- Brachytherapy is preferred over EBRT for treatment of the primary tumor. A total dose of 50–60 Gy EQD2 is prescribed. If external irradiation is however required (eg, pelvic lymph node involvement), proton beam therapy is prefered. Brachytherapy is the preferred irradiation modality to boost the primary tumor and minimize doses to organs at risk [IV, B].
  There are few systematic indications for EBRT in vaginal RMS. Only the rare cases with initial lymph node involvement, should receive EBRT. In this case, proton beam therapy is the preferred modality [IV, B].

Vaginal RMS - Metastatic Sites

- In patients with limited (oligo) metastatic disease and favorable response after chemotherapy, focal treatment of metastatic sites could be considered [IV, C].
- There is insufficient data to recommend specific focal treatment for metastatic tumor sites (ie,.surgery, stereotaxic radiotherapy) and management should be individualized depending on each patients' and tumor profile and also symptoms [V, C].

2. Pediatric germ cell tumors (GCT)

GCT - Chemotherapy Schedule

- Neoadjuvant chemotherapy is recommended as standard approach [IV, A].
- As a principle, chemotherapy should include **platinum** derivates regimens. The number of courses, the dose and the used drugs (3 to 4) should be adapted to extent of disease, dissemination pattern and the age of the patient [IV, A].

GCT - Tumour Assessment During Neoadjuvant Therapy

- Regular ultrasound evaluation is recommended for response assessment during treatment, consolidated by an MRI at the end of cytotoxic treatment [IV, A].
- Tumor biomarker evaluation should include regular measurement of serum alpha-fetoprotein (AFP) [IV, A].

GCT - Local Therapy

Surgery should be reserved for situations where there is still persistent disease after completion of neoadjuvant chemotherapy. Surgery should aim for complete removal of the lesion and should be adapted to the anatomical site so that unnecessary radical or mutilating treatment is avoided. In the case of extravaginal, including lymph node spread, an initial surgical resection is not recommended, as this is treated by chemotherapy with excellent response and surgical discussion should be postponed after tumor reduction following induction chemotherapy [IV, A].

1.5.2 The German Society of Gynecology and Obstetrics (DGGG)/German Cancer Society (DKG) Guideline of the Diagnosis, Therapy, and Follow-Up of Vaginal Cancer and its Precursors (2018)

In 2018, the Gynecological Oncology Working Group of the German Cancer Society (DKG) and the German Society for Gynecology and Obstetrics (DGGG) published their guidelines for the diagnosis, management, and follow up of vaginal cancer and its precursors.[4]

Table 5. Summary of the DGGG/DKG 2018 Recommendations for Vaginal Cancer

Consensus-based statements **Expert consensus Strength of consensus +++**
Vaginal Intraepithelial Neoplasia (VaIN)
VaIN 1 (condylomatous lesion) low-grade squamous intraepithelial lesion (LGSIL), flat condyloma
Regular monitoring, in exceptional cases destruction, excision, local application of imiquimod (off-label use)
VaIN 2–3 high-grade intraepithelial neoplasia (HGSIL)
Extensive biopsy, followed by destruction or surgical removal (excision, skinning colpectomy, skinning excision, partial/total colpectomy) or radiotherapy
Recurrence and progression rates

Patients treated for VaIN must be offered regular follow-up examinations for the rest of their lives because the rate of recurrence for VaIN is high.
FIGO stage I
Surgery may be used to treat FIGO stage I vaginal carcinoma.
Circumscribed FIGO stage I tumors should be excised locally with tumorfree margins; the surgical treatment of larger tumors should consist of colpectomy or hysterectomy, if necessary.
FIGO stage II
Radio(chemo)therapy is the standard therapy for tumor stages II to IV. Exenteration to treat stage IV vaginal carcinoma is an individual therapy decision.
Stage III/IV
The standard therapy consists of radio(chemo)therapy. In cases with infiltration through the wall into adjacent organs (bladder and/or rectum), anterior and/or posterior exenteration with creation of a neobladder and/or a colostomy is a surgical option which has to be decided on in the context of an individual therapy decision.
Planning primary radio(chemo)therapy
If SLN imaging is carried out preoperatively followed by intraoperative SLN biopsy, the findings should be taken into consideration when planning the radiation fields for primary radiotherapy.
Treatment planning for vaginal carcinoma should be based on the flowchart showing the diagnostic workup and treatment of vaginal carcinoma.
Radiotherapy of the Tumor Region
In primary radio(chemo)therapy, the target volume should cover the primary tumor including the safety margin with a dose of > 70 Gy.
There is no evidence which specifies a minimal histological safety margin between the tumor and the edge of the resected specimen nor that resec- tion margins below such a minimal histological safety margin represent an indication for administering radiotherapy to the tumor region postopera- tively.
Postoperative radiotherapy of the tumor region must be recommended after R1 and R2 resection if a second resection is not feasible.
Radio(chemo)therapy
Primary radiotherapy should also be offered in the form of simultaneous radiochemotherapy.

The inguinofemoral and pelvic lymphatic drainage areas on both sides should also be irradiated if surgical lymph node staging was indicated but surgical staging was not carried out.
The patient's comorbidities, own wishes, and clinical situation need to be considered before administering cisplatin ± 5-fluorouracil (5-FU) or mitomycin ± 5-FU.
In primary radiotherapy, achieving sufficiently high tumor doses is decisive for the success of therapy. Brachytherapy, possibly in combination with percutaneous radiotherapy, plays an important role in this context.
As with vulvar cancer, adjuvant radio(chemo)therapy after R1/R2 resection should be administered to the tumor area and the affected groin area if inguinal metastasis is present and bilaterally if there is pelvic metastasis.
Systemic therapy
Neoadjuvant Chemotherapy
The use of neoadjuvant chemotherapy to treat vaginal cancer is currently still an experimental concept.
Radio(chemo)therapy
Using radio(chemo)therapy to treat vaginal cancer is analogous to using radio(chemo)therapy to treat cervical and vulvar cancer.
Treatment of Locoregional Recurrence
The decision to treat local or locoregional recurrence depends on the previous therapy, the extent of recurrence, and the patient's general condition. The decision is made an individual basis; treatment options include surgery, radiotherapy, radio(chemo)therapy and best supportive care.
The decision about the appropriate treatment approach for a patient with local or locoregional recurrence must be made by an interdisciplinary tumor board.

Figure 1 details a flowchart for the diagnostic workup and treatment of vaginal carcinoma with the option of carrying out a sentinel lymph node procedure or not.

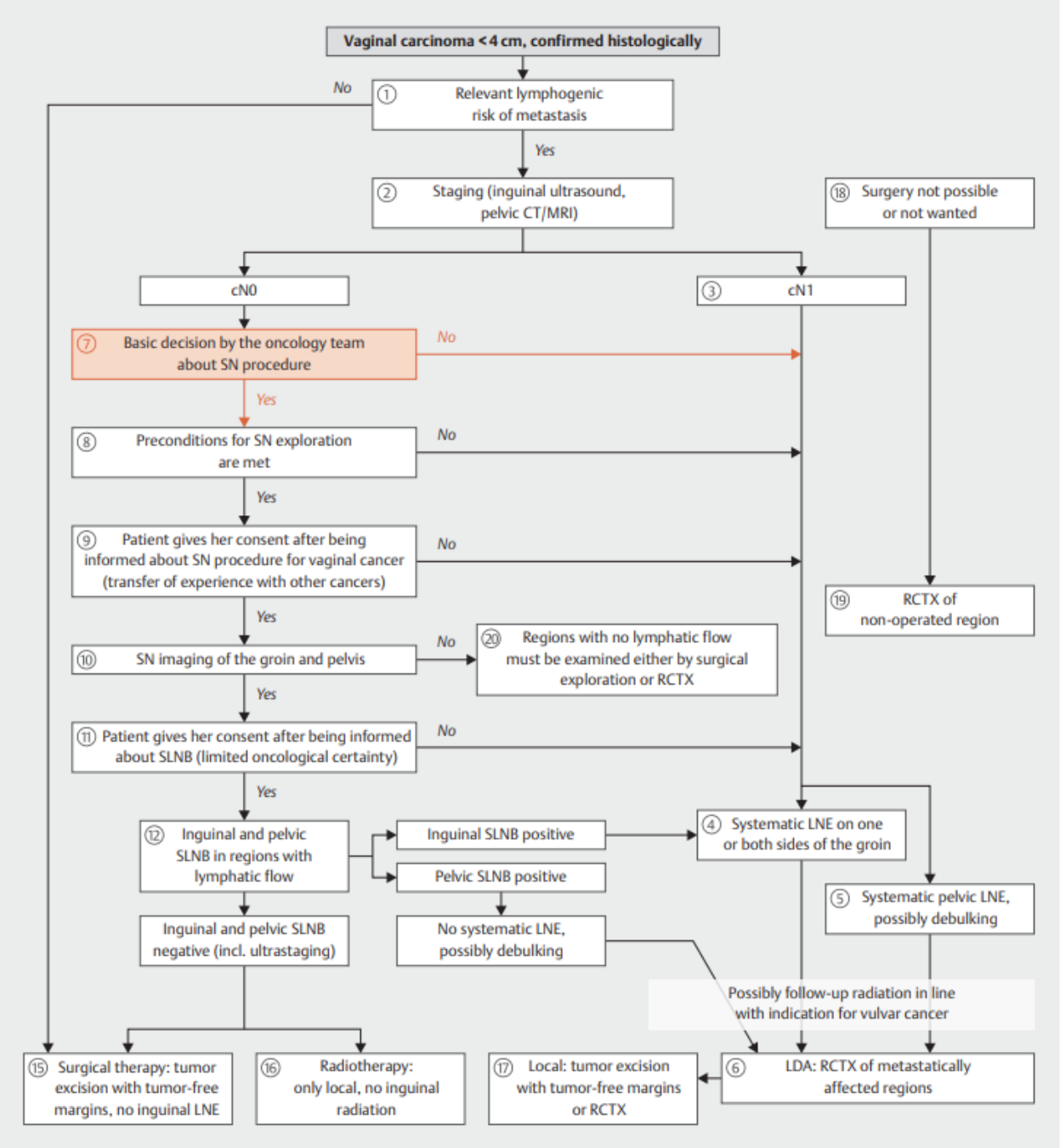

Figure 1. *Diagnostic workup and treatment of vaginal carcinoma (retrieved from the DGGG/DKG 2018 guideline)*

1.6 International Guidelines

1.6.1 Japan Society of Gynecologic Oncology Guidelines for the Treatment of Vulvar Cancer and Vaginal Cancer (2015)

The Japan Society of Gynecologic Oncology (JSGO) published a clinical practice guideline in 2015 for the management of vulvar and vaginal cancer. The guideline provides recommendations for diagnostic and management decisions, and for limiting unnecessary treatments and cost.[5]

This section will focus on the management of vaginal cancer, while section 2.6.1 will detail the recommendations related to vulvar cancer.

Table 6. JSGO 2015 Recommendations for the Management of Vaginal Intraepithelial Neoplasm and Vaginal Cancer

Recommendations	***Strength***
Vaginal intraepithelial neoplasia VAIN	
(1) Conduct periodic follow-up for low-grade squamous intraepithelial lesion (LSIL)	Grade A
(2) Surgical therapies may include local, partial, or total vaginectomy, depending on the case for high-grade squamous intraepithelial lesion (HSIL). Laser vaporization may be considered for more conservative therapy	Grade C1
(3) Loop electrosurgical excision procedure (LEEP) is not recommended due to the risk of injury to the urinary bladder or rectum	Grade D
Radiation Therapy	
(1) Brachytherapy may be performed alone or in combination with external beam irradiation for stage I vaginal cancer with tumor thickness of ≤ 5 mm.	Grade C1
(2) External beam irradiation may be performed in combination with brachytherapy or alone for stage I vaginal cancer with tumor thickness > 5 mm, or for vaginal cancer in stages II to IVA.	Grade C1
(3) Concurrent chemotherapy with a single platinum-based drug or combination of this drug may be considered.	Grade C1
Surgical Treatment	
(1) Surgical therapy may be considered in clinical stages I and II if the tumor is located in the upper third of the vagina	Grade C1

(2) Surgical therapies may include radical hysterectomy, or modified radical hysterectomy and pelvic lymphadenectomy, and vaginectomy with sufficient excision margin	Grade C1
(3) Pelvic exenteration may also be considered in clinical stage IVA disease	Grade C1
Follow-up	
(1) A rough guide to the intervals for periodic follow-up after treatment is as follows: • First and second years: once every 1–3 months • Third to fifth years: once every 6 months • Sixth and subsequent years: once a year	Grade C1
(2) Conduct medical interviews, inspection, palpation, cytology, biopsy, chest X-ray examination, tumor markers and CT.	Grade C1
Malignant Melanoma of the Vulva and Vagina	
(1) Excision of the primary lesion is recommended if distant metastasis is not confirmed.	Grade B
(2) SLN biopsy with cooperation of dermatologists may be useful for determining the disease stage.	Grade C1
(3) Dacarbazine-based chemotherapy may be considered.	Grade C1

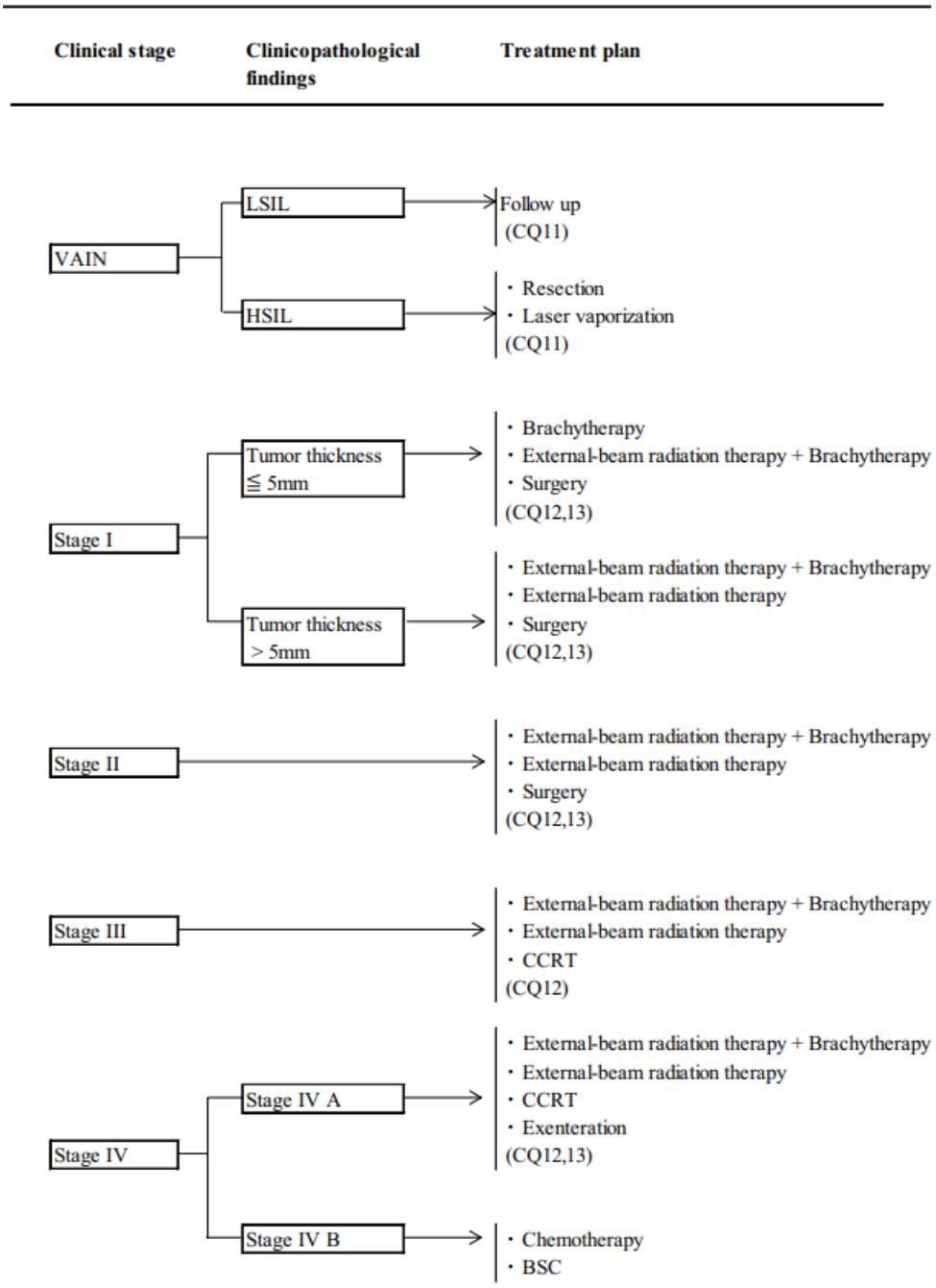

Figure 2. *Primary treatment for vaginal cancer (retrieved from the JSGO 2015 guideline)*

1.7 Systematic Reviews/Meta-Analyses

Author (year)	Primary Objective	Outcomes	Results
Inamaya et al. (2021)[6]	Investigate the efficacy of topical imiquimod in VaIN 2–3.	CR = complete response	Five articles (N = 37 women with VaIN 2–3 who underwent imiquimod treatment) The discontinuation of the treatment was required in only one patient of the reported cases. <u>Regardless of a history of hysterectomy:</u> • The pooled CR rate: 0.76 (95% CI, 0.59–0.87) • The pooled response rate (RR) of imiquimod: 0.89 (95% CI, 0.71–0.97) <u>In the subgroup analysis:</u> CR rate • patients with hysterectomy: 0.98 (95% CI, 0.11–1.0) • without hysterectomy: 0.60 (95% CI, 0.30–0.84) • Rate ratio was 0.83 (95% CI, 0.48–1.19). RR • The pooled response rates with and without a history of hysterectomy were not estimated. • Rate ratio was 0.83 (95% CI, 0.54–1.09).

1.8 Secondary and Tertiary Resources

The international guidelines detailed in previous sections being most updated (as recently as December 2023), a detailed search of secondary and tertiary resources for additional guidelines, such as Google Scholar, the Ovid Health Technology Assessment Database, the National Institute for Health and Care Research Journals Library, and UpToDate did not yield any additional data that hasn't already been described.

Section 2.0 Summary of Reviewed Clinical Guidelines & Evidence (Vulvar Cancer)

2.1 KSA Guidelines

There are no guidelines published by Saudi medical bodies on the management of vulvar cancers.

2.2 World Health Organization (WHO) Classification (2021)

Histopathological diagnosis of vulvar cancer is important in the selection process of proper treatment regimen, especially in advanced disease. The World Health Organization (WHO) published its fifth edition of the Classification of Female Genital Tumors in 2021 including benign and malignant tumors. The different histopathology of malignant vaginal tumors is detailed in table 7.[2]

Table 7. World Health Organization (WHO) Classification of the Malignant Tumors of the Vulva (Fifth Edition)

WHO Classification of malignant Vulva Tumors, Fifth Edition	
Epithelial Tumors	Squamous intraepithelial lesions HPV-associate
	Vulvar intraepithelial neoplasia, HPV-independent
	Squamous cell carcinoma, HPV-associated
	Squamous cell carcinoma, HPV-independent
	Squamous cell carcinoma NOS
	Basal cell carcinoma
	Phyllodes tumor (biphasic neoplasia)
	Adenocarcinoma of mammary gland type
	Bartholin gland carcinomas
	Paget disease
	Carcinomas of sweat gland origin
	Adenocarcinoma of intestinal type
Germ cell tumors	Germ cell tumor NOS
	Yolk sac tumor NOS

2.3 International Federation of Gynecology and Obstetrics (FIGO) Staging System (2021)

The most recent FIGO classification system published in 2021 is detailed in table 5 in comparison to other staging systems such as TNM and AJCC systems.[7]

Table 8. Staging of Vulvar Cancer Using FIGO, TNM, and AJCC Systems

AJCC stage	Stage grouping	FIGO stage	Stage description*
IA	T1a N0 M0	IA	The cancer is in the vulva or the perineum (the space between the rectum and the vagina) or both and has grown no more than 1 mm into underlying tissue (stroma) and is 2 cm or smaller (about 0.8 inches) (T1a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IB	T1b N0 M0	IB	The cancer is in the vulva or the perineum or both and is either more than 2 cm (0.8 inches) or it has grown more than 1 mm (0.04 inches) into underlying tissue (stroma) (T1b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II	T2 N0 M0	II	The cancer can be any size and is growing into the anus or the lower third of the vagina or urethra (the tube that drains urine from the bladder) (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIA	T1 or T2 N1 M0	IIIA	Cancer is in the vulva or perineum or both (T1) and may be growing into the anus, lower vagina, or lower urethra (T2). It has either spread to a single nearby lymph node with the area of cancer spread 5 mm or more OR it has spread to 1 or 2 nearby lymph nodes with both areas of cancer spread less than 5 mm (N1). It has not spread to distant sites (M0).

IIIB	T1 or T2 N2a or N2b M0	IIIB	Cancer is in the vulva or perineum or both (T1) and may be growing into the anus, lower vagina, or lower urethra (T2). The cancer has spread either to 3 or more nearby lymph nodes, with all areas of cancer spread less than 5 mm (N2a); OR the cancer has spread to 2 or more lymph nodes with each area of spread 5 mm or greater (N2b). It has not spread to distant sites (M0).
IIIC	T1 or T2 N2c M0	IIIC	Cancer is in the vulva or perineum or both (T1) and may be growing into the anus, lower vagina, or lower urethra (T2). The cancer has spread to nearby lymph nodes and has started growing through the outer covering of at least one of the lymph nodes (called extracapsular spread; N2c). It has not spread to distant sites (M0).
IVA	T1 or T2 N3 M0	IVA	Cancer is in the vulva or perineum or both (T1) and may be growing into the anus, lower vagina, or lower urethra (T2). The cancer has spread to nearby lymph nodes and has become stuck (fixed) to the underlying tissue or has caused an ulcer(s) to form on the lymph node(s)(ulceration) (N3). It has not spread to distant sites (M0).
	OR		
	T3 Any N M0	IVA	The cancer has spread beyond nearby tissues to the bladder, rectum, pelvic bone, or upper part of the urethra or vagina (T3). It might or might not have spread to nearby lymph nodes (any N). It has not spread to distant sites (M0).
IVB	Any T Any N M1	IVB	The cancer has spread to distant lymph nodes (pelvic) or organs such as lung or bone (M1). The cancer can be any size and might or might not have spread to nearby organs (Any T).

			It might or might not have spread to nearby lymph nodes (Any N).

* The following additional categories are not listed on the table above:

- TX: Main tumor cannot be assessed due to lack of information.
- T0: No evidence of a primary tumor.
- NX: Regional lymph nodes cannot be assessed due to lack of information.

2.4 Northern American Guidelines

2.4.1 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines – Vulvar Cancer (Version 3.2024)

The National Comprehensive Cancer Network (NCCN) published its updated recommendations for the management of Vulvar cancers in December 2023, including recommendations for the diagnosis, staging, and principles of treatment of vulvar cancers.[8]

PRINCIPLES OF RADIATION THERAPY (RT)

General Principles

- RT is often used in the treatment of patients with vulvar cancer as adjuvant therapy following initial surgery, as part of primary therapy in locally advanced disease, or for secondary therapy/palliation in recurrent/metastatic disease.
- Radiation technique and doses are important to maximize tumor control while limiting adjacent normal tissue toxicity.
- Tumor-directed RT refers to RT directed at sites of known or suspected tumor involvement. In general, tumor-directed EBRT is directed to the vulva and/or inguinofemoral, external, and internal iliac nodal regions. Brachytherapy can sometimes be used as a boost to anatomically amenable primary tumors. Careful attention should be taken to ensure adequate tumor coverage by combining clinical examination, imaging findings, and appropriate nodal volumes at risk to define the target volume. For example, invasion into the anus above the pectinate line would necessitate coverage of the perirectal nodes.
- Ensure coverage of gross tumor burden with margin. In highly selected cases where only a superficial vulvar target is to be treated, an enface electron beam may be used.

- Utilization of imaging studies are an important part of the treatment planning process. The use of CT-based treatment planning and conformal blocking is considered the standard of care for EBRT.
- Acute effects during RT (eg, diarrhea, bladder irritation, fatigue, mucocutaneous reaction) are expected to some degree in most patients, and can be further accentuated by concurrent chemotherapy. These toxicities should be aggressively managed (eg, local skin care, symptomatic medications), and treatment breaks should be avoided or minimized. Many patients may develop an overgrowth of Candida albicans; treatment with oral and local antifungal agents will markedly reduce skin reaction. If a bacterial infection develops, prompt recognition and appropriate treatment is essential. These acute effects generally resolve several weeks after completion of radiation.
- Postoperative adjuvant treatment should be initiated as soon as adequate healing is achieved, preferably within 6–8 weeks.

Dosing Prescription Regimen

- The target tissues should be treated once daily, 5 days per week. Breaks from treatment should be minimized. Adequate dosing is crucial and can be accomplished with either 3D conformal approaches or intensity-modulated radiation therapy (IMRT) as long as care is given to assure adequate dosing and coverage of tissues at risk for tumor involvement.
- Doses range from 45–50.4 Gy in 25–28 fractions (1.8 Gy fractions) for adjuvant therapy to 59.4–64.8 Gy in 33–36 total fractions (1.8 Gy fractions) for unresectable disease. In select cases, bulky/persistent primary disease or large nodes that are unresectable may be boosted to 70 Gy.

Suggested dosing to areas of risk:

- Gross primary vulva disease = 60–70 Gy
- Primary surgical bed (postoperative, negative margins) = 45–50 Gy
- Primary surgical bed (postoperative close or positive margins) = 54–60 Gy
- Clinically and/or radiographically uninvolved inguinofemoral LNs = 45–50 Gy
- Inguinofemoral LNs (positive, no extracapsular extension [ECE] or gross residual disease) = 50–55 Gy
- Inguinofemoral LNs (ECE) = 54–64 Gy
- LNs (gross residual or unresectable disease) = 60–70 Gy

PRIMARY TREATMENT

Early-stage disease

For stage I tumors with less than or equal to 1 mm depth of invasion, the panel recommends simple partial vulvectomy; inguinofemoral lymph node (IFLN) evaluation is not required due to the low risk of LN metastasis in these patients.

In treatment for patients with stage IB (>1-mm invasion) or select stage II tumors, primary treatment is dictated by tumor location. Patients with lateralized lesions located greater than or equal to 2 cm from the vulvar midline should undergo radical partial vulvectomy accompanied by ipsilateral IFLN evaluation.

Clinicians should strive for primary tumor resection with oncologically appropriate margins of 1 to 2 cm if feasible.

Locally advanced disease

Patients with locally advanced tumors (unresectable without removing proximal urethra/bladder/anus) should undergo radiologic imaging to examine potential nodal involvement. All patients with locally advanced disease should receive EBRT with concurrent chemotherapy.

Agents recommended for chemoradiation include **cisplatin** (preferred) and **carboplatin** if the patient is intolerant to cisplatin. The panel also lists **cisplatin/fluorouracil** under “other recommended regimens” (table 9).

Metastasis beyond the pelvis

Primary treatment options for extra-pelvic metastatic disease include EBRT for control of locoregional disease and symptom palliation, and/or systemic therapy. Best supportive care is also an alternative in this setting.

Data on systemic treatments for vulvar cancer with distant metastasis is extremely limited.

RECURRENT/METASTATIC DISEASE

No standard systemic therapy regimens exist for treating advanced or recurrent/metastatic disease. Several reports provide anecdotal evidence for various regimens, at times extrapolating from regimens with known activity in advanced cervical and anal cancers and other SCCs.

Preferred, first-line regimens recommended by the panel for treating advanced, recurrent/metastatic disease include cisplatin/paclitaxel, carboplatin/paclitaxel, and cisplatin/paclitaxel/bevacizumab. Carboplatin/paclitaxel/bevacizumab is included as a category 2B regimen under the preferred, first-line options. Other recommended regimens include single-agents cisplatin and carboplatin.

Cemiplimab as a second-line or subsequent therapy option is included under "other recommended regimens." The recommendation of cemiplimab has been extrapolated from its efficacy shown in cervical cancer and in advanced cutaneous SCC.

Monoclonal antibodies targeting the PD-1 pathway may also be effective in tumors that have high TMB (TMB-H) or are deficient in MMR (dMMR)/have high levels of MSI (MSI-H).

Larotrectinib and entrectinib are recommended as second-line or subsequent, useful in certain circumstances options for NTRK gene fusion-positive tumors and recently changed the category of evidence from category 2B to category 2A.

SYSTEMIC THERAPY

Table 9. Systemic Therapy for Vulvar Cancer (Adapted from the NCCN Guidelines Version 3.2024)

Chemoradiation	**Advanced or Recurrent/Metastatic Disease**	
	First-line Therapy	**Second or subsequent line of therapy**
Preferred Regimens • Cisplatin • Carboplatin (if patient is cisplatin intolerant) **Other Recommended Regimens** • Cisplatin/fluorouracil • If cisplatin or carboplatin are unavailable: Capecitabine/ mitomycin, Gemcitabine, or Paclitaxel can be used.	**Preferred Regimens** • Cisplatin/paclitaxel/ bevacizumab • Cisplatin/paclitaxel • Carboplatin/paclitaxel • Carboplatin/paclitaxel/ bevacizumab (category 2B) **Other Recommended Regimens** • Cisplatin • Carboplatin	**Other Recommended Regimens:** • Paclitaxel • Cemiplimab • Erlotinib (category 2B) • Cisplatin/gemcitabine (category 2B) **Useful in Certain Circumstances (Biomarker directed therapy)** • Pembrolizumab: (for TMB-high [TMB-H], PD-L1–positive, or MSI-high [MSI-H]/MMR deficient [dMMR] tumors) • Nivolumab: HPV-related tumors

		• Larotrectinib or Entrectinib*: NTRK* gene fusion-positive tumors

2.5 European Guidelines

2.5.1 British Gynecological Cancer Society (BGCS) Vulval Cancer Guidelines (2023)

In 2023, the BGCS published their updated guidelines for the diagnosis and management of adult patients with vulva carcinoma. Their recommendations are detailed in the tables below.[9]

Treatment of primary disease

- **Surgery**

Table 10. Recommendations for Surgical Treatment of Primary Site of Vulval Squamous Cell Carcinoma (VSCC)

Recommendation	Grade of recommendation
The excised skin specimen should be secured in a way that allows accurate orientation by the pathologist (e.g., marker suture and pinned to cork board)	Grade D
Excision should be planned with macroscopic clearance of tumour with the goal of achieving clear margins (R0) on pathological assessment.	Grade C
Optimal radicality (margins) of the excision is unclear. It is acceptable (and often desirable) to limit radicality to preserve structure and function (e.g., preservation of clitoris, anus and urethra)	Grade D
Excision margins should be extended superficially to include adjacent differentiated vulvar intraepithelial neoplasia (VIN) and/or lichen sclerosus to reduce risk of local recurrence	Grade D
Discrete multi-focal disease may be managed with multiple wide local excision. Vulvectomy may be required for those with multifocal invasion arising on a background of vulvar dermatosis	Grade D

If VSCC extends to the pathological excision margins, reexcision is the treatment of choice.	Grade D
Some patients require access to reconstructive techniques at the time of vulval surgery.	Grade D
Joint pre-operative planning with gynaecological oncology and reconstructive surgeons, including an examination under anaesthetic should be considered for those with large lesions.	Grade D

Table 11. Recommendations for Treatment of Rare Vulval Malignancies

Recommendation	Grade of recommendation
Bartholin's Carcinoma	
Patients with Bartholin's gland carcinoma may need multi-modal treatment and full body imaging with CT of chest, abdomen, and pelvis is recommended prior to surgery, as disease is more likely to present at an advanced stage.	Grade D
Adenoid cystic carcinoma of the vulva	
Adequate surgical excision is key to survival	Grade D
In patients with involved resection margins, postoperative radiotherapy can reduce the risk of recurrence	Grade D
Distant metastases appear to be relativley common and data to support adjuvant systemic therapies are very limited	Grade D
Vulval Paget's Disease	
Investigations to exclude a co-existing malignancy, e.g., of the breast, gynaecological, urological and colorectal tracts, are only required if there are symptoms concerning for other malignancies.	Grade D
Surgery should aim to remove invasive visible disease with macroscopically clear margins. Microscopic involvement of the margins is common and reexcision may not be of benefit.	Grade C
Imiquimod may be of benefit and reduce the need for surgery, if invasive disease is excluded.	Grade C
Radiotherapy or photodynamic therapy have been used in VPD, but the certainty of this evidence is very low and should be considered with caution.	Grade C
Vulval Malignant Melanoma	

Patients should be treated with close collaboration of the gynae-oncology and melanoma MDTs.	Grade D
Surgery should aim to achieve an R0 resection (no microscopic disease within < 1 mm of margins) with the least radicality.	Grade C
Sentinel node dissection may help to guide adjuvant immunotherapy and should be considered after discussion with the Melanoma MDT.	Grade C
Metastatic regional nodal disease may be considered for removal as treatment may improve quality of life, but without evidence of survival benefit.	Grade D

- **Radiotherapy and Chemotherapy**

Table 12. Recommendations for Neoadjuvant/Adjuvant Treatment of Advanced Disease at Presentation

Recommendation	Grade of recommendation
Adjuvant (chemo)radiotherapy should ideally take place within 6 weeks of surgery.	(Grade B)
Postoperative radiotherapy is to be considered when:	
Positive excision margins of the primary tumour, and further surgical excision not possible,	Grade D
Pathological margins < 2 mm, where repeat excision is not recommended, even though no consensus for the threshold of pathological margin distance exists. Each case should be individualized and discussed with a multidisciplinary team, taking into account patient factors (co-morbidities, previous treatment), location of close margins, and need for groin/pelvic radiotherapy	Grade D
Following inguinofemoral lymphadenectomy, presence of > 1 metastatic lymph node and/or the presence of extracapsular lymph node involvement	Grade B
Following SLNB: micrometastasis present Grade B Definitive chemoradiation, generally weekly cisplatin with IMRT, is the treatment of choice in patients with locally unresectable disease.	Grade B

Consideration needs to be given to enrolling patients into clinical trials to explore primary chemoradiation (no surgery) alone for patients with earlier stages of locally advanced vulval cancer to avoid exenterative surgery	Grade D

- **Treatment of recurrent disease**

Table 13. Recommendations for Treatment of Recurrent Disease

Recommendation	Grade of recommendation
Surgical re-excision of local and/ or groin relapse should be considered in patients with relapsed disease amenable to surgery, in analogy with the primary presentation of the disease.	Grade D
Imaging by CT (or PET-CT when appropriate) of the thorax/abdomen/pelvis is recommended prior to any treatment to tailor adequate approaches.	Grade D
SLNB can be considered for recurrent disease, if the new focus of invasion meets criteria for primary SLNB. Data regarding the safety and efficacy of this approach is very limited	Grade D
In patients not amenable to surgery, palliative chemotherapy, or radiotherapy, or combination of both should be considered, depending on the previous treatment modalities of the patient, her preferences and her fitness status.	Grade C
Systemic treatment may be considered in patients with distant metastases, but published data are insufficient to recommend a preferred protocol.	Grade D

2.5.2 European Society of Gynecological Oncology (ESGO) Guidelines for the Management of Patients with Vulvar Cancer (2023)

ESGO first published clinical guidelines for the management of patients with vulvar cancer in 2017. The updated 2023 guidelines cover comprehensively diagnosis and referral, staging, pathology, pre-operative investigations, surgical management (local treatment, groin treatment, sentinel lymph node procedure, reconstructive surgery), (chemo)radiotherapy, systemic treatment, treatment of recurrent disease (vulvar, inguinal, pelvic, and distant recurrences), and follow-up. Management algorithms are also defined.[10]

General recommendations

- Planning of staging investigations and treatment should be made on a multidisciplinary basis (generally at a tumor board meeting) and based on the comprehensive and precise knowl- edge of prognostic and predictive factors for oncological outcome, side effects, and quality of life [V, B].
- Patients should be carefully counseled about the suggested diagnostic and treatment plan and potential alternatives, including risks and benefits of all options [V, B].
- Treatment should be undertaken by a dedicated team of specialists in the diagnosis and management of vulvar cancers [V,B].
- Enrolment of patients with vulvar cancer in clinical trials is encouraged [V, B].
- Centralization of care in specialized centers and referral network is encouraged [V, B].
- Supportive care and psychological support should be offered to all patients with vulvar cancer throughout their pathway [V, B].

Surgical management

Local treatment

- Radical local excision is recommended with the aim to obtain histological tumor-free margins [III, B].
- Extending primary excision in a superficial fashion to include adjacent differentiated vulvar intraepithelial neoplasia is highly recommended [IV, B].
- In multifocal invasive disease, radical excision of each lesion as a separate entity may be considered. Vulvectomy may be required in cases with multifocal invasion arising on a back- ground of extensive vulvar dermatosis [IV, C].
- The optimal radicality of the excision remains to be defined. It is acceptable and often desirable to limit radicality in order to preserve structure and function (eg, preservation of midline structures such as clitoris, anus, and urethra) [IV, C].
- When invasive disease extends to the excision margins of the primary tumor, re-excision is the treatment of choice if feasible [III, A].
- Advanced-stage patients should be evaluated in a multidisci- plinary setting to determine the optimal choice and order of treatment modalities [V, B].

Groin treatment

- Groin treatment should be performed for tumors >T1a (method of measurement of depth of invasion according to the 8th version of the TNM classification) [IV, B]. Surgical bilateral eval- uation should be performed for non-lateralized tumors (medial border <1 cm from midline) [III, B].
- For unifocal tumors <4 cm without suspicious inguinofemoral lymph nodes on clinical examination and imaging the SLN procedure is recommended [III, B].
- For tumors ≥4 cm and/or in case of multifocal invasive disease, inguinofemoral lymphadenectomy by separate incisions is mandatory. In lateralized tumors at least ipsilateral inguinofem- oral lymphadenectomy should be performed [III, A]. Contralat- eral inguinofemoral lymphadenectomy may be performed when ipsilateral lymphadenectomy has demonstrated meta- static disease [IV, C].
- When lymphadenectomy is indicated, superficial and deep femoral nodes should be removed [IV, B].
- Preservation of the saphenous vein is recommended [IV, C].
- The optimal management of the groin for enlarged, proven metastatic nodes (inguinofemoral lymphadenectomy or isolated removal/debulking only) remains to be defined and treatment needs to be individualized [IV, C].

Reconstructive surgery

- Availability of reconstructive surgical skills as part of the multidisciplinary team is required in early as well as advanced-stage disease. The type of reconstruction is based on patient/tumor characteristics and experience of the surgical team [IV, B].

SLN procedure

- The SLN procedure is recommended in patients with unifocal cancers of <4 cm, >T1a, without suspicious inguinofemoral nodes [II, B].
- There are insufficient data to confirm the efficacy and safety of the SLN procedure in the case of recurrent disease [IV, C].
- Use of radioactive tracer (Tc99/nanocolloid) is mandatory [II, A].
- Combination detection techniques with isotope and either blue dye or ICG are recommended [II, B].
- When used as part of combination technique, ICG appears more effective than blue dye in the detection of the SLN although the imaging protocol is still to be defined [II, B].

- Lymphoscintigraphy is advised to enable the pre-operative identification, location, and number of SLN [III, C].
- Intra-operative frozen section is optional, balancing the impor- tance of accurate measurement of size of lymph node metas- tasis and increased risk of missing micrometastases on final pathology against the impact of a second surgical procedure [IV, C].
- When a SLN is not found (method failure), inguinofemoral lymphadenectomy should be performed [I, A].
- For tumors involving the midline, bilateral SLN detection is mandatory. When only unilateral SLN detection is achieved, contralateral inguinofemoral lymphadenectomy should be performed [I, A].
- When tumor cells, both metastases and isolated tumor cells, are identified in the SLN, additional treatment to the involved inguinofemoral area is indicated [I, A].
- When macrometastatic (>2 mm) disease is identified in the SLN, inguinofemoral lymphadenectomy of the affected site should be performed [I, A].
- Inguinofemoral lymphadenectomy can safely be omitted in favor of radiotherapy when micrometastatic disease (≤2 mm) or isolated tumor cells are identified in the metastatic SLN [III, B].
- For patients undergoing a bilateral SLN procedure, who are found to have unilateral metastasis, the incidence of contralateral metastasis is low and further treatment may be limited to the affected groin [III, B].

(Chemo)radiotherapy

Adjuvant radiotherapy/chemoradiotherapy

- Post-operative radiotherapy to the vulva:
    - When invasive disease extends to the pathological excision margins of the primary tumor, and further surgical excision is not feasible, post-operative radiotherapy to the vulva is indicated [IV, B].
    - In case of close but clear pathological margins with exten- sive LVSI, perineural involvement or lymph node involvement, post-operative vulvar radiotherapy may be considered on an individualized basis to reduce the frequency of local recurrences [IV, C].
- Post-operative radiotherapy to the inguinofemoral region:

- SLN metastasis ≤2 mm and isolated tumor cells can be treated with post-operative radiotherapy as a safe alternative to inguinofemoral lymphadenectomy with fewer long-term side effects [III, B].
- After inguinofemoral lymphadenectomy:
  - Radiotherapy is recommended for cases with more than one metastatic lymph node and/or extracapsular spread [II, A].
  - Concurrent radiosensitizing chemotherapy should be considered [IV, B].

- Target volume and dose for adjuvant (chemo)radiotherapy should be defined on individual basis according to tumor and patient characteristics [III, A].
- Radiotherapy should be started as soon as possible (total time from surgery to completion of radiotherapy preferably less than 104 days).Treatment breaks should be avoided [IV, B].
- Radiotherapy should be performed with intensity-modulated radiotherapy techniques [III, B].

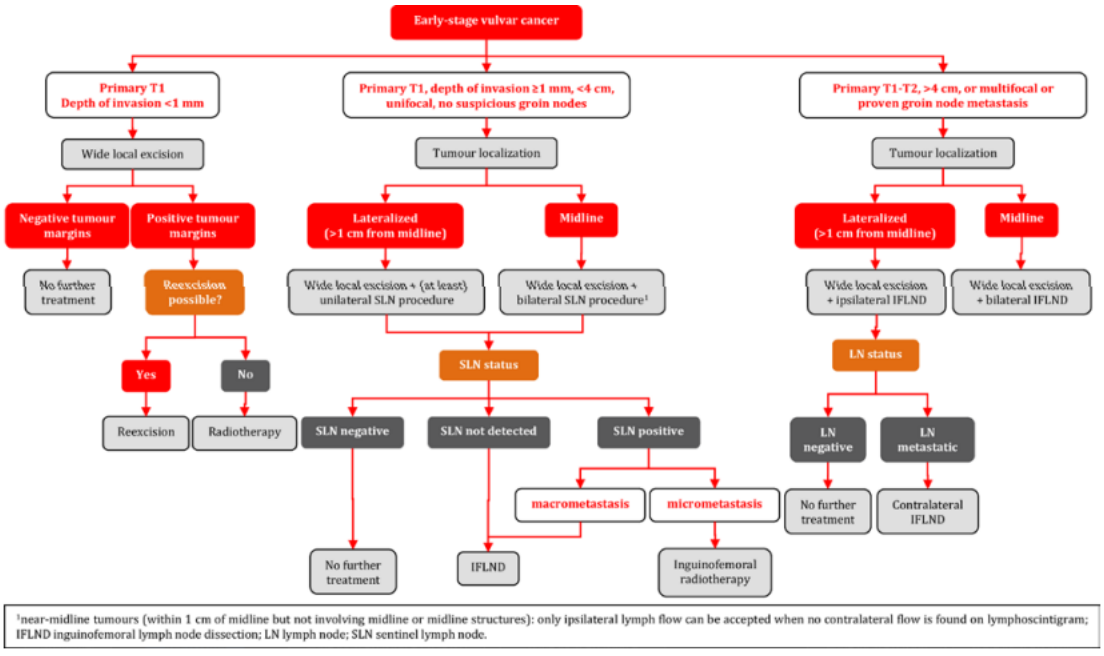

Figure 3. *Primary treatment of early-stage vulvar cancer (retrieved from the ESGO 2023 guidelines)*

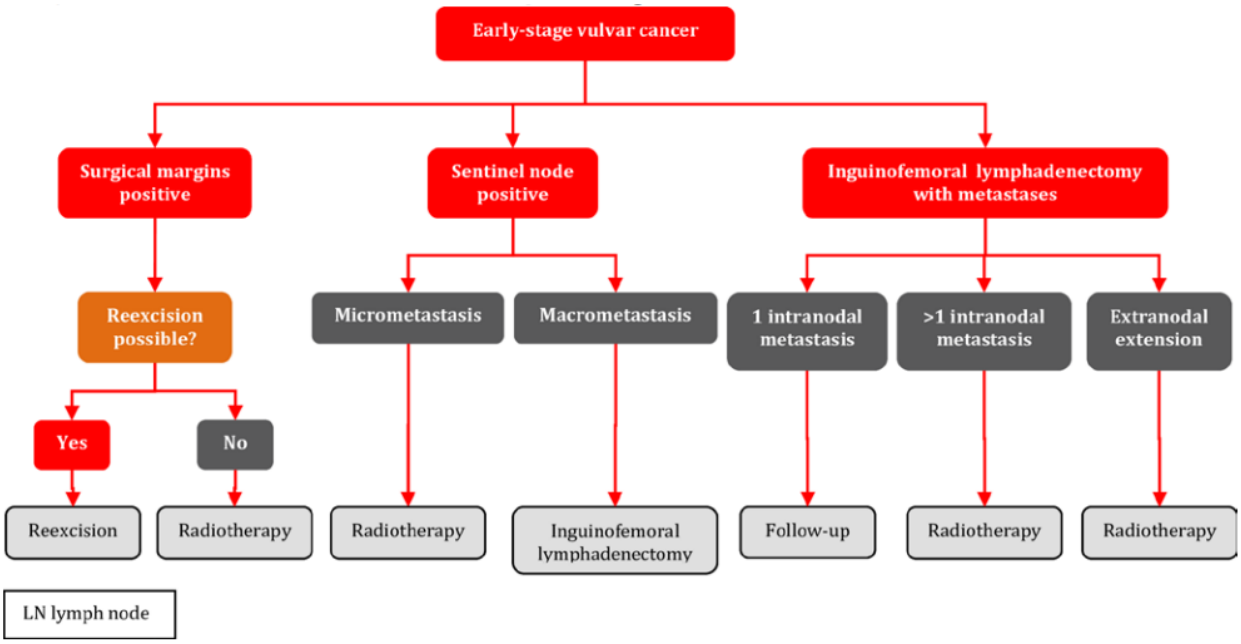

Figure 4. *Adjuvant treatment of early-stage vulvar cancer (retrieved from the ESGO 2023 guidelines)*

Primary chemoradiotherapy

- Primary chemoradiotherapy should be performed in a specialized gynecological radiotherapy center [V, B].
- Primary chemoradiotherapy is the treatment of choice in patients with unresectable disease and should be considered for tumors which would otherwise need exenterative surgery with stoma formation [III, B].
- Appropriate tumor and lymph node imaging (MRI and/or ^{18}F-FDG-PET-CT) should be performed prior to commencing chemoradiotherapy [IV, A].
- Assessment of response should be performed at 12 weeks following completion of treatment (clinically, imaging and/ or biopsy if residual tumor is suspected). In case of residual disease surgery should be considered [III, B].
- Treatment breaks should be avoided, as a prolonged treatment time of >50 days is associated with higher recurrence rates for primary therapy [IV, B].

Systemic treatment

Neoadjuvant chemotherapy for locally advanced disease

- In selected patients, not eligible/fit for upfront surgery or chemoradiotherapy, **neoadjuvant platinum-based combination chemotherapy** may be considered after a multidisciplinary assessment [IV, C].

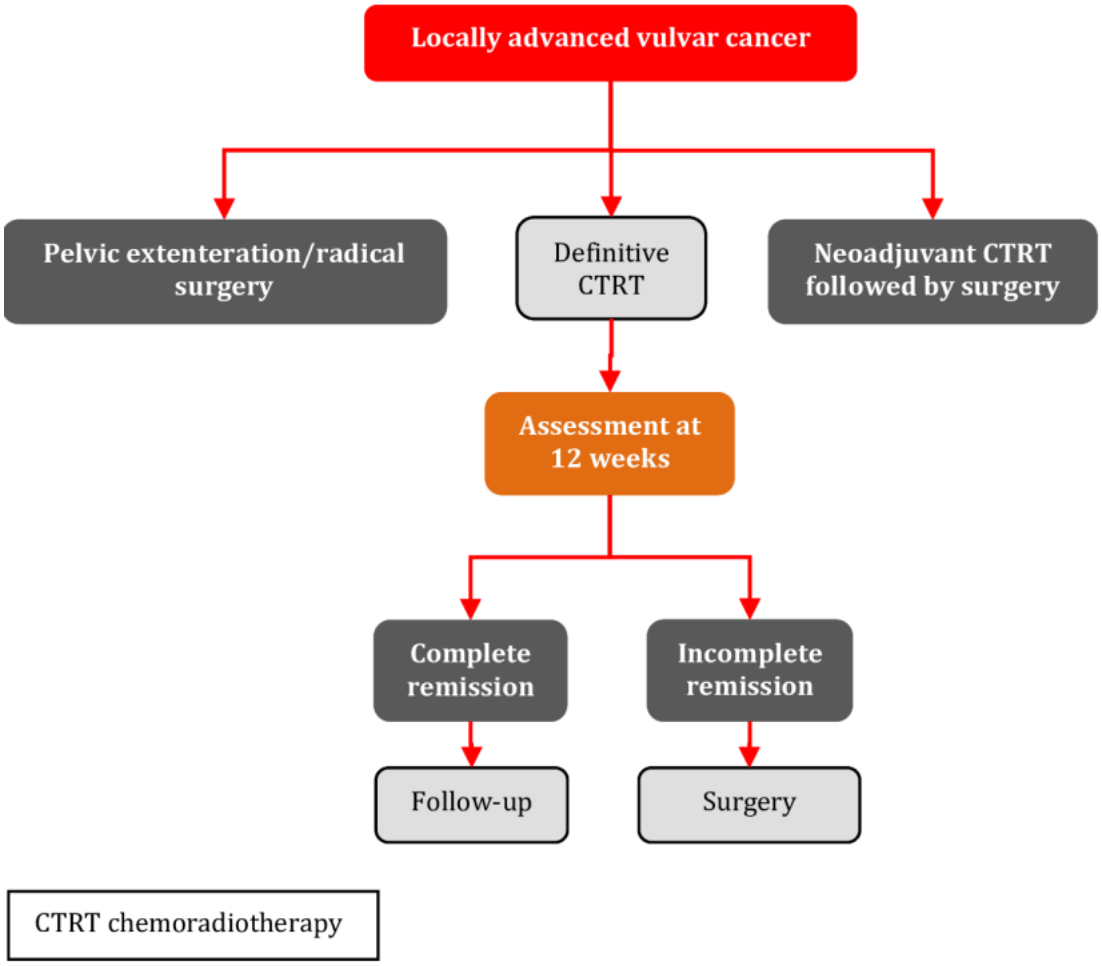

Figure 5. *Treatment of locally advanced vulvar cancer (retrieved from the ESGO 2023 guidelines)*

Systemic treatment for metastatic or recurrent unresectable disease

- **Platinum-based combination chemotherapy** should be considered as first-line treatment for metastatic or recurrent unresectable disease [III, B].
- Although the best combination partner for platinum is unclear, **cisplatin or carboplatin and-paclitaxel** could be considered the preferred regimen [IV, C].
- Based on cervical cancer data, the addition of pembrolizumab in cases with PD-L1 expression with CPS≥1 and/or bevaci- zumab to platinum-based chemotherapy may be considered for selected patients in first line, although these drugs do not have specific approval for vulvar cancer [IV, C].
- After progressing to platinum-based first-line chemotherapy, there are no standard treatments. Immune checkpoint inhibi- tors can be considered as monotherapy [III, B]. Chemotherapy or epidermal growth factor receptor

targeting inhibitors may be considered as possible alternatives, taking into account that there is no specific approval for any drug [III, C].

Treatment of recurrent disease

General recommendations

- All patients with a recurrence after primary vulvar cancer should be discussed by a multidisciplinary team and treated at a specialized center [V, B].
- Before treatment of recurrent disease, vulvar examination, with biopsies from all suspicious areas, is recommended. Evaluation with ultrasound, MRI, and/or CT (or ^{18}F-FDG-PET) of the thorax/abdomen/pelvis should be performed. When suspecting nodal or distant recurrence, a biopsy is recommended if feasible [V, B].
- In case of incurable recurrent disease, early palliative care referral should be offered [V, B].

Treatment of local recurrence

- For treatment of vulvar recurrence, radical local excision is recommended [IV, B].
- Since many vulvar recurrences could be classified as new primary disease, arising from underlying pre-malignant skin conditions, surgical groin re-staging should be considered in clinically negative inguinofemoral lymph nodes [V, B].
- In case of resection of the tumor with involved margins, re-excision (if feasible) or post-operative radiotherapy is recommended [IV, B].
- In locally advanced disease, definitive (chemo)radiotherapy is recommended in radiotherapy-naïve patients. In selected cases, pelvic exenteration can be considered [IV, B].

Treatment of inguinofemoral and pelvic lymph node recurrence

- Preferred treatment of an inguinofemoral nodal recurrence is inguinofemoral lymphadenectomy or debulking of suspicious inguinofemoral lymph nodes, followed by (chemo)radiotherapy in radiotherapy-naïve patients [IV, B].
- In case of pelvic lymph node recurrence with or without inguinofemoral lymph node recurrence, (chemo)radiotherapy is recommended [V, B]. Debulking of enlarged pelvic lymph nodes may be considered prior to commencing the treatment [V, C].
- In previously irradiated women, complete resection and/or stereotactic radiotherapy can be considered for oligometastatic inguinofemoral/pelvic

disease [V, B]. Systemic therapy may be an option when local therapies are not feasible [V, C].

- Based on evidence from other squamous cell cancers such as cervical and anal cancer, the addition of radio-sensitizing chemotherapy to radiotherapy can be considered [V, B].

Treatment of distant recurrence

- For treatment of distant metastases, systemic therapy may be considered [V, C].
- Stereotactic radiotherapy or surgery can be considered for oligometastatic disease [V, C].

2.5.3 German Society of Gynaecology and Obstetrics (DGGG)/German Cancer Society (DKG) Guideline on the Diagnosis, Therapy and Follow-Up of Vulvar Cancer and its Precursors (2015)

In 2015, the Gynecological Oncology Working Group of the German Cancer Society (DKG) and the German Society for Gynecology and Obstetrics (DGGG) published their guidelines for the diagnosis, management, and follow up of vulvar cancer and its precursors.[11]

Table 14. Summary of the DGGG/DKG 2015 Recommendations for Vulvar Cancer

Consensus-based statements **Expert consensus Strength of consensus +++ (expert consensus).**
Treatment of VIN and Paget's Disease
There is no reliable data on the adequate margin of healthy tissue when resecting HSIL, including multifocal HSIL
HSIL and dVIN lesions must either be resected by histologically complete excision or removed by laser evaporation until tissue margins are healthy. Excision should be used to treat dVIN lesions while laser evaporation is the treatment of choice for HPV-associated HSIL
• The primary treatment for extramammary Paget's disease consists of surgical excision of the lesion. Surgical excision should include wide excision margins extending well into healthy tissue, both in the horizontal and the vertical planes. • Depending on the location and size of the lesion, plasty may be considered to cover the defect, with careful attention paid to any comorbidities
Surgical Treatment of Invasive Carcinoma

Standard treatment for primary vulvar cancer

The surgical specimen must be excised in such way that an R0 resection status is achieved on all sides. The minimum tumor-free tissue margin should be at least 3 mm on histological examination.

If vulvectomy is indicated and there is no increased risk of skin bridge metastasis, the approach must be the triple incision technique, i.e. vulvectomy and lymphadenectomy are performed using different incisions.

After local excision or vulvectomy, primary reconstruction plasty (pudendal flaps, Limberg flaps or others) should be considered; careful attention is necessary to ensure tension-free coverage of the wound, good functionality**,** and appearance.

Recommendations for treatment according to stage

Stage T1

Unifocal stage T1a or T1b vulvar cancer must be treated by local resection into healthy tissue (radical local excision).

Stage T2

Depending on the clinical status, local radical excision or vulvec- tomy combined with resection of any involved structures of the urethra, vagina, or anus is indicated for stage T2 disease. Primary radio(chemo)therapy is an alternative if surgery would otherwise put continence at risk.

Stage T3 (equivalent to FIGO stage IVA)

- Primary radiochemotherapy should be done if stage T3 (= FIGO stage IVA) lesions are present to preserve the function of adjacent organs (micturition and/or defecation) where possible. Alternatively, patients should receive neoadjuvant radio(chemo)therapy to reduce the extent of subsequent surgery.
- If there is infiltration into adjacent organs and/or fistula formation, primary exenteration should be performed if there is no distant metastasis. Primary exenteration should also be done as a palliative therapy when infiltration into adjacent organs and/or fistula formation has occurred.

Lymphatic Vessel Surgery

- Systematic inguinofemoral lymphadenectomy must always include removal of both the superficial (inguinal) and the deep (femoral) lymph nodes below the cribriform fascia.
- Staging of the inguinofemoral lymph nodes must not be done in cases with stage pT1a vulvar cancer (infiltration depth 1 mm or less), basal cell carcinoma, or verrucous carcinoma of the vulva.
- Surgical staging of the inguinofemoral lymph nodes must be done in cancers where the infiltration depth is more than 1.0 mm (≥ pT1b)**.**

Radiotherapy and Radio(chemo)therapy

Postoperative (adjuvant) radiotherapy

Postoperative tumor bed irradiation

Postoperative irradiation of the tumor bed must be done after R1/ R2 resection. Tumor bed irradiation should be considered if the resection margin in health tissue is 3 mm (in the histological specimen) or less and a second resection is not possible or/and functionally not expedient or the patient does not want it.

Postoperative irradiation of the inguinal lymphatics

Postoperative irradiation of the affected inguinal region(s) should be done:

- If lymph node involvement is present with involvement of 2 or more inguinal lymph nodes, irrespective of the size of the metastases
- If one lymph node is affected and the metastasis is at least 5 mm or larger
- Always if extracapsular growth is present (FIGO IIIC)
- Iffixed/ulceratedlymphnodesarepresent (FIGOIVAii)

Postoperative irradiation of pelvic lymphatics

To avoid overtreatment and unnecessary therapy-related toxicity, postoperative irradiation of the pelvic lymphatics should be reserved for patients with histologically verified pelvic lymph node metastasis

Treatment of Recurrence disease

Treatment of local recurrence without involvement of the urethra or anus

Treatment of local recurrence should consist of resection with cancer-free resection margins (R0)

Treatment of local recurrence when R0 resection is not possible

The treatment of choice for inoperable recurrence should be chemoradiotherapy or radiation therapy

If locoregional recurrence occurs in a previously irradiated region and surgery or repeated radiotherapy is not an option, the patient should receive palliative care.

Treatment of inguinal recurrence

Distant metastasis must be excluded prior to carrying out radical surgery for inguinal and/or pelvic recurrence

Treatment for distant metastasis

Because of the poor response rates, monotherapy should be the systemic therapy of choice. The diagnostic criteria for prescribing systemic therapy should be very strict.

2.6 International Guidelines

2.6.1 Japan Society of Gynecologic Oncology Guidelines for the Treatment of Vulvar Cancer and Vaginal Cancer (2015)

The Japan Society of Gynecologic Oncology (JSGO) Created a clinical practice guideline in 2015 for the management of vulvar and vaginal cancer. The guideline provides recommendations for diagnostic and management decisions, and for limiting unnecessary treatments and cost.[5]

Surgical treatment

- Periodic follow-up is recommended for LSIL (Grade A).
- Wide local excision, simple vulvectomy, or laser vapori- zation may be considered, depending on the case, or laser vaporization may be combined with either of the first two for HSIL or differentiated VIN (dVIN) (Grade C1).
- Radical vulvectomy is recommended in cases where the focus of disease is localized to the vulva or perineum when the diameter of the tumor is >2 cm and the stromal invasion is > 1 mm deep (Grade B).
- Resection of vulvar tumors and inguinal lymph nodes through separate incisions is recommended (Grade B).
- Wide local excision is recommended in cases where the diameter of the tumor is ≤ 2 cm and the stromal invasion is ≤1 mm deep (Grade B).
- Radical local excision can be considered with an excision margin of 2 cm in cases where the diameter of the tumor is ≤2 cm but the stromal invasion is >1 mm deep; or the diam- eter of the tumor is >2 cm but the lesion is localized laterally to the vulva or to the perineum (Grade C1).
- Pelvic exenteration is considered if there is no apparent lymph node metastasis and complete excision is anticipated (Grade C1).
- Preoperative concurrent chemoradiotherapy (CCRT) or chemotherapy is also considered to avoid quality of life decline associated with pelvic exen- teration (Grade C1).
- Inguinal lymphadenectomy can be omitted in cases where the tumor is ≤ 2 cm in diameter and the depth of the stromal invasion is ≤ 1 mm (Grade B).
- Inguinal lymphadenectomy includes resection of both the superficial and deep inguinal lymph nodes (Grade C1).

- Ipsilateral lymphadenectomy alone can be considered in cases of a tumor located laterally in which the tumor is ≤ 2 cm in diameter (Grade C1).
- Postoperative radiation therapy for the groin and pelvis is recommended in cases that are positive for metastasis in the inguinal lymph nodes, where radical vulvectomy and inguinal lymphadenectomy have been conducted (Grade B).
- It is recommended at a minimum that the enlarged lymph nodes be resected if possible, to conduct a histological exam- ination for possible metastasis (Grade B).
- SLN biopsy may be performed as a means to avoid an inguinal lymphadenectomy in cases in which metastasis to the inguinal lymph nodes is not suspected clinically. In view of the current status of experience in the procedure in Japan, this action should be considered as an experimental approach (Grade C1).

Radiation therapy for vulvar cancer

- Postoperative irradiation of the primary site may be considered if the excision margin is <8 mm, or advanced vascular space invasion is confirmed (Grade C1).
- Postoperative irradiation of the groin and pelvis is recommended, if two or more metastases or extracapsular invasion of lymph node metastasis is confirmed in the inguinal lymph nodes (Grade B).
- Omission of postoperative irradiation may be considered, when one metastasis alone of the inguinal lymph nodes has occurred without extracapsular invasion (Grade C1).
- Definitive radiation therapy may be considered in inoperable cases (Grade C1).
- Preoperative irradiation may be considered as a means of preserving the function of adjacent organs in locally advanced cases (Grade C1).
- Concurrent chemotherapy with a single platinum-based drug or combination of this drug may be considered (Grade C1).

Chemotherapy for the vulvar cancer

In contrast to the effectiveness of radiation therapy in the treatment of advanced vulvar cancer, there are few reports for chemotherapy which has been regarded as ineffective.

- Preoperative chemotherapy may be considered for locally advanced cases (Grade C1).

- Systemic chemotherapy may be considered for cases of progression or recurrence of distant metastasis (Grade C1).

Follow-up and treatment for recurrent diseases

- A rough guide for the intervals in periodic follow-up after treatment is as follows (Grade C1):
    - First and second years: every one to three months
    - Third to fifth years: every six months
    - Sixth and subsequent years: once a year
- Conduct medical interviews, inspection, palpation, cytology, biopsy, chest X-ray, tumor markers and computed tomography (CT). Monitor not only for recurrence but also for complications (Grade C1).
- Re-excision is considered for postoperative localized recurrence (Grade C1). (2) CCRT is considered for local recurrence unresectable or infiltrating adjacent organs, if unirradiated (Grade C1).
- Systemic chemotherapy is considered for recurrences in the pelvis, with distant metastasis or with multiple lesions (Grade C1).
- Best supportive care (BSC) is considered if no other effective treatments are left (Grade C1).

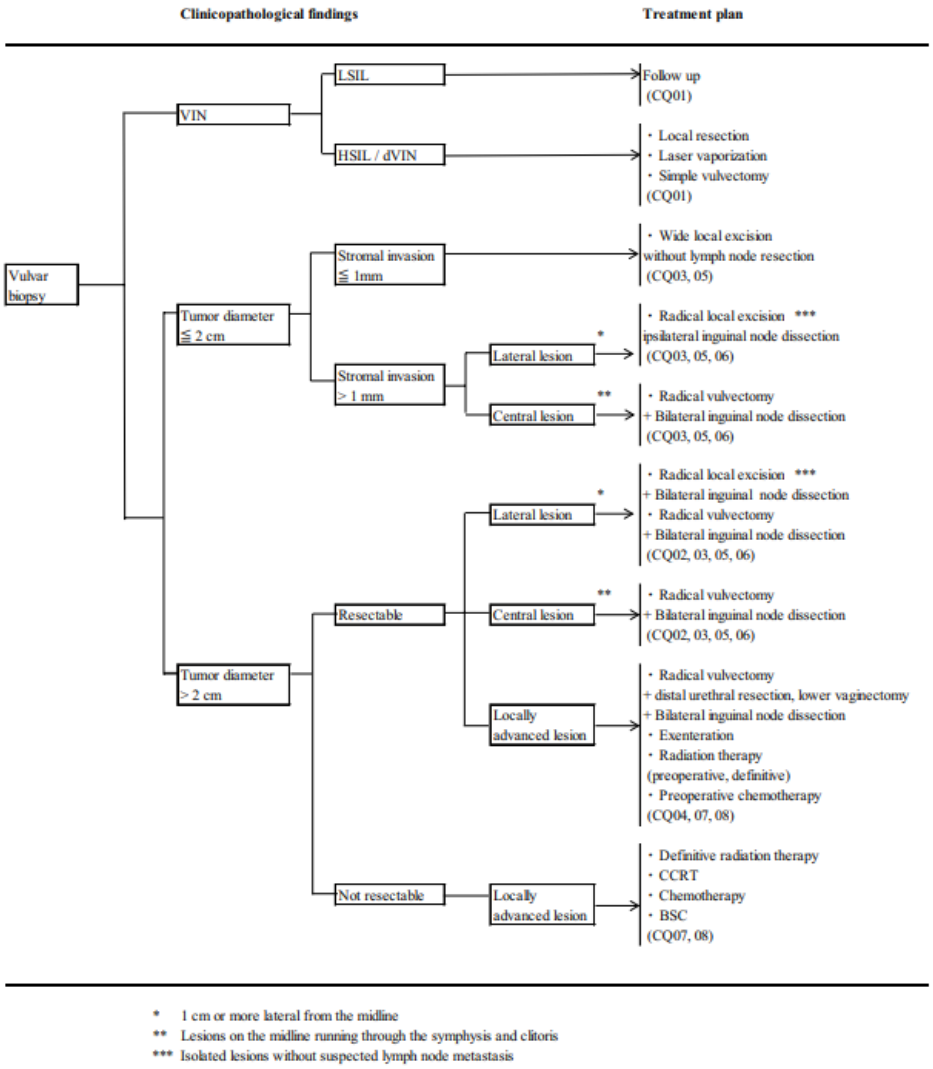

Figure 6. *Primary treatment for vulvar cancer (retrieved from the JSGO 2015 guidelines)*

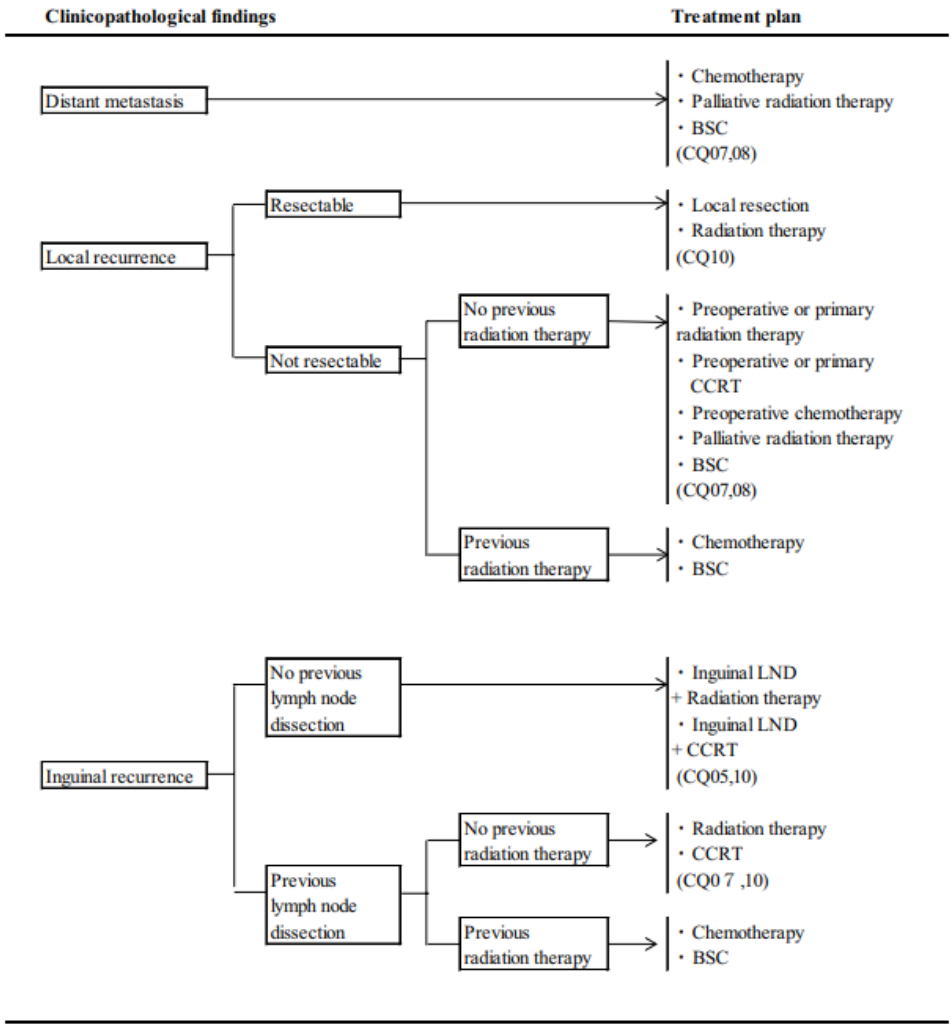

Figure 7. *Treatment of distant metastasis, recurrent tumor in vulvar cancer (retrieved from the JSGO 2015 guidelines)*

2.7 Systematic Reviews/Meta-Analyses

A thorough search for systematic reviews and meta-analyses on drug therapy in vulvar cancer did not yield any articles that have been recently published.

2.8 Secondary and Tertiary Resources

The international guidelines detailed in previous sections being most updated (as recently as December 2023), a detailed search of secondary and tertiary resources for additional guidelines, such as Google Scholar, the Ovid Health Technology Assessment Database, the National Institute for Health, and Care Research Journals Library, and UpToDate did not yield any additional data that hasn't already been described.

Section 3.0 Drug Therapy

3.1 Alkylating Agents

3.1.1 Carboplatin

Table 15. Carboplatin Drug Information

SCIENTIFIC NAME CARBOPLATIN[12,13]	
Trade Name(s) on Saudi Market	Carboplatin Ebewe; Cartinum; Carboplatin
SFDA Classification	Prescription
SFDA Approved Indication	No; data on vaginal and vulvar tumors are not available
FDA approved/off label	No
EMEA approved/off label	No
MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C51, C52
Drug Class	Antineoplastic Agent
Drug Sub-Class	Alkylating Agent
SFDA Registration Number (New)	Carboplatin Ebewe 450 mg: 3-355-01 Carboplatin Ebewe 150 mg: 2-355-01 Cartinum 150 mg: 21-5223-19 Cartinum 450 mg: 22-5223-19 Carboplatin 150 mg: 15-5287-20 Carboplatin 450 mg: 16-5287-20
ATC Code	L01XA02
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	*Refer to individual protocols*
Adjustment	Renal impairment prior to treatment initiation: Dose determination with Calvert formula uses glomerular filtration rate

	(GFR) and, therefore, inherently adjusts for kidney dysfunction. Hepatic impairment prior to treatment initiation: No dosage adjustments
Maximum Daily Dose Adults*	N/A
Prescribing Edits*	CU, MD, ST, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Can be used as monotherapy or as part of a combination regimen. Used in combination with anti-emetic agents.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Vulvar cancer (in combination with chemoradiation): to be used if patient intolerant to cisplatin. Advanced or recurrent/metastatic vulvar cancer: used as first- or second-line therapy. First-line option in pediatric germ cell tumors.
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: decreased electrolytes, nausea and vomiting, anemia, leukopenia, increased serum alkaline phosphatase, increased blood urea nitrogen. - Most serious: acute interstitial nephritis, hemorrhage, anaphylaxis.
Drug Interactions*	Live Vaccines: Immunosuppressants (Cytotoxic Chemotherapy) may enhance the adverse/toxic effect of Live Vaccines (Risk X)

	Taxane Derivatives: Platinum Derivatives may enhance the myelosuppressive effect of Taxane Derivatives (Risk D) Topotecan: Platinum Derivatives may enhance the adverse/toxic effect of Topotecan (Risk D)
Special Population	N/A
Pregnancy	Carboplatin may cause fetal harm if administered during pregnancy.
Lactation	Breastfeeding should be discontinued with carboplatin therapy; platinum levels in breast milk should be monitored if breastfeeding is desired.
Contraindications	Known hypersensitivity to the product or its components. Canadian labeling: Additional contraindications (not in the US labeling): Preexisting severe renal impairment.
Monitoring Requirements	CBC (with differential and platelet count), serum electrolytes, serum creatinine and BUN, LFTs. Hepatitis B screening.
Precautions	- Bone marrow suppression - Gastrointestinal toxicity - Hepatic function abnormalities - Hypersensitivity - Neurotoxicity - Ototoxicity - Renal toxicity - Vision loss
Black Box Warning	- Experienced physician - Bone marrow suppression - Hypersensitivity - Vomiting
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of carboplatin for the treatment of vaginal and vulvar tumors.** Nevertheless, carboplatin has been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – CARBOPLATIN

Carboplatin is recommended as a single agent or in combination for concurrent chemoradiation therapy in local disease and systemic therapy in advanced or recurrent vaginal or vulvar cancers.

3.1.2 Cisplatin

Table 16. Cisplatin Drug Information

SCIENTIFIC NAME CISPLATIN[12,14]	
Trade Name(s) on Saudi Market	Cisplatin (Ebewe, Hospira), Cipalin, Tinplat
SFDA Classification	Prescription
SFDA approved Indication	No; data on vaginal and vulvar tumors are not available
FDA approved / off label	No
EMEA approved / off label	No
MHRA approved / off label	No
PMDA approved / off label	No
Indication (ICD-10)	C51, C52
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent
SFDA Registration Number (New)	**Cisplatin Ebewe:** 0409222579 (10mg); 409222580 (50mg) **CIPALIN**: 288-334-18 (10mg); 289-334-18 (25mg); 290-334-18 (50mg) **Cisplatin Hospira:** 4-5287-19 (50mg) **Tinplat:** 29-5223-19 (10mg); 30-5223-19 (50mg)
ATC Code	L01XA01

Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	*Refer to individual protocols*
Dose (Pediatrics)	Germ cell tumors: Limited data available: Cushing 2004: - Infants: IV: 0.7 mg/kg on days 1 to 5 of a 21-day cycle (in combination with bleomycin and etoposide). - Children and Adolescents: IV: 20 mg/m2 on days 1 to 5 of a 21-day cycle (in combination with bleomycin and etoposide). Pinkerton 1986: - Children and Adolescents: IV: 100 mg/m2 on day 1 of a 21-day cycle (in combination with bleomycin and vinblastine or etoposide). Lopes 2016: Children and Adolescents: - Intermediate risk: PE regimen: IV: 35 mg/m2 on days 1, 2, and 3 of a 21-day cycle for 3 cycles (weeks 1, 4, and 7) in combination with etoposide; a fourth cycle may be considered depending on response. - High risk: PEI regimen: IV: 35 mg/m2 on days 1, 2, and 3 of a 21-day cycle for 4 cycles (weeks 1, 4, 7, and 11) in combination with etoposide and ifosfamide; a fifth or sixth cycle may be considered depending on response.
Adjustment	Renal Impairment (Adult): - CrCl ≥60 mL/mine: IV: No adjustment - CrCl 50 to <60 mL/min: IV: 75% of the dose - CrCl 40 to <50 mL/minute: IV: 50% of the dose

	- CrCl <40 mL/minute: Not recommended - Hemodialysis/PD: Poorly dialyzable due to rapid and high degree of protein binding: 50% of the dose after dialysis - CRRT/PIRRT: Use is not recommended - Nephrotoxicity during treatment: Patients that develop AKI (SCr >2 times baseline) may require discontinuation of therapy Renal Impairment (Pediatric): - GFR >50 mL/min/1.73 m^2: No adjustment - GFR 10 to 50 mL/min/1.73 m^2: 75% of dose - GFR <10 mL/minute/1.73 m2: 50% of dose - Hemodialysis: Partially cleared by hemodialysis: Administer 50% of dose post hemodialysis - PD: Administer 50% of dose - CRRT: 75% of dose
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Prescribing edits*	CU, MD, ST, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Can be used as monotherapy or as part of a combination regimen. Used in combination with anti-emetic agents.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Vulvar cancer (in combination with chemoradiation): first-line treatment.

	Advanced or recurrent/metastatic vulvar cancer: used as first- or second-line therapy. First-line option in pediatric germ cell tumors.
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Neurotoxicity, nausea and vomiting, nephrotoxicity, anemia, leukopenia, thrombocytopenia, increased liver enzymes, ototoxicity - Most serious: Neurotoxicity, anemia, leukopenia, thrombocytopenia, hearing loss
Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating)
Special Population	Renal Impairment
Pregnancy	Pregnancy Category D: Not used in pregnancy

	Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Cisplatin is present in breast milk. Breastfeeding is not recommended.
Contraindications	Severe hypersensitivity to cisplatin or any component of the formulation
Monitoring Requirements	Blood counts, serum creatinine, BUN, CrCl, and serum electrolytes Neurological examination, consider audiometric and vestibular testing Monitor closely for signs/symptoms of infection, hypersensitivity reactions, neuropathy, ocular toxicity, tumor lysis syndrome, and secondary malignancies
Precautions	- Bone marrow suppression - Extravasation - GI toxicity - Hypersensitivity - Nephrotoxicity - Neurotoxicity - Ocular toxicity - Ototoxicity - Secondary malignancies - Tumor lysis syndrome
Black Box Warning	- Myelosuppression - Nausea and vomiting - Nephrotoxicity - Peripheral neuropathy
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of cisplatin for the treatment of vulvar and vaginal tumors.** Nevertheless, cisplatin has been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – CISPLATIN

Cisplatin is recommended as a single agent or in combination for concurrent chemoradiation therapy in local disease and systemic therapy in advanced or recurrent vaginal or vulvar cancers.

3.2 Antimetabolites

3.2.1 Capecitabine

Table 17. Capecitabine Drug Information

SCIENTIFIC NAME CAPECITABINE [12,15]	
Trade Name(s) on Saudi Market	XELODA, DIROGIT, CAPECITABINE SPC, Aceda, Pitacro, Emcap, Xelobine, Catabina, Capecitabine NEAPOLIS.
SFDA Classification	Prescription
SFDA Approved Indication	No; data on vaginal and vulvar tumors are not available
FDA approved/off label	No
EMEA approved/off label	No
MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C51
Drug Class	Antineoplastic Agent
Drug Sub-Class	Antimetabolite (Pyrimidine analog)
SFDA Registration Number (New)	XELODA: 500 mg [251-24-04], 150 mg [250-24-04] DIROGIT: 500 mg [189-172-18] CAPECITABINE SPC: 500 mg [2-5171-18], 150 mg [1-5171-18] Aceda: 500 mg [7-5223-18], 150 mg [8-5223-18] Pitacro: 500 mg [2611200294], 150 mg [2611200293] Emcap: 500 mg [1510200212] Xelobine: 500 mg [2202210536], 150 mg [2202210537] Catabina: 500 mg [0706210768]

	Capecitabine NEAPOLIS: 500 mg [2808234063]
ATC Code	L01BC06
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Film coated tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	*Refer to individual protocols*
Adjustment	Severe hepatic impairment: Use is not recommended; avoid use
Maximum Daily Dose Adults*	N/A
Prescribing Edits*	CU, MD, ST, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Used in combination with mitomycin.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Vulvar cancer (in combination with radiation therapy): second-line treatment (after cisplatin or carboplatin).
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Bone marrow depression - Cardiotoxicity: Edema - Dermatologic reaction: Dermatitis, and palmar-plantar erythrodysesthesia GI toxicity: abdominal pain, anorexia, constipation, decreased appetite, diarrhea, nausea, stomatitis, vomiting - Hepatic: Hyperbilirubinemia - Nervous system: Asthenia, fatigue, pain, paresthesia.

Drug Interactions*	Risk X: Abrocitinib, Allopurinol, Aminolevulinic Acid, Baricitinib, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Live vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Pimozide, Ritlecitinib, Ruxolitinib, Sertindole, Tacrolimus, Talimogene Laherparepvec, Tofacitinib, Upadacitinib.
Special Population	– Dihydropyrimidine dehydrogenase deficiency – Older adults
Pregnancy	Capecitabine may cause fetal harm if administered during pregnancy.
Lactation	Breastfeeding is not recommended by the manufacturer during Capecitabine therapy and for 1 week after the last dose.; It is not known if capecitabine is present in breast milk.
Contraindications	Known hypersensitivity to capecitabine, fluorouracil, or any component of the formulation. Canadian labeling: Additional contraindications (not in the US labeling): Known complete absence of dihydropyrimidine dehydrogenase (DPD) activity; concomitant administration with sorivudine or chemically related analogues (eg, brivudine).
Monitoring Requirements	CBC with differential (at baseline and prior to each cycle), hepatic function (as clinically indicated), and kidney function (at baseline and as clinically indicated). Monitor INR closely/more frequently if receiving a concomitant vitamin K antagonist. Monitor hydration status at baseline and as clinically indicated.

	Monitor for signs/symptoms of diarrhea, dehydration, hand-foot syndrome, new or worsening serious skin reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis), stomatitis, hepatotoxicity, nephrotoxicity, and cardiotoxicity. Promptly evaluate any symptoms suggestive of cardiotoxicity. Consider monitoring ECG in patients on concomitant QT-prolonging medications. Monitor adherence.
Precautions	- Hepatotoxicity, Kidney impairment, and Proton pump inhibitors
Black Box Warning	Vitamin K antagonist interaction
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of capecitabine for the treatment of Vaginal tumors.** Nevertheless, capecitabine has been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – CAPECITABINE

Capecitabine is recommended in combination with mitomycin as an alternative to platinum-based concurrent chemoradiation in localized vaginal and vulvar cancers.

3.2.2 Fluorouracil

Table 18. Fluorouracil Drug Information

SCIENTIFIC NAME FLOUROURACIL[12,16]	
Trade Name(s) on Saudi Market	Fluorouracil (Ebewe, HOSPIRA), FLORYL
SFDA Classification	Prescription
SFDA Approved Indication	No; data on vaginal and vulvar tumors are not available
FDA approved/off label	No
EMEA approved/off label	No
MHRA approved/off label	No

PMDA approved/off label	No
Indication (ICD-10)	C51, C52
Drug Class	Antineoplastic Agent
Drug Sub-Class	Antimetabolite (Pyrimidine analog)
SFDA Registration Number (New)	**Fluorouracil Ebewe:** 16-355-01 (500 mg), 18-355-01 (1 g), 42-355-07 (5 g). **Fluorouracil HOSPIRA:** 22-237-97 (500 mg) **FLORYL:** 18-5223-19 (250 mg), 17-5223-19 (500 mg), 16-5223-19 (1 g), 15-5223-19 (5 g).
ATC Code	L01BC02
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	*Refer to individual protocols*
Adjustment	Severe hepatic impairment: Use is not recommended; avoid use
Maximum Daily Dose Adults*	N/A
Prescribing Edits*	CU, MD, ST, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Used in combination with cisplatin (vulvar cancer, vaginal cancer) or mitomycin (vaginal cancer). Used in combination with antiemetic agents.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Vulvar cancer (in combination with chemoradiation and cisplatin): second-line treatment (after cisplatin or carboplatin).
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	

Main Adverse Drug Reactions (most common and most serious)	Alopecia, changes in nails, dermatitis, hyperpigmentation (supravenous), maculopapular rash (pruritic), palmar-plantar erythrodysesthesia, diarrhea, esophagopharyngitis, nausea, stomatitis, tissue sloughing (gastrointestinal), vomiting, Agranulocytosis, anemia, leukopenia (nadir: days 9 to 14; recovery by day 30), pancytopenia, thrombocytopenia
Drug Interactions*	Live Vaccines, Immunosuppressants: may enhance the adverse/toxic effect of Live Vaccines (Risk X) Allopurinol: May decrease serum concentrations of the active metabolite(s) of Fluorouracil Products. (Risk X) Sertindole, Pimozide: May enhance the QTc-prolonging effect of QT-prolonging Agents (Risk X)
Special Population	N/A
Pregnancy	Fluorouracil may cause fetal harm if administered during pregnancy.
Lactation	Breastfeeding should be discontinued with Fluorouracil therapy; It is not known if fluorouracil is present in breast milk.
Contraindications	There are no contraindications listed in the manufacturer's US labeling. Canadian labeling: Known hypersensitivity to fluorouracil or any component of the formulation; debilitated patients; poor nutritional state; depressed bone marrow function following radiotherapy or therapy with other antineoplastic agents; potentially serious infections.

Monitoring Requirements	CBC (with differential and platelet), renal function tests, LFTs, INR, and prothrombin time. ECG in patients on concomitant QT prolonging medications. Hepatitis B virus (HBV) screening
Precautions	- Bone marrow suppression - Cardiotoxicity - GI toxicity - Hand-foot syndrome - Hyperammonemic encephalopathy - Neurotoxicity - Dihydropyrimidine dehydrogenase deficiency - Concomitant warfarin - Administration safety issues - Antidote
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of fluorouracil for the treatment of vaginal tumors.** Nevertheless, fluorouracil has been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – FLUOROURACIL

Fluorouracil can be used as an option in combination with platinum based concomitant chemoradiation therapy for locally advanced vaginal and vulvar cancers. It is also used as a local therapy for the management of high-grade vaginal intraepithelial neoplasia.

3.2.3 Gemcitabine

Table 19. Gemcitabine Drug Information

SCIENTIFIC NAME GEMCITABINE [12,17]	
Trade Name(s) on Saudi Market	GEMCITABIN EBEWE, CITABOL, GEMCITABINE JAZEERA, GEMZAR, GEMCITABINE GLENMARK, CITAROX, GEBTIN, and Gemcitabine BOS.
SFDA Classification	Prescription
SFDA Approved Indication	No; data on vaginal and vulvar tumors are not available
FDA approved/off label	No
EMEA approved/off label	No
MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C51
Drug Class	Antineoplastic Agent
Drug Sub-Class	Antimetabolite (Pyrimidine analog)
SFDA Registration Number (New)	EBEWE: 200 mg [48-355-11], 1000 mg [50-355-11] CITABOL: 200 mg [4-796-15], 1000 mg [3-796-15] GEMCITABINE JAZEERA: 200 mg [0712222984], 1000 mg [0712222985] GEMZAR: 200 mg [1-5396-19] GLENMARK: 200 mg [1-5438-20], 1000 mg [2-5438-20] CITAROX: 200 mg [1-5251-19], 1000 mg [10-5251-20] GEBTIN: 200 mg [73-5286-20], 1000 mg [72-5286-20] Gemcitabine BOS: 1000 mg [0301221548]
ATC Code	L01BC05
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	

Dosage Form	Concentrate for solution for injection and powder for solution for injection.
Route of Administration	Intravenous
Dose (Adult) [DDD]*	*Refer to individual protocols*
Adjustment	**Altered kidney function:** - No dosage adjustment necessary. However, risk of hematologic toxicity may be increased in patients with CrCl <30 mL/minute, which may require gemcitabine dose modification **Hepatic impairment:** Serum bilirubin >1.6 mg/dL: Use initial dose of 800 mg/m2; may escalate if tolerated. Total bilirubin ≥1.6 mg/dL: May begin with 80% of the usual gemcitabine dose and increase the dose if tolerated or may consider initiating with full dose and careful active monitoring
Maximum Daily Dose Adults*	N/A
Prescribing Edits*	CU, MD, ST, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Used in combination with radiation therapy (chemoradiation) or other chemotherapeutic agents (cisplatin). Used in combination with antiemetic agents.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Vulvar cancer: second-line treatment in combination with radiation therapy (after cisplatin or carboplatin).

	Advanced or recurrent/metastatic vulvar cancer: second-line treatment (in combination with cisplatin)
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	Most common: Peripheral edema and edema, drowsiness, Skin rash and alopecia, nausea and vomiting, diarrhea, and stomatitis, proteinuria, hematuria, anemia, neutropenia, thrombocytopenia, hemorrhage, increased serum alanine aminotransferase, increased serum aspartate aminotransferase, increased serum alkaline phosphatase, hyperbilirubinemia Infection, increased blood urea nitrogen, dyspnea, flu-like symptoms, and Fever.
Drug Interactions	Risk X: Abrocitinib, Baricitinib, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Live vaccines, Natalizumab, Pimecrolimus, Ritlecitinib, Ruxolitinib (topical), Tacrolimus (topical), Talimogene Laherparepvec, Tofacitinib, and Upadacitinib.
Special Population	- Older adult ≥ 65 year of age. - Radiation therapy recipients
Pregnancy	Based on the mechanism of action and on findings from animal reproduction studies, gemcitabine may cause fetal harm if administered during pregnancy.
Lactation	It is not known if gemcitabine is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not

	recommended during treatment and for at least 1 week after the last gemcitabine dose.
Contraindications	Known hypersensitivity to gemcitabine or any component of the formulation.
Monitoring Requirements	CBC with differential and platelet count; LFTs, renal function; monitor electrolytes, including potassium, magnesium, and calcium (when in combination therapy with cisplatin). Evaluate pregnancy status prior to treatment initiation. Monitor pulmonary function. Monitor for signs/symptoms of capillary leak syndrome, hemolytic uremic syndrome (HUS; assess for HUS if anemia with microangiopathic hemolysis, elevation of bilirubin or lactate dehydrogenase, reticulocytosis, severe thrombocytopenia, and/or renal failure [increased serum creatinine or BUN] develops), hepatotoxicity, hypersensitivity, posterior reversible encephalopathy syndrome (confirm diagnosis with MRI), and pulmonary toxicity.
Precautions	Bone marrow suppression, capillary leak syndrome, Hemolytic uremic syndrome, Hepatotoxicity, Hypersensitivity, Posterior reversible encephalopathy syndrome, Pulmonary toxicity
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA):

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of gemcitabine for the treatment of vulvar tumors.** Nevertheless, Gemcitabine has been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – GEMCITABINE

Gemcitabine is recommended in combination with radiation therapy as a second-line option for the management of localized vulvar cancer. In combination with cisplatin, it is recommended as a second-line option for advanced or recurrent/metastatic disease. The recommendation is based on the extrapolated evidence on cervical cancer.

3.3 Antimicrotubular Agents

3.3.1 Paclitaxel

Table 20. Paclitaxel Drug Information

SCIENTIFIC NAME PACLITAXEL[12,18]	
Trade Name(s) on Saudi Market	ANZATAX, Ebetaxel, ROTUB
SFDA Classification	Prescription
SFDA approved Indication	No, data on vaginal and vulvar tumors are not available
FDA approved / off label	No
EMEA approved / off label	No
MHRA approved / off label	No
PMDA approved / off label	No
Indication (ICD-10)	C51
Drug Class	Antineoplastic agent
Drug Sub-class	Antimicrotubular
SFDA Registration Number (New)	ANZATAX: 30 mg [4-5669-22], 150 mg [5-5669-22] Ebetaxel: 30 mg [36-355-06], 30 mg [35-355-06], 150 mg [34-355-06], 300 mg [33-355-06] ROTUB: 30 mg [1-5190-18], 100 mg [2-5190-18], 150 mg [3-5190-18], 300 mg [4-5190-18] ABRAXANE: 100 mg [9-5550-22]
ATC Code	L01CD01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	

Dosage Form	Concentrate for solution for injection, and powder for suspension.
Route of Administration	Intravenous
Dose (Adult) [DDD]*	*Refer to individual protocols*
Adjustment	**Altered kidney function:** No dosage adjustment likely to be necessary for any degree of kidney impairment **Hepatic Impairment:** 3-hour infusion: - Transaminases <10 times ULN and bilirubin level ≤1.25 times ULN: 175 mg/m^2 - Transaminases <10 times ULN and bilirubin level 1.26 to 2 times ULN: 135 mg/m^2 - Transaminases <10 times ULN and bilirubin level 2.01 to 5 times ULN: 90 mg/m^2 - Transaminases ≥10 times ULN or bilirubin level >5 times ULN: Avoid use
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Prescribing Edits*	CU, MD, ST, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Used in combination with radiation therapy (chemoradiation) or other chemotherapeutic agents (cisplatin, cisplatin/bevacizumab, carboplatin, carboplatin/bevacizumab). Used as monotherapy in advanced or recurrent/metastatic disease. Used in combination with antiemetic agents.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A

ST (Step Therapy):	Vulvar cancer: second-line treatment in combination with radiation therapy (after cisplatin or carboplatin). Advanced or recurrent/metastatic vulvar cancer: first-line treatment (in combination with cisplatin, cisplatin/bevacizumab, carboplatin, or carboplatin/bevacizumab); second-line treatment as monotherapy.
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	Most common: ECG abnormality, edema, hypotension, alopecia, diarrhea, nausea and vomiting, stomatitis, anemia, hemorrhage, leukopenia, neutropenia, thrombocytopenia, increased serum alkaline phosphatase, increased serum aspartate aminotransferase, hypersensitivity reaction, infection, injection-site reaction, asthenia, peripheral neuropathy, arthralgia, myalgia, and fever
Drug Interactions*	Risk X: Abrocitinib, Atazanavir, Baricitinib, Brivudine, Bromperidol, Cladribine, Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Live vaccines, Nadofaragene Firadenovec, Pimecrolimus, Ritlecitinib, Ruxolitinib (topical), SORAfenib, Tacrolimus (topicsl), Talimogene Laherparepvec, Tertomotide, Tofacitinib, and Upadacitinib
Special Population	Older adults and pediatrics
Pregnancy	Paclitaxel crosses the placenta. Use of paclitaxel may be appropriate for the treatment of breast cancer and some

	gynecologic cancers during pregnancy. In general, if chemotherapy is indicated, it should be avoided in the first trimester and there should be a 3-week time period between the last chemotherapy dose and anticipated delivery, and chemotherapy should not be administered beyond week 33 of gestation. Close monitoring is recommended
Lactation	Paclitaxel is present in breast milk. Due to the potential for serious adverse reactions in a breastfeeding infant, breastfeeding is not recommended by the manufacturer. Avoidance of breastfeeding for 6 to 10 days after the last paclitaxel dose, based on the serum half-life, has been suggested
Contraindications	Hypersensitivity to paclitaxel, polyoxyl 35/polyoxyethylated castor oil (Cremophor EL), or any component of the formulation; treatment of solid tumors in patients with baseline neutrophil counts <1,500/mm3.
Monitoring Requirements	CBC with differential and platelet count, liver and kidney function. Monitor for hypersensitivity reactions, vital signs, continuous cardiac monitoring (patients with conduction abnormalities). Monitor for signs/symptoms of peripheral neuropathy. Monitor infusion site during infusion. Hepatitis B virus screening.
Precautions	Cardiovascular effects, extravasation, hepatic impairment, older adult and pediatrics, excipients (Cremophor EL), and intraperitoneal administration
Black Box Warning	- Experienced physician - Hypersensitivity - Bone marrow suppression
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of paclitaxel for the treatment of vulvar or vaginal tumors.** Nevertheless, paclitaxel has been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – PACLITAXEL

Paclitaxel is recommended in the first line setting for the management of advanced, metastatic, or recurrent vulvar carcinoma as a part of 2 and 3-drug combinations with cisplatin, carboplatin, cisplatin/bevacizumab, and carboplatin/bevacizumab. It is also recommended as a monotherapy to be used as an alternative to platinum agents in the setting of chemoradiotherapy and recommended in the second line for the management of advanced, metastatic, or recurrent vulvar carcinoma. The recommendations are based on the extrapolated evidence of a phase 3 randomized trial of advanced or recurrent/metastatic cervical cancer.

3.4 Topoisomerase I Inhibitors

3.4.1 Topotecan

Table 21. Topotecan Drug Information

SCIENTIFIC NAME TOPOTECANIN[12,19]	
Trade Name(s) on Saudi Market	HYCAMTIN
SFDA Classification	Prescription
SFDA approved Indication	No, data on vaginal and vulvar tumors are not available
FDA approved / off label	No
EMEA approved / off label	No
MHRA approved / off label	No
PMDA approved / off label	No
Indication (ICD-10)	C51, C52
Drug Class	Antineoplastic agent
Drug Sub-class	Topoisomerase I Inhibitor
SFDA Registration Number (New)	HYCAMTIN: 4 mg [3-5773-23]
ATC Code	L01XX17
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents

DRUG INFORMATION	
Dosage Form	Powder for concentrate for solution for infusion
Route of Administration	Intravenous
Dose (Adult) [DDD]*	*Cervical cancer, recurrent or persistent: IV: 0.75 mg/m2/day for 3 days (days 1, 2, and 3; in combination with cisplatin on day 1 only [with hydration]) every 21 days for a maximum of 6 cycles (in nonresponders) or until disease progression or unacceptable toxicity*
Dose (Pediatrics)	*Refer to individual protocols*
Adjustment	Renal impairment: IV (single agent topotecan): - CrCl 20 to 39 mL/minute: Reduce dose to 0.75 mg/m2/dose - CrCl <20 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (insufficient data available for dosing recommendation). IV (when used in combination with cisplatin): There are no dosage adjustments provided in the manufacturer's labeling. Hepatic impairment: IV: There are no dosage adjustments provided in the manufacturer's labeling. A small phase I study in patients with hepatic impairment (total bilirubin >1.2 mg/dL), found no pharmacokinetic or pharmacodynamic alterations and suggests that dosage adjustment is not likely necessary
Maximum Daily Dose Adults*	4 mg
Maximum Daily Dose Pediatrics*	2 mg/m2
Prescribing edits*	CU, MD, ST, PE
AGE (Age Edit):	N/A

CU (Concurrent Use Edit):	Used in combination with cisplatin or paclitaxel/bevacizumab. Used in combination with antiemetic agents.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Topotecan is an option (as part of a combination regimen) in the setting of advanced, metastatic, and recurrent vaginal and vulvar carcinoma.
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Central nervous system: Fatigue. - Dermatologic: Alopecia - Gastrointestinal: Nausea, diarrhea, vomiting, anorexia. - Hematologic & oncologic: Anemia neutropenia, thrombocytopenia, febrile neutropenia, neutropenic infection
Drug Interactions*	Risk X: Cladribine, Dipyrone, Fexinidazole, Lasmiditan, Leniolisib, live vaccines, Pacritinib, P-glycoprotein/ABCB1 Inhibitors, Sparsentan, Taurursodiol, Velpatasvir, and Voxilaprevir.
Special Population	N/A
Pregnancy	Based on the mechanism of action and data from animal reproduction studies, in utero exposure to topotecan may cause fetal harm.
Lactation	It is not known if topotecan is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer

	recommends lactating females not breastfeed during therapy and for 1 week following the last topotecan dose.
Contraindications	Severe hypersensitivity to topotecan or any component of the formulation Canadian labeling: Additional contraindications (not in the US labeling): Severe renal impairment (CrCl <20 mL/minute); pregnancy; breastfeeding; preexisting severe bone marrow depression
Monitoring Requirements	CBC with differential and platelet count, renal function tests, bilirubin. Verify pregnancy and hepatitis B virus status. Monitor for symptoms of interstitial lung disease; diarrhea symptoms/hydration status; monitor infusion site. Monitor adherence (for oral therapy).
Precautions	Bone marrow suppression, extravasation, GI toxicity, hypersensitivity, neutropenic enterocolitis, pulmonary toxicity, renal impairment, and medication safety.
Black Box Warning	Bone marrow suppression
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of topotecan for the treatment of vaginal tumors.** Nevertheless, topotecan has been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – TOPOTECAN

Topotecan is an option in combination of paclitaxel/bevacizumab in the setting of advanced, metastatic, and recurrent vaginal and vulvar carcinoma. It also can be used in combination with cisplatin in patients who are not candidates for taxanes. The recommendation is based on the extrapolated evidence randomized trials of advanced or recurrent/metastatic cervical cancer.

3.5 Topoisomerase II Inhibitors

3.5.1 Etoposide

Table 22. Etoposide Drug Information

SCIENTIFIC NAME ETOPOSIDE[12,20]	
Trade Name(s) on Saudi Market	Etoposid Ebewe; Lastet
SFDA Classification	Prescription
SFDA Approved Indication	No, data on vaginal and vulvar tumors are not available
FDA approved/off label	No
EMEA approved/off label	No
MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C52
Drug Class	Antineoplastic Agent
Drug Sub-Class	Topoisomerase II Inhibitor
SFDA Registration Number (New)	Etoposid Ebewe 200 mg: 26-355-01 Etoposid Ebewe 100 mg: 25-355-01 Lastet 100 mg: 2-202-01
ATC Code	L01CB01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution for infusion
Route of Administration	Intravenous
Dose (Adult) [DDD]*	100 mg/m2 *Refer to individual protocols*
Adjustment	Renal impairment prior to treatment initiation: - CrCl 15 to 50 mL/minute: Administer 75% of dose - CrCl <15 mL minute: Data not available; consider further dose reductions Hepatic impairment prior to treatment initiation:

	Bilirubin 1.5 to 3 mg/dL or AST >3 times ULN: Administer 50% of dose
Maximum Daily Dose Adults*	N/A
Prescribing edits*	CU, MD, ST, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Used in combination with cisplatin or radiation therapy. Used in combination with antiemetic agents.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Etoposide is recommended in combination with cisplatin for the management of small cell carcinoma of the vagina in early stage, locally advanced and metastatic disease as a concurrent chemoradiation and a systemic therapy.
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: alopecia, nausea and vomiting, leukopenia, hypotension (due to rapid infusion) - Most serious: interstitial pneumonitis, ischemic heart disease, ovarian failure, Stevens-Johnson syndrome
Drug Interactions*	CYP3A4 Inducers (Strong): May decrease the serum concentration of Etoposide (Risk D) Vaccines (Live): Immunosuppressants (Cytotoxic Chemotherapy) may enhance the adverse/toxic effect of Vaccines (Risk X)
Special Population	N/A

Pregnancy	Adverse events were observed in animal reproduction studies. Fetal growth restriction and newborn myelosuppression have been observed following maternal use of regimens containing etoposide during pregnancy.
Lactation	Etoposide is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of treatment to the mother.
Contraindications	Known hypersensitivity to the product or its components. Canadian labeling: Additional contraindications (not in the US labeling): Severe leukopenia or thrombocytopenia; severe hepatic impairment; severe renal impairment.
Monitoring Requirements	At baseline and periodically: - CBC, LFTs, Albumin, and Renal function Hepatitis B screening
Precautions	- Bone marrow suppression - Extravasation - Hypotension - Hypersensitivity - Secondary malignancies
Black Box Warning	- Experienced physician: Etoposide should be administered under the supervision of a qualified health care provider experienced in the use of cancer chemotherapeutic agents. - Bone marrow suppression: Severe myelosuppression, with resulting infection or bleeding, may occur.
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of etoposide for the treatment of vaginal cancer.** Nevertheless, etoposide has been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – ETOPOSIDE

Etoposide is recommended in combination with cisplatin for the management of small cell carcinoma of the vagina in early stage, locally advanced and metastatic disease as a concurrent chemoradiation and a systemic therapy.

3.6 Vascular Endothelial Growth Factor (VEGF) Inhibitors

3.6.1 Bevacizumab

Table 23. Bevacizumab Drug Information

SCIENTIFIC NAME BEVACIZUMAB[12,21]	
Trade Name(s) on Saudi Market	Avastin; Zirabev; Mvasi
SFDA Classification	Prescription
SFDA Approved Indication	No, data on vaginal and vulvar tumors are not available
FDA approved/off label	No
EMEA approved/off label	No
MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C51
Drug Class	Antineoplastic agent, monoclonal antibody
Drug Sub-Class	Vascular Endothelial Growth Factor (VEGF) Inhibitor
SFDA Registration Number (New)	Avastin 100mg: 269-24-14 Avastin 400mg: 270-24-14 Zirabev 100mg: 2411200290 Zirabev 400mg: 2411200291 Mvasi 100mg: 2402210547 Mvasi 400mg: 2402210550
ATC Code	L01XC07

Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	*Refer to individual protocols*
Dose (Pediatric)	*Refer to individual protocols*
Adjustment	Renal impairment prior to treatment: No dosage adjustment Renal impairment during treatment: - Nephrotic syndrome (proteinuria >3.5 g per 24 hours): discontinue bevacizumab and refer to a kidney specialist. - Proteinuria ≥2 to ≤3.5 g per 24 hours: Withhold bevacizumab and resume therapy if and when urine protein levels are <2 g per 24 hours. Hepatic impairment prior to or during treatment: No dosage adjustment
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Prescribing Edits*	CU, MD, ST, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Used in combination with other chemotherapeutic agents (cisplatin/paclitaxel, carboplatin/paclitaxel).
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Advanced or recurrent/metastatic vulvar cancer: first-line treatment (in combination with cisplatin/paclitaxel or carboplatin/paclitaxel.
EU (Emergency Use):	N/A

PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: increased ALTs, increased alkaline phosphatase, thrombocytopenia, leukopenia, hypoalbuminemia, hyponatremia, hypocalcemia, hyperglycemia, hypertension - Most serious: nephrotic syndrome
Drug Interactions*	Anthracyclines: enhanced cardiotoxicity (risk X) Cladribine, dipyrone, fexinidazole: enhanced myelosuppressive effect (risk X) Sunitinib: increased risk of microangiopathic hemolytic anemia (risk X)
Special Population	Patients ≥ 65 years of age have an increased incidence of arterial thrombotic events.
Pregnancy	Based on findings in animal reproduction studies and on the mechanism of action, bevacizumab may cause fetal harm if administered during pregnancy. Information from post-marketing reports following systemic exposure in pregnancy is limited.
Lactation	It is not known if bevacizumab is present in breast milk.
Contraindications	Known hypersensitivity to the product or its components
Monitoring Requirements	Proteinuria/nephrotic syndrome Blood pressure Pregnancy status HBV screening prior to initiation (do not delay treatment for screening results)
Precautions	- GI perforation/fistula - Heart failure

	- Hemorrhage - Hypertension - Infusion reactions - Necrotizing fasciitis - Osteonecrosis of the jaw - Ocular adverse events - Posterior reversible encephalopathy syndrome - Proteinuria/nephrotic syndrome - Wound healing complications - Thromboembolism
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of bevacizumab for the treatment of vulvar tumors.**

CONCLUSION STATEMENT – BEVACIZUMAB

Bevacizumab is recommended in the first-line setting for the treatment of advanced, metastatic, or recurrent vaginal or vulvar carcinoma in combination with cisplatin/paclitaxel or carboplatin/paclitaxel. The recommendation is based on the extrapolated evidence of phase 3 randomized trial of advanced or recurrent/metastatic cervical cancer.

3.7 Immune Checkpoint Inhibitors

3.7.1 Nivolumab

Table 24. Nivolumab Drug Information

SCIENTIFIC NAME NIVOLUMAB[12,22]	
Trade Name(s) on Saudi Market	OPDIVO
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered; data on vaginal and vulvar tumors are not available
FDA approved/off label	No
EMEA approved/off label	No

MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C51
Drug Class	Antineoplastic Agent
Drug Sub-Class	Immune Checkpoint Inhibitor, Anti-PD-1 Monoclonal Antibody
SFDA Registration Number (New)	OPDIVO: 40 mg [2-960-15], 1000 mg [3-960-15]
ATC Code	L01XC17
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	Weight-based protocol: 3 mg/kg every 14 days Flat dosing: 240 mg every 14 days or 480 mg every 28 days
Adjustment	**Altered kidney function:** No dosage adjustment likely for any degree of kidney dysfunction Hepatic Impairment: Mild or moderate: There are no dosage adjustments provided in the manufacturer's labeling; however, there is no clinically important effect on nivolumab clearance in this setting. Severe (total bilirubin >3 × ULN and any AST) impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Adjustment is required for toxicities.
Maximum Daily Dose Adults*	N/A
Prescribing Edits*	MD, PA, ST, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist

PA (Prior Authorization):	To be used in as second-line treatment in patients with advanced or recurrent/metastatic vulvar cancer that are HPV-related.
QL (Quantity Limit):	N/A
ST (Step Therapy):	Advanced or recurrent/metastatic vulvar cancer: second-line or subsequent therapy in HPV-related tumors.
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	Cardiovascular toxicity, Dermatologic toxicity, Endocrine toxicity, GI toxicity, Hematologic toxicity, Hepatotoxicity, Nephrotoxicity, Neurologic toxicity, Ophthalmic toxicity, Pulmonary toxicity
Drug Interactions*	Risk C: Acetaminophen, Antibiotics, Corticosteroids, Desmopressin, Efgartigimod Alfa, Proton pump inhibitors, and Ketoconazole
Special Population	Older adults (≥ 75 years old)
Pregnancy	Based on information from animal reproduction studies and the mechanism of action, in utero exposure to nivolumab may cause fetal harm.
Lactation	It is not known if nivolumab is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends discontinuing breastfeeding during treatment and for 5 months after the last nivolumab dose.
Contraindications	There are no contraindications listed in the manufacturer's US labeling. Canadian labeling: Hypersensitivity to nivolumab or any component of the formulation

Monitoring Requirements	PD-L1 expression, hepatic (ALT, AST, and total bilirubin; kidney function, thyroid function, monitor blood glucose. Verify pregnancy status prior to treatment initiation. Monitor closely for signs/symptoms of immune-mediated adverse reactions. Monitor for signs/symptoms of infusion-related reactions. Hepatitis B virus (HBV) screening CBC with differential, serum chemistries, creatine kinase, comprehensive clinical assessment including performance status, weight, body mass index, comprehensive cardiac assessment; assess history of autoimmune conditions, organ-specific disease, endocrinopathies, neuropathy, and infectious disease; assess bowel habits, respiratory symptoms, skin (for rash), arthralgias, and neurologic symptoms.
Precautions	- Adverse reaction (immune mediated), Autoimmune disorders, Hematopoietic cell transplant, Multiple myeloma, myasthenia gravis, Polysorbate 80 content and Appropriate use
Black Box Warning	NA
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of nivolumab for the treatment of vulvar tumors.**

CONCLUSION STATEMENT – NIVOLUMAB

Nivolumab can be used as a second-line, for HPV-related advanced or recurrent/metastatic vulvar or vaginal cancers. Nivolumab monotherapy has been studied in a single-arm phase I/II CheckMate 358 trial enrolling a small cohort of 5

patients with recurrent or metastatic vaginal or vulvar cancer who were HPV-positive or had an unknown HPV status. The 6-month PFS was 40% and the 12- and 18-month OS rates for the combined cohort were 40% and 20%, respectively.

3.7.2 Pembrolizumab

Table 25. Pembrolizumab Drug Information

SCIENTIFIC NAME PEMBROLIZUMAB[12,23]	
Trade Name(s) on Saudi Market	KEYTRUDA
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered; data on vaginal and vulvar tumors are not available
FDA approved/off label	No
EMEA approved/off label	No
MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C51
Drug Class	Antineoplastic Agent
Drug Sub-Class	Immune Checkpoint Inhibitor, Anti-PD-1 Monoclonal Antibody
SFDA Registration Number (New)	KEYTRUDA: 2501233168 (100 mg)
ATC Code	L01XC
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	200 mg every 3 weeks or 400 mg every 6 weeks
Adjustment	Hepatic impairment: Moderate (total bilirubin > 1.5 to 3 times ULN and any AST) to severe (total bilirubin >3 times ULN and any AST) impairment: (has not been studied).
Maximum Daily Dose Adults*	N/A
Prescribing Edits*	MD, PA, ST, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A

G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	To be used in as second-line treatment in patients with advanced or recurrent/metastatic vulvar tumors that are TMB-high [TMB-H], PD-L1–positive, or MSI-high [MSI-H]/MMR deficient [dMMR].
QL (Quantity Limit):	N/A
ST (Step Therapy):	Advanced or recurrent/metastatic vulvar cancer: second-line or subsequent therapy in tumors that are TMB-high [TMB-H], PD-L1–positive, or MSI-high [MSI-H]/MMR deficient [dMMR].
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	Skin rash, hyperglycemia, hyperkalemia, hypertriglyceridemia, hypoalbuminemia, hyponatremia, hypophosphatemia, Constipation, diarrhea, Anemia, increased INR, leukopenia, increased serum alanine aminotransferase, increased serum alkaline phosphatase, increased serum aspartate aminotransferase, fatigue, musculoskeletal pain, increased serum creatinine, Cough, upper respiratory tract infection
Drug Interactions*	Risk X: Thalidomide Analogues
Special Population	N/A
Pregnancy	Pembrolizumab may cause fetal harm if administered during pregnancy.
Lactation	Breastfeeding should be discontinued during therapy and for 4 months following the last pembrolizumab dose. It is not known if pembrolizumab is present in breast milk.

Contraindications	There are no contraindications listed in the manufacturer's US labeling. *Canadian labeling:* Hypersensitivity to pembrolizumab or any component of the formulation.
Monitoring Requirements	PD-L1 expression; tumor specimen microsatellite instability-high (MSI-H) status, mismatch repair deficient (dMMR) status, mismatch repair proficient status, and/or tumor mutational burden-high (TMB-H) status. CBC with differential, serum chemistries, creatine kinase, LFTs, Scr, Thyroid function, and Blood glucose. Hepatitis B screening, blood cortisol (at baseline, prior to surgery, and as clinically indicated), and signs/symptoms of immune-mediated adverse reactions.
Precautions	- Adverse reactions (immune-mediated) - Infusion-related reactions - Autoimmune disorders - Hematopoietic stem cell transplant - Multiple myeloma - Myasthenia gravis - Polysorbate 80 - Appropriate use
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of pembrolizumab for the treatment of vulvar tumors.**

CONCLUSION STATEMENT – Pembrolizumab

Pembrolizumab is recommended for disease progression on or after chemotherapy in patients whose tumors express PD-L1 (combined positive score [CPS] ≥1) or for the treatment of patients with unresectable or metastatic tumor mutational burden-

high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

3.8 Tyrosine Kinase Inhibitors

3.8.1 Erlotinib

Table 26. Erlotinib Drug Information

Scientific Name Erlotinib[12,24]	
Trade Name(s) on Saudi Market	Tyrox, Erlotinib EPC, Erloz, Erlotinib SPC, Tarceva, Pulectus
SFDA Classification	Prescription
SFDA Approved Indication	Yes
FDA approved/off label	Yes
EMEA approved/off label	Yes
MHRA approved/off label	Yes
PMDA approved/off label	Yes
Indication (ICD-10)	C51
Drug Class	Antineoplastic Agent
Drug Sub-Class	Kinase Inhibitor
SFDA Registration Number (New)	Tyrox: 2611200295 Erlotinib SPC: 2701210477 Erlotinib EPC: 0703233340 Erloz: 1111211298 Tarveca: 0304233462 Pulectus: 190-172-18
ATC Code	Tyrox: L01XE03 Erlotinib SPC: L01XE03 Erlotinib EPC: QL01XE03 Erloz: L01XE03 Tarveca: L L01XE0301XE03 Pulectus: L01XE03
Pharmacological Class (ASHP)	Antineoplastic Agents
Pharmacological Sub-Class (ASHP)	Tumor growth inhibitor
Drug Information	
Dosage Form	Tablet

Route of Administration	Oral use
Dose (Adult) [DDD]*	N/A
Adjustment	Renal toxicity during treatment: Grades 3/4 renal toxicity: Withhold erlotinib and consider discontinuing. If erlotinib is resumed, reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤ grade 1. Hepatic Impairment: If total bilirubin >3 times ULN or transaminases >5 times ULN: Interrupt erlotinib and consider discontinuing. If erlotinib is resumed, reinitiate with a 50 mg dose reduction after bilirubin and transaminases return to baseline or ≤ grade 1. Discontinue if hepatotoxicity does not improve within 3 weeks.
Maximum Daily Dose Adults*	300 mg
Prescribing Edits (Appendix C)	AGE, MD, ST, PE
AGE (Age Edit):	Not approved for use in pediatric patients.
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Advanced or recurrent/metastatic vulvar cancer: second-line or subsequent treatment option.
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
Safety	
Main Adverse Drug Reactions (most common and most serious)	Most common: Diarrhea, Decrease Appetite, Chest pain, skin rash Most serious: Cerebrovascular (MI), GI perforation, hemolytic anemia

Drug Interactions*	Antacids: May decrease the serum concentration of Erlotinib, consider modification. Ciprofloxacin (Systemic): May increase the serum concentration of Erlotinib, consider therapy modification.
Special Population	N/A
Pregnancy	It crosses the placenta, therefore it can cause fetal harm if taken during pregnancy
Lactation	Unknown, lactating women should not breastfeed during treatment and for 2 weeks after the final erlotinib dose.
Contraindications	N/A
Monitoring Requirements	LFT, renal function, hydration status, ocular testing
Precautions	Cerebrovascular, ototoxicity, GI toxicity
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of erlotinib for the treatment of vulvar tumors.**

CONCLUSION STATEMENT – ERLOTINIB

Erlotinib is recommended in the second line for the management of advanced, metastatic, or recurrent vulvar carcinoma.

3.8.2 Larotrectinib

Table 27. Larotrectinib Drug Information

SCIENTIFIC NAME LAROTRECTINIB [12,25]	
Trade Name(s) on Saudi Market	Vitrakvi
SFDA Classification	Prescription
SFDA Approved Indication	No
FDA approved/off label	No

EMEA approved/off label	No
MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C51
Drug Class	Antineoplastic Agent
Drug Sub-Class	Tropomyosin Receptor Kinase (TRK) Inhibitor
SFDA Registration Number (New)	Vitrakvi 25 mg capsule: 2004200055 Vitrakvi 100 mg capsule: 2004200060 Vitrakvi 20 mg/mL solution: 2004200059
ATC Code	N/A
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Capsule; oral solution
Route of Administration	Oral
Dose (Adult) [DDD]*	100 mg twice daily (off-label)
Adjustment	<u>Renal impairment prior to treatment initiation</u>: No dosage adjustment necessary. <u>Hepatic impairment prior to treatment initiation</u>: - Mild impairment (Child-Pugh class A): No dosage adjustment necessary. - Moderate to severe impairment (Child-Pugh classes B and C): Reduce the initial larotrectinib dose by 50%. <u>Hepatic toxicity during treatment</u>: Grade 3 or 4 hepatic adverse reactions: Withhold larotrectinib until adverse reaction resolves to baseline or grade 1; if resolution occurs within 4 weeks, resume at the next lower dosage level. Discontinue permanently if the adverse reaction does not resolve within 4 weeks or if unable to tolerate larotrectinib after 3 dose reductions.
Maximum Daily Dose Adults*	N/A
Prescribing Edits*	MD, ST, PA, PE

AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	NTRK gene fusion-positive tumors.
QL (Quantity Limit):	N/A
ST (Step Therapy):	Advanced or recurrent/metastatic vulvar cancer: second-line or subsequent treatment option in NTRK gene fusion-positive tumors.
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: edema, rash, hypoalbuminemia, anemia, increased LFTs - Most serious: pneumonia, myasthenia
Drug Interactions*	CYP3A4 Inducers (Strong): May decrease the serum concentration of Larotrectinib (risk D). CYP3A4 Inhibitors (Strong): May increase the serum concentration of Larotrectinib (risk D). Grapefruit Juice: May increase the serum concentration of Larotrectinib (risk D).
Special Population	N/A
Pregnancy	Based the mechanism of action and available human and animal data, larotrectinib may cause fetal harm if administered to a pregnant female.
Lactation	It is not known if larotrectinib is present in breast milk. Due to the potential for adverse events in a breastfed infant, breastfeeding is not recommended during therapy and for 1 week after the final larotrectinib dose.

Contraindications	Known hypersensitivity to the product or its components
Monitoring Requirements	- LFTs (at baseline and periodically) - Pregnancy status - Hepatitis B screening prior to initiation
Precautions	- CNS effects - Fractures - Hepatotoxicity
Black Box Warning	N/A
REMS*	N/A

*Larotrectnib is approved by the FDA and the EMA for the treatment of solid tumors with NTRK gene fusion.

HEALTH TECHONOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of vulvar cancer treatment options by the following agencies/institutes/authorities: NICE, CADTH, and PBAC as applicable.

Table 28. Larotrectinib HTA Analysis

Medication	Agency	Date – HTA Recommendation
Larotrectinib	NICE[26]	**May 2020**: Larotrectinib is recommended for use within the Cancer Drugs Fund as an option for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumors in adults and children if: ▪ the disease is locally advanced or metastatic or surgery could cause severe health problems and ▪ they have no satisfactory treatment options. It is recommended only if the conditions in the managed access agreement for larotrectinib are followed.
	CADTH[27]	**September 2021:** Reimbursed by public drug plans for treating adult and pediatric patients with locally advanced or metastatic solid tumors who have a neurotrophic

		tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options, but only if certain conditions are met: ▪ reimbursed as single-agent therapy if it is prescribed by a clinician with expertise in the use of antineoplastic drugs. ▪ the cost is reduced.
	PBAC[28]	**March 2022**: The PBAC recommended the listing of Larotrectinib for the treatment of patients with tropomyosin receptor kinase (NTRK) fusion tumors that are either unresectable locally advanced, metastatic, or locally advanced and unsuitable for surgery.

CONCLUSION STATEMENT – LAROTRECTINIB

Larotrectinib is recommended as a second-line option for the management of advanced, metastatic, or recurrent vulvar carcinoma in the setting of biomarker directed therapy for NTRK gene fusion positive tumors.

3.8.3 Entrectinib

Table 29. Entrectinib Drug Information

SCIENTIFIC NAME ENTRECTINIB [12,29]	
Trade Name(s) on Saudi Market	Rozlytrek
SFDA Classification	Prescription
SFDA Approved Indication	No
FDA approved/off label	No
EMEA approved/off label	No
MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C51
Drug Class	Antineoplastic Agent
Drug Sub-Class	Tropomyosin Receptor Kinase (TRK) Inhibitor

SFDA Registration Number (New)	Rozlytrek 100 mg: 0301221550 Rozlytrek 200 mg: 0301221552
ATC Code	N/A
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Hard capsule
Route of Administration	Oral
Dose (Adult) [DDD]*	600mg daily
Adjustment	Renal impairment prior to treatment initiation: No dosage adjustment is necessary. Hepatic impairment prior to treatment initiation: No dosage adjustment is necessary. Hepatic toxicity during treatment: - Grade 3: Withhold entrectinib until recovery to ≤ grade 1 or to baseline; resume at the same dose if recovery occurs within 4 weeks. Permanently discontinue entrectinib if recovery does not occur within 4 weeks. For recurrent grade 3 toxicity, resume at a reduced dose if toxicity resolves within 4 weeks. - Grade 4: Withhold entrectinib until recovery to ≤ grade 1 or to baseline; resume at a reduced dose if recovery occurs within 4 weeks. Permanently discontinue entrectinib if recovery does not occur within 4 weeks. Permanently discontinue for recurrent grade 4 toxicity. - ALT or AST >3 times ULN with concurrent total bilirubin >1.5 times ULN (in the absence of cholestasis or hemolysis): Permanently discontinue entrectinib.
Maximum Daily Dose Adults*	N/A
Prescribing Edits*	MD, ST, PA, PE
AGE (Age Edit):	N/A

CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by an oncologist
PA (Prior Authorization):	NTRK gene fusion-positive tumors.
QL (Quantity Limit):	N/A
ST (Step Therapy):	Advanced or recurrent/metastatic vulvar cancer: second-line or subsequent treatment option in NTRK gene fusion-positive tumors.
EU (Emergency Use):	N/A
PE (Protocol Edit):	To be used as part of a treatment protocol
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: edema, fatigue, dizziness, hyperuricemia, hypernatremia, anemia, dyspnea - Most serious: pulmonary embolism, cardiac failure, myocarditis, suicidal ideation
Drug Interactions*	CYP3A4 Inducers (Moderate/Strong): May decrease the serum concentration of Entrectinib (Risk X) CYP3A4 Inhibitors (Moderate/Strong): May increase the serum concentration of Entrectinib (Risk D) Domperidone: QT-prolonging agents may enhance the QTc-prolonging effect of Domperidone (Risk D) Grapefruit juice: May increase the serum concentration of Entrectinib (Risk X) Levoketoconazole/Posaconazole: QT-prolonging CYP3A4 Substrates may enhance the QTc-prolonging effect of Levoketoconazole (Risk X)
Special Population	N/A
Pregnancy	Based on the mechanism of action and data from animal reproduction studies, in utero exposure to entrectinib may cause fetal harm.

Lactation	It is not known if entrectinib is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during therapy and for 7 days after the last entrectinib dose.
Contraindications	Known hypersensitivity to the product or its components
Monitoring Requirements	NTRK gene fusion status prior to initiation LFTs (at baseline and periodically) Left ventricular ejection fraction prior to initiation Pregnancy status prior to initiation Hepatitis B screening
Precautions	- Cardiac effects - CNS effects - Fractures - Hepatotoxicity - Hyperuricemia - Ocular toxicity - QT interval prolongation
Black Box Warning	N/A
REMS*	N/A

*Entrectinib is approved by the FDA and the EMA for the treatment of solid tumors with NTRK gene fusion.

HEALTH TECHONOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of vulvar cancer treatment options by the following agencies/institutes/authorities: NICE, CADTH, and PBAC as applicable.

Table 30. Entrectinib HTA Analysis

Medication	Agency	Date – HTA Recommendation
Entrectinib	NICE[30]	**August 2020**: Entrectinib is recommended for use within the Cancer Drugs Fund as an option for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-

		positive solid tumors in adults and children 12 years and older if: ▪ the disease is locally advanced or metastatic or surgery could cause severe health problems and ▪ they have not had an NTRK inhibitor before and ▪ they have no satisfactory treatment options. It is recommended only if the conditions in the managed access agreement for entrectinib are followed.
	HAS[31]	**July 2021:** Unfavorable opinion for reimbursement in adult and pediatric patients 12 years of age and older with solid tumors expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, who have not received a prior NTRK inhibitor, and who have no satisfactory treatment options.
	IQWIG[32]	**November 2020:** The data presented by the company are insufficient in the preparation presented with the dossier and are not suitable for the benefit assessment of entrectinib.

CONCLUSION STATEMENT – ENTRECTINIB

Entrectinib is recommended as a second-line option for the management of advanced, metastatic, or recurrent vulvar carcinoma in the setting of biomarker directed therapy for NTRK gene fusion positive tumors.

Section 4.0 Key Recommendations Synthesis

In general, management of vaginal and vulvar cancers depends on the stage of the disease and will typically include surgery, radiation therapy, chemotherapy, and chemoradiation. Details on the treatment options can be found in tables 31 (vaginal cancer) and 32 (vulvar cancer).

Table 31. Treatment Options for Vaginal Cancer

Stage (FIGO Staging System)		Treatment Options
FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; SCC = squamous cell carcinoma; VaIN = vaginal intraepithelial neoplasia.		
VaIN		Laser therapy
		Wide local excision
		Vaginectomy
		Intravaginal chemotherapy
		Intracavitary radiation therapy
		Imiquimod
Stage I vaginal cancer	SCC	Radiation therapy
		Surgery
	Adenocarcinoma	Surgery
		Radiation therapy
		Combined local therapy
Stages II, III, and IVa vaginal cancer (SCC and adenocarcinoma)		Radiation therapy
		Surgery
		Chemoradiation
Stage IVb vaginal cancer (SCC and adenocarcinoma)		Radiation therapy

Table 32. Treatment Options for Vulvar Cancer

Stage (FIGO Staging Criteria)	Treatment Options
VIN	Surgery
	Topical imiquimod
Stages I and II vulvar cancer	Surgery
	Surgery and radiation therapy
	Radiation therapy alone
Stage III vulvar cancer	Surgery with or without radiation therapy
	Radiation therapy or chemoradiation therapy followed by surgery
	Radiation therapy with or without chemotherapy
Stage IVA vulvar cancer	Surgery
	Surgery and radiation therapy
	Radiation therapy or chemoradiation therapy followed by surgery
	Radiation therapy with or without chemotherapy
Stage IVB vulvar cancer	Chemotherapy
Recurrent vulvar cancer	Wide local excision with or without radiation therapy
	Radical vulvectomy and pelvic exenteration
	Synchronous radiation therapy and cytotoxic chemotherapy with or without surgery

Platinum-based regimens, in combination with radiation therapy, are considered first-line treatment options. In vulvar cancer, primary chemoradiation may confer a survival benefit over primary RT. Agents recommended for chemoradiation include cisplatin (preferred) and carboplatin if the patient is intolerant to cisplatin. Cisplatin/fluorouracil is also an option. In addition, if cisplatin or carboplatin are unavailable, capecitabine/mitomycin, gemcitabine, and paclitaxel are options that may be considered. These radiosensitizers were added based on a few early-phase studies extrapolated from cervical cancer that have shown their efficacy and tolerability when administered concomitantly with radiation.

Due to the rarity of vulvar cancer, especially advanced disease, prospective randomized trials on adjuvant therapy are extremely limited. Much of the common adjuvant treatment approaches have been drawn from studies describing heterogenous, often-individualized treatment approaches, or extrapolated from effective adjuvant therapies for cervical and anal cancers.

Section 5.0 Conclusion

The recommendations provided in this report are intended to assist in the **management of vaginal and vulvar cancers**. These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 7.0 Appendices

Appendix A. Prescribing Edits Definition

Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Level of Evidence Description

I. Level of Evidence Adopted

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

II. NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category C	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

All recommendations are category 2A unless otherwise indicated.

III. NCCN Categories of Preference

Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

IV. ESTRO/ESGO/SIOPe Guidelines Levels of Evidence

Levels of Evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grades of Recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

V. Japan Society of Gynecologic Oncology

Quality of Evidence	
Level I	Meta-analysis of multiple randomized controlled trials
Level II	Randomized controlled trials or well-designed non-randomized controlled trials
Level III	Well-designed quasi-experimental studies, comparative studies, correlation studies, case-comparison studies, or other well-designed non-experimental descriptive studies
Level IV	Reports and opinions of specialized committees or clinical experiences of authoritative persons
Grades of Recommendations	
A	Action is strongly recommended In principle at least one Level I item of evidence indicating efectiveness is present
B	Action is recommended In principle at least one Level II item of evidence indicating efectiveness is present
C1	Action may be considered, but scientifc grounds are not yet sufcient (Alternatively, scientifc grounds are not yet sufcient, but the possibility exists that efectiveness can be expected) Multiple Level III items of evidence indicating efectiveness are present, and results are generally consistent
C2	Scientifc grounds are not sufcient and application in routine treatment is not recommended
D	Action is not recommended Usefulness/efectiveness is not evident, and indeed the treatment may be harmful
In addition to the question of evidence, recommendation Grade A can be applied based on judgment on the level of general common sense. Because evidence is extremely sparse in the case of rare diseases, recommendation grades are decided based on the judgment of the Drafting Committee	

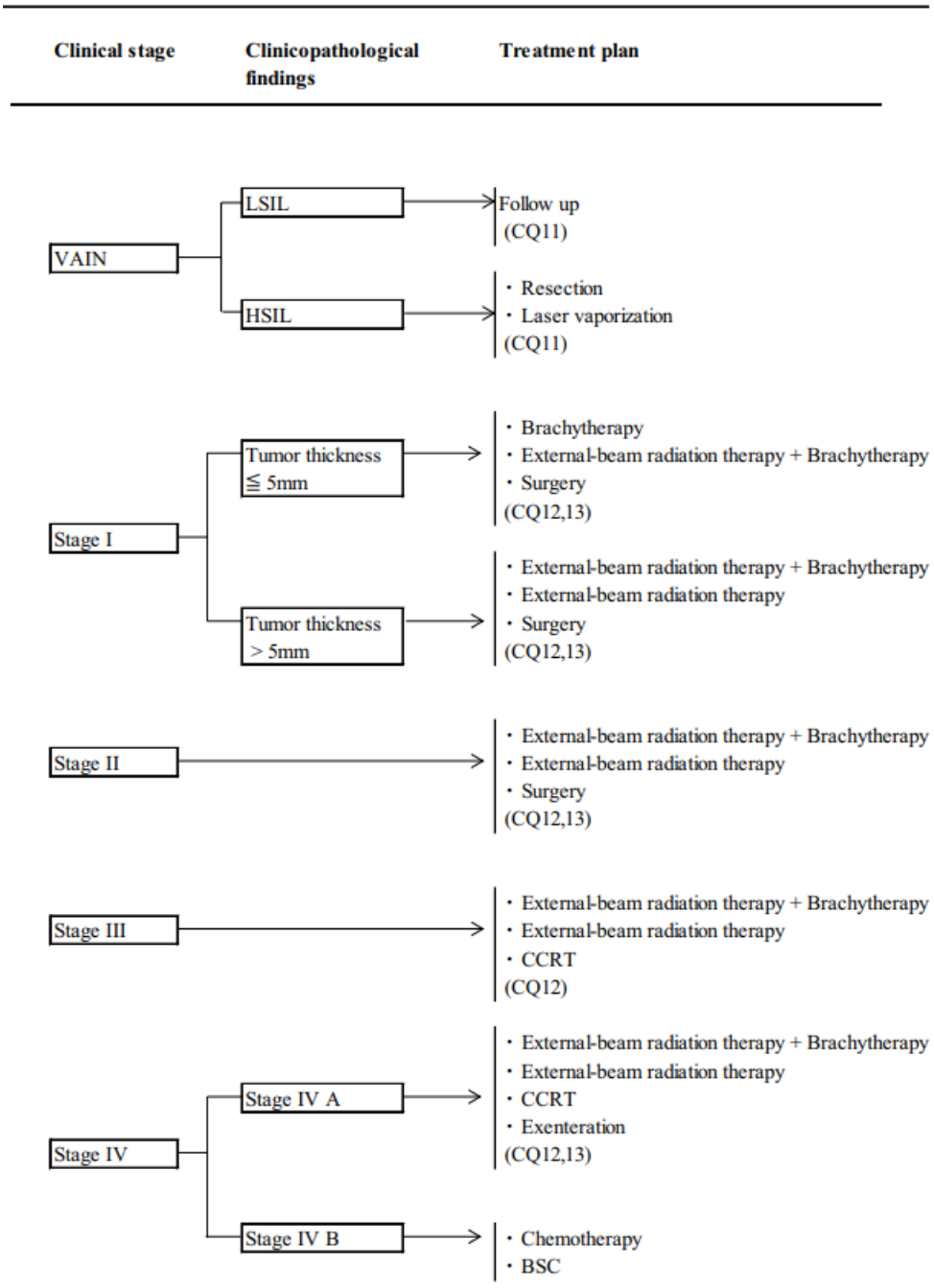
Appendix C. PubMed Search Details

The following is the result of the PubMed search conducted for vaginal and vulvar cancers guideline search:

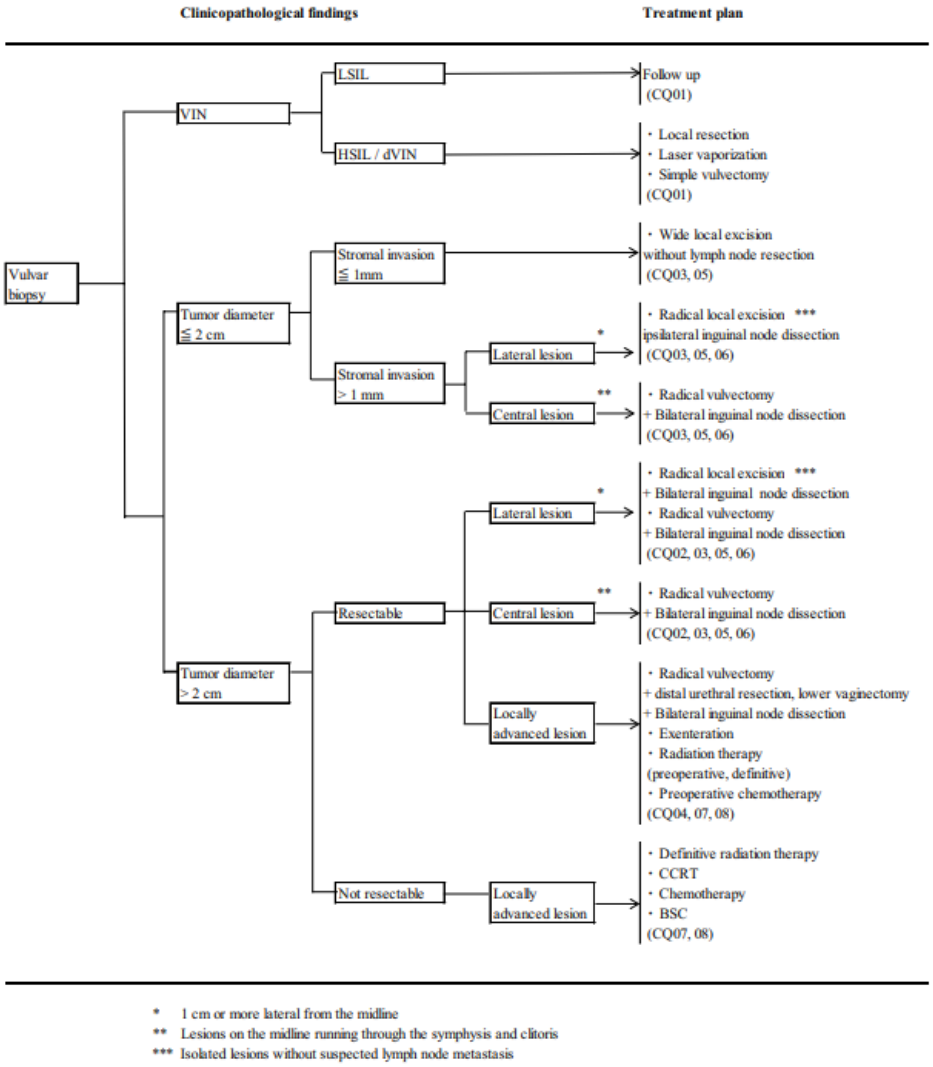
Query	Filters	Search Details	Results
((vaginal) AND (cancer)) NOT (cervical)	Guideline, in the last 10 years	((vaginal) AND (cancer)) NOT (cervical)AND ((y_10[Filter]) AND (guideline[Filter]))	31
((vulvar) AND (cancer)) NOT (cervical)	Guideline, in the last 10 years	((vaginal) AND (cancer)) NOT (cervical)AND ((y_10[Filter]) AND (guideline[Filter]))	16

Appendix D. Treatment Algorithms

Primary treatment for vaginal cancer (retrieved from the JSGO 2015 guideline)



Primary treatment for vulvar cancer (retrieved from the JSGO 2015 guidelines)



* 1 cm or more lateral from the midline
** Lesions on the midline running through the symphysis and clitoris
*** Isolated lesions without suspected lymph node metastasis