
# Final PMB definition guidelines for vaginal and vulvar cancer, excluding vulvar or vaginal melanoma

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DISCLAIMER

The vaginal and vulvar cancer benefit definition has been developed for the majority of standard patients. The benefit definition is subject to the provisions of Regulations 15H and 15I. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetist drugs and nursing care. However, these interventions form part of care and are prescribed minimum benefits.

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ABBREVIATIONS

| | | |
|---|---|---|
| PMBs | - | Prescribed minimum benefits |
| DTPs | - | Diagnosis treatment pairs |
| CMS | - | Council for medical schemes |
| SCC | - | Squamous cell carcinoma |
| ISSD | - | International society for the study of vulvovaginal disease |
| LSIL | - | Low-grade squamous intraepithelial lesion |
| HPV | - | Human papilloma virus |
| VIN | - | Vulvar intraepithelial neoplasia |
| VaIN | - | Vaginal intraepithelial neoplasia |
| FBC | - | Full blood count |
| UEC | - | Urea, electrolytes and creatinine |
| CD4 | - | Cluster of Differentiation 4 |
| FIGO | - | International Federation of Gynecology and Obstetrics |
| CT | - | Computer tomography |
| FDG-PET/CT | - | Positron Emission Tomography–Computed Tomography |
| MRI | - | Magnetic Resonance Imaging |
| EUA | - | Examination-under-anaesthesia |
| EBRT | - | External-beam radiation therapy |

## 1. INTRODUCTION

1.1. Legislation governing the provision of prescribed minimum benefits (PMBs) is contained in the regulations enacted by the Medical Schemes Act 131 of 1998 (hereafter called 'the Act'). Medical scheme beneficiaries sometimes find it difficult to establish their entitlements beforehand in respect of some of the diagnosis treatment pairs (DTPs). Additionally, medical schemes interpret these benefits differently – resulting in a lack of uniformity regarding benefit entitlements.

1.2. The benefit definition project is undertaken by the CMS with the aim of defining the PMB package, as well as to guide the interpretation of the PMB provisions by relevant stakeholders.

## 2. SCOPE AND PURPOSE

2.1. This is a recommendation for the diagnosis, treatment and care of individuals with vaginal and vulvar cancer in any clinically appropriate setting as outlined in the Act.

2.2. The purpose is to provide detailed clarification in respect of benefit and entitlements to members and beneficiaries of medical schemes.

2.3. Where there is any difference in the management of vaginal or vulvar cancers, this is specified. If not specified, it can be assumed that this will be the same for both conditions.

*Table 1: Possible ICD10 codes for identifying vulvar and vaginal cancer*

| ICD 10 code | WHO description |
|---|---|
| C51.0 | Malignant neoplasm, labium majus |
| C51.1 | Malignant neoplasm, labium minus |
| C51.2 | Malignant neoplasm, clitoris |
| C51.8 | Malignant neoplasm, overlapping lesion of vulva |
| C51.9 | Malignant neoplasm, vulva, unspecified |
| C52 | Malignant neoplasm of vagina |
| C57.7 | Malignant neoplasm, other specified female genital organs |
| C57.8 | Malignant neoplasm, overlapping lesion of female genital organs |
| C57.9 | Malignant neoplasm, female genital organ, unspecified |
| D07.1 | Carcinoma in situ, vulva |
| D07.2 | Carcinoma in situ, vagina |
| D07.3 | Carcinoma in situ other and unspecified female genital organs |

2.4. The CMS acknowledges that some patients will not qualify for PMB entitlements under the definition of treatable cancers as outlined in explanatory note 3, Annexure A of the Act. In these instances, when the treatment intent is no longer curative, DTP 260S may be applied, depending on the clinical case.

*Table 2: Applicable PMB code for a non-curative setting in vaginal and vulvar cancer*

| PMB Code | PMB Description | | ICD10 Code | ICD10 Description |
|---|---|---|---|---|
| 260S | # Imminent death regardless of diagnosis | # Comfort care; pain relief; hydration | Z51.5 | Palliative care |

## 3. EPIDEMIOLOGY AND BURDEN OF DISEASE

3.1. Vulvar cancer is rare worldwide with an incidence rate that increases with age. Vulvar cancer is the fourth most common gynecologic cancer and constitutes 2%-5% of all gynecologic (Siegel, Naishadham & Jemal, 2013; Rogers & Cuello, 2018). An increasing incidence has been reported, especially among those aged between 35 and 40 (Butt & Botha, 2017). The worldwide burden of vulvovaginal cancer is likely thought to continue increasing.

3.2. Vaginal cancer is also an uncommon disease, with primary vaginal cancer contributing to 3% of malignant neoplasms of the female genital tract (Bailey & Luesley, 2013; Berek & Hacker, 2010; Fu, 2002; Palmer & Gillespie, 2010; Rogers & Cuello, 2018; Siegel et al., 2013).

3.3. The estimated incidence of invasive vaginal cancer is 0.42 per 100.000 women and has remained relatively unchanged since the 1980s (Di Donato et al., 2012). The age-standardizsd incidence rate of vaginal and vulvar cancer is 1.5 women per 100 000, where the age-standardised mortality rate is 6.05 per 100 000 (Buttmann-Schweiger et al, 2015). Only about 1 of every 1,100 women will develop vaginal cancer in her lifetime.

3.4. Vulvovaginal cancer can be classified into two groups according to predisposing factors; human papillomavirus (HPV) associated and that which is not HPV associated (Alkatout et al., 2015). An increase in vulvar cancer in young women is attributed to infection with oncogenic human papillomavirus (HPV).

3.5. The disease stage of vaginal or vulvar cancer is the major prognostic factor in terms of the ultimate outcome. The rate of survival, distant metastasis and local control are strongly correlated with tumour stage. The overall five-year survival is 70% (Di Donato et al., 2012).

## 4. PATHOLOGY OF VULVAR AND VAGINAL CANCER

### 4.1. Vulvar Intraepithelial Neoplasia (VIN)

4.1.1. Vulvar cancer has several histological subtypes with approximately ninety percent being squamous cell carcinoma (SCC). Other less frequent histologies include extramammary Paget's disease, Bartholin gland adenocarcinoma, verrucous carcinoma, basal cell carcinoma, and sarcoma (Gunther et al., 2012).

4.1.2. An International Society for the study of Vulvovaginal Disease (ISSD) revision of terminology has characterised vulvar intraepithelial neoplasia into low-grade squamous intraepithelial lesion (LSIL), squamous intraepithelial lesions (HSIL) and differentiated VIN (Bornstein et al., 2016, 2016). Similar to cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia is traditionally graded from VIN I to VIN III, with LSIL corresponding to HPV and VIN I, whereas HSIL corresponds to VIN II and VIN III.

4.1.3. Infections with human papilloma virus (HPV) have been linked to the development of a number of cancers including vulvar, vaginal and cervical, anal cancer (Chung & Gillison, 2009; Fakhry et al., 2012). Vulvar cancer can be subdivided into two clinically distinct types of HPV independent and HPV dependent types (Alonso et al, 2011). These subcategories of vaginal cancer are clinically distinct regarding response to treatment and survival outcome, with HPV positivity as a favourable prognostic biomarker (Chung et al., 2009 & Fakhry et al, 2009).

4.1.4. LSIL and HSIL are attributable to HPV infections whereas differentiated VIN is related to chronic inflammation known as lichen sclerosis (Almadrones-Cassidy, 2010). Separation is not always possible as patients can have both HPV infection and lichen sclerosis, although immunohistochemistry (e.g. p16 and p53) may aid in the differentiation. As with HPV, underlying lichen sclerosis can influence the choice of treatment for either vulvar or vaginal cancer. Lichen sclerosis is a chronic inflammatory dermatosis commonly presenting in the anogenital region of postmenopausal women and older women, and has a 3% to 5% risk of progression to vulvar cancer (Neill, Tatnall & Cox, 2002). Besides the HPV infection's involvement, other risk factors include the number of lifetime sexual partners, history of sexually transmitted disease, cigarettes smoking and past abnormal pap smear results (Gershenson & McGuire, 1988).

4.1.5. Vulvar cancers attributable to the human papilloma virus (HPV) infection range has been estimated at between 30% and 69% (Gallison, Chaturvedi & Lowy, 2008; Watson et al., 2008 & Gargano et al., 2012). Human papillomavirus (HPV) is reported as present in approximately 40% of vulvar carcinomas, with HPV 16 accounting for most HPV-positive cases (Bornstein et al., 2016).

### 4.2. Vaginal Intraepithelial Neoplasia (VaIN)

4.2.1. Squamous cell cancer (SCC) accounts for approximately 85% of vaginal cancer cases and a squamous cell intraepithelial lesion of the vagina falls within the more general category known as vaginal intraepithelial neoplasia (VaIN). VaIN is defined by the presence of squamous cell atypia without invasion and is graded according to the thickness of epithelial involvement (Smith et al., 2009).

4.2.2. Intraepithelial neoplasms of the vagina are less frequent than those of the cervix, accounting for 0.4% to 0.5% of all intraepithelial neoplasms of the female lower genital tract (Brown et al, 2005).

## 5. SCREENING OF VULVAR AND VAGINAL CANCER

5.1. There is no evidence to support screening strategies for the prevention of vaginal and vulvar cancer (Hacker, N.F., Eifel, P.J. and van der Velden, 2012).

5.2. Routine screening for vaginal cancer following hysterectomy for benign disease is also not recommended as these women are at extremely low risk of developing vaginal cancer. However, women with a history of cervical intraepithelial or invasive neoplasia are at an increased risk, but regular cytologic screening gives a low yield (Orr, Leath & Barnett, 2011).

5.3. Screening for vulvar and vaginal cancer is not currently recommended as PMB level of care.

## 6. DIAGNOSTIC INVESTIGATIONS FOR VAGINAL AND VULVAR CANCERS

### 6.1. Consultations

6.1.1. The presentation of vulvar cancer can be widely varied. Clinical features strongly indicating vulvar cancer include an irregular, fungating mass, an irregular ulcer or enlarged groin nodes. In patients with HPV-negative tumours, vulvar cancer often presents as a single mass or ulcer on the labia majora or minora. In HPV-positive tumours, multifocal lesions and concurrent cervical neoplasia are more common.

6.1.2. Diagnosis of vulvovaginal cancers is confirmed by a gynaecologist who then refers the patient to an oncologist. The consultations recommended below include the diagnosis, staging and risk assessment of a patient with vulvovaginal cancer.

*Table 3: Recommended consultations for the diagnosis, staging and risk assessment of vaginal and vulvar cancers cancer*[1]

| Treating provider | Number of consultations |
|---|---|
| GP or physician | 1 |
| Specialist (Gynaecologist / Gynaecology oncologist / Oncologist/ Surgeon ) | 4 |

[1] Please note that this will depend on the patients specific clinical circumstances. This is just a recommended minimum, for diagnosis and the staging phase.

### 6.2. Histopathology

6.2.1. Detection of VIN and VaIN are histologic diagnoses based upon vulvar or vaginal biopsy and a biopsy is recommended as PMB level of care.

6.2.2. Vulvar and vaginal intraepithelial neoplasia share many of the clinical and histologic features of cervical intraepithelial neoplasia. Histologically, these lesions are characterised by disruption of the normal epithelial architecture with various degrees of cytoplasmic and nuclear maturation (Alkatout et al., 2015).

6.2.3. Special stains are not done routinely and hence not recommended as PMB level care. However, immunohistochemistry may sometimes be performed not only to distinguish between lichen sclerosis related VIN vs HPV related VIN but may also sometimes be performed to distinguish between VIN I and VIN II.

### 6.3. Laboratory investigations

Once a diagnosis of vaginal and vulvar cancer is suspected, initial laboratory investigation workup should include:

- Full blood count (FBC) including platelets
- Liver and renal function tests
- Urea, electrolytes and creatinine (UEC)
- HIV diagnostic test. A CD4 T-cell count and an HIV viral load will be required if not already done within the previous 6 months

## 7. STAGING AND RISK ASSESSMENT FOR VAGINAL AND VULVAR CANCERS

### 7.1. Staging for vulvar cancer

Vulvar and most vaginal cancers are staged using the American Joint Committee on Cancer TNM staging system and the International Federation of Gynecology and Obstetrics (FIGO) staging systems (Pecorelli, 2009 & Edge, Byrd, Compton, Fritz, Greene & Trotti, 2010) as shown in the table below. These staging systems are very similar and are based on size, spread to regional contiguous organs or regional lymph nodes (Alkatout et al., 2015; Almadrone-Cassidy, 2011).

The TNM system classifies the diseases in Stages 0 through IV depending on the extent of the tumour (T), whether cancer has spread to lymph nodes (N) and whether it has spread to distant sites (M) for metastasis. The risk of nodal metastasis increases with the stage of disease, the size of the lesion, and the depth of invasion, (Creasman, Phillips & Menck,1997; Al-Najar, Alkatout & Al-Sanabani, 2011) and these are the most important prognostic factors for vulvar cancer (Alkatout et al., 2010).

*Table 4: FIGO staging for vulvovaginal cancer*

| FIGO stage | Description |
|---|---|
| I | Tumor confined to the vulva/vagina |
| IA | Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.00 mm[a], no nodal metastasis. |
| IB | Lesions > 2cm in size with stromal invasion > 1.00 mm[a], confined to the vulva or perineum, with negative nodes. |
| II | Tumor of any size with extension to adjacent perineal structures(lower third of urethra, lower third of vagina, anus) with negative nodes. |
| III | Tumor of any size with extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with positive inguinofemoral nodes. |
| IIIA | 1. With1lymphnodemetastasis(≥5mm), or<br>2. With1–2lymphnodemetastasis(es)(<5mm) |
| IIIB | 1. With2ormorelymphnodemetastases(≥5mm), or<br>2. With3ormorelymphnodemetastases(<5mm) |
| IIIC | With positive nodes with extracapsular spread |
| IV | Tumor invades other regional (upper 2/3 urethra, upper2/3 vagina), or distant structures |
| IVA | Tumor invades any of the following:<br>1. upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed pelvic bone or<br>2. fixed or ulcerated inguinofemoral lymph nodes |
| IVB | Any distant metastasis including pelvic lymph nodes |

[a]The depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

## 7.2. Imaging radiology for a staging and risk assessment for vaginal and vulvar cancers

7.2.1. Imaging radiology is only for staging purposes and not diagnostic.

7.2.2. Imaging tests are therefore only done once a diagnosis is confirmed.

7.2.3. Computer tomography (CT) of the chest/abdomen/pelvis, fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) are recommended as PMB level of care (Kataoka et al., 2010, Cohn et al., 2002; Kamran et al., 2014; Peiro, 2013; Robertson et al.,2016).

7.2.4. FDG-PET/CT scan can depict metabolically active tissue that may be present in the absence of definite structural abnormalities detected with conventional imaging, including CT and MRI. Its sensitivity and specificity in identifying vulvar cancer lymph node metastases has been reported at 80% and 90% respectively (Cohn et al., 2002). PET scan is recommended as PMB level of care for staging of patients with vulvar carcinoma considered for surgery (Vorster et al., 2016).

7.2.5. Very few studies, however, have reported on FDG-PET/CT in the staging of vaginal cancer. However, vaginal cancer should be staged the same as a vulva or cervical cancer so a squamous vaginal cancer would be best staged with a PET/CT for nodes.

7.2.6. MRI is useful in delineating tumour size and extent and is more sensitive than physical examination in assessing paravaginal or parametrial involvement in patients with cervical cancer. Pelvic MRI aids in surgical and/or radiation treatment planning and can be considered as PMB level of care (Kataoka et al., 2010; Bipat et al., 2003; Hricak et al.,2005).

*Table 5: Recommended imaging radiology for staging and risk assessment for vaginal and vulvar cancers*

| Description | Comment (When necessary) |
|---|---|
| Ultrasound: abdominal / pelvic and / or transvaginal | |
| Chest x-ray | |
| CT chest, abdomen and pelvis | |
| Bone scan | Not routine in vulvar or vaginal cancer as a CT scan can show evidence of sclerotic involvement; on motivation only if clinically indicated. |
| PET scan | Whole body PET/CT on motivation on a case by case basis for T2 or larger tumours or if nodal or distant metastasis is suspected in vulvar carcinoma (Robertson et al., 2016). |
| MRI abdomen and pelvis | MRI is useful in delineating tumour size and extent for surgical candidates (Bipat et al., 2003 & Hricak et al., 2005) |

7.3. Procedures for staging and risk assessment for vaginal and vulvar cancers

7.3.1. Examination-under-anaesthesia (EUA) cystoscopy or proctoscopy are recommended as PMB level of care and should be considered as indicated (Coppleson 1986; Khan 2007).

7.3.2. Patients with previous hysterectomy and abnormal cytologic findings should also undergo vaginal colposcopy (Darragh et al, 2012).

7.3.3. Proctosigmoidoscopy and fine needle aspiration FNA) are recommended as PMB level of care.

*Table 6: Procedures recommended as PMB level of care for staging of vaginal and vulvar cancers*

| Description |
|---|
| Cystoscopy / proctoscopy |
| Proctosigmoidoscopy |
| Pap smear +/- biopsy of cervix |
| Bailey & Luesley, 2013). |

## 8. Treatment options

Surgery is the most common treatment for vulvar cancer, regardless of the stage of the cancer. The goal is to remove all cancer without any loss of sexual function. Some patients may need more than one type of treatment in combination (Bailey & Luesley, 2013).

### 8.1. Recommended surgical procedures for vulvar and vaginal cancer

Due to their anatomical setting and histological similarity of the vulva and vagina, some procedures are similar in the early stage of vulvar or vaginal cancer.

#### 8.1.1. Recommended surgical procedures for early vulvar and vaginal cancer

8.1.1.1. Wide local excision – an excision with 1cm disease free margin around the lesion to prevent recurrence (Rogers & Cuello, 2018). Nearby lymph nodes may also be removed and examined for signs of cancer cells (Hacker, Eifel & Van Der Velden, 2012; Alkatout et al,2015).

8.1.1.2. Radical local excision – performed at this stage for both vulvar and vaginal cancer. This is a surgical procedure to remove the cancer and a large amount of normal tissue around it. This excision should also observed 1cm disease free margin. Nearby lymph nodes in the groin may also be removed (Roswell, 2017 ; Alkatout et al., 2015).

8.1.1.3. Pelvic exenteration – this is a surgical procedure to remove the lower colon, rectum, and bladder. The cervix, vagina, ovaries, and nearby lymph nodes are also removed. Artificial openings (stoma) are made for urine and stool to flow from the body into a collection bag. It may be performed on patients with advanced primary or recurrent vulvar or vaginal cancer who do not have the option of treatment with radiation therapy (Diver, Rauh-Hain & del Carmen, 2012).

8.1.1.4. Lymph node dissection – evidence suggests that sentinel node dissection, performed by a multidisciplinary team, should be part of the standard treatment in selected patients with early-stage vulvar cancer or vaginal cancer (Van Der Zee et al., 2008; Higgins, 2016). Moreover, recent national and international studies continue to prove the value of sentinel lymph node technology, which is moving toward a new standard of care for women with early stage vulvar cancer or vaginal cancer. Two trials [GROINSS-V-I and GOG-273] have set sentinel node mapping in vulvar cancer as the standard of care based on adequate detection rate and reduced morbidity compared with inguinofemoral lymphadenectomy (Ramirez & Levenback, 2016).

#### 8.1.2. Specific procedures for early vulvar cancer

8.1.2.1. Modified (or partial) radical vulvectomy – this is surgery to remove part of the vulva, including the clitoris, vaginal lips, and the opening to the vagina and sometimes lymph nodes in the groin area.

8.1.2.2. Vulvar reconstructive surgery is done when large parts of the vulva and surrounding area are lost as a result of vulvar surgery (Saito et al., 2015).

8.1.3. Specific procedures for early vaginal cancer

8.1.3.1. Vaginectomy (partial or total) is when the vagina is removed, and in some cases also the surrounding supporting tissue (radical vaginectomy).

8.1.3.2. Hysterectomy (vaginal or abdominal): During this type of vaginal cancer surgery, the cervix and the uterus are removed. In a radical hysterectomy, all of the surrounding tissue (the parametria), the upper part of the vagina and the lymph nodes in the pelvis are removed as well. For young women, the ovaries may be left behind to preserve ovarian function.

8.1.3.3. Vaginal reconstruction: In cases where the vagina must be removed, tissues from other parts of the body can be used to reconstruct a new vagina. These may be skin, intestinal tissue, or myocutaneous (muscle and skin) grafts.

8.2. Recommended surgical procedure for advanced vulvar cancer ( FIGO III-IV stage)

8.2.1. Advanced vulvar cancer includes tumours that extend beyond the vulva, and or where there are bulky positive groin nodes (Rodgers & Cuello, 2018). Its management involves a multidisciplinary team. The status of the groin nodes should be determined before treatment is planned.

8.2.2. Radical wide local excision with a disease-free margin of at least 1cm around the lesion. This is a surgical procedure to remove the cancer and a large amount of normal tissue around it (Rogers & Cuello, 2018).

8.2.3. In advanced vulvar cancer, the excision of the primary tumor with clear surgical margins and without sphincter damage is the treatment of choice. It remains important to palliate symptoms such as local pain and offensive discharge (Rogers & Cuello, 2018; Almadrones-Cassidy, 2010).

8.2.4. In the presence of negative nodes, bilateral inguinal lymphadenectomy is performed. The current standard involves resection of the primary tumor and lymph nodes through separate incisions. This approach allows better healing compared with en bloc resection of the vulva and groins (Rogers & Cuello, 2018).

8.2.5. In presence of positive nodes, removal of enlarged groin and pelvic nodes is considered (Rogers & Cuello, 2018).

8.3. Recommended surgical procedures for an advanced stage of vaginal cancer (FIGO stage III & IV)

8.3.1. For Stage III disease, a pelvic exenteration or a combination of radiation and exenteration may be considered. However, a combination of external-beam radiation therapy is usually adopted.

8.3.2. For Stage IV, exenteration with vaginal reconstruction using gracilis myocutaneous flap or rectus abdominus myocutaneous may be the treatment of choice for patients with a good medical condition who do not have distant spread (Di Donato et al, 2012).

*Table 7: PMB level of care for surgical management of vulvar and vaginal cancer*

| Vulva | Vagina | Comment |
|---|---|---|
| Wide local excision / radical excision | | Surgery is the preferred primary treatment of vulvovaginal carcinoma if feasible with 1cm disease free margin. |
| Lymph node dissection | | Reduce mortality in early vulvar cancer. |
| | Hysterectomy | Surgical management of stage I disease. |
| Pelvic exenterating | | Mainly on patients with advanced primary or recurrent vulvar or vaginal cancer who do not have the option of treatment with radiation therapy. |
| | Radical hysterectomy | Surgical management of stage I disease. |
| Excision of the secondary lesion(s) in advanced cancer | | |
| Vulvectomy (partial / radical) | Vaginectomy (partial / radical) | Management of the disease of stage I & II. To prevent local recurrence. |
| Skin flaps and reconstruction | | For large lesions in palliative management. |
| Urine diversion | | Palliative management of recurrent or advanced disease. |
| Lymphoscintigram with/without Sentinel lymph node biopsy– including methylene blue | | Included if there are clinically negative nodes. |
| Completion surgery | | After radiotherapy if there is residual disease. |

8.4. Radiation therapy (RT)

The risk of local and regional recurrence and occasionally, a lack of surgical candidacy have ensured a dominant role of radiotherapy in ultimate curative treatment programs. RT has a major role in curative treatment of vulvar cancer patients in both postoperative and preoperative settings (Gaffney et al., 2016). Concurrent chemotherapy is offered in neoadjuvant and definitive cases based on TN stage. Early stage disease does not require concurrent chemotherapy.

The indications of adjuvant radiation in postoperative setting are (Almadrones-Cassidy, 2010):

- Positive surgical margin
- Surgery margin less than 8mm
- One or more positive inguinal lymph nodes >5mm
- Grossly positive inguinal lymph nodes
- Capsular nodal extension

8.4.1. Neo-adjuvant radiotherapy for vulvar and vaginal cancers

8.4.1.1. The concept of primary chemoradiation as a neoadjuvant therapy represents a promising option to reduce the volume of the tumour, achieve resectability of the tumour and reduce the extent of surgery for patients with advanced vulvar cancer (Hoffman, 2003).

8.4.1.2. There is no significant difference in overall survival rates or in treatment-related adverse events when chemoradiation (primary or neoadjuvant) is compared with primary surgery (Shylasree Bryant & Howells, 2011 and Hacker, Eifel & van der Velden, 2015).

8.4.1.3. If the aim is neoadjuvant then pelvis dose of 45-50.4Gy is required, followed by a boost to around 60Gy then an assessment for surgery based on response. If incomplete response the patient may continue with RT to 60-66Gy.

8.4.2. Definitive radiotherapy for vulvar and vaginal cancers

8.4.2.1. Definitive radiotherapy as primary treatment for advanced vulvar cancer (from stage II) is an option to treat patients not suitable for a surgical approach or where surgery is not planned for different reasons, like localisation of the tumour or comorbidities) (Woelber et al., 2013, & Jewell, 2017).

8.4.2.2. Radical treatment will usually require a prophylactic dose (45–50 Gy) to be delivered to the primary and nodal sites and the tumour is then boosted by a second phase of treatment by electrons, to a total dose of 60-66 Gy, depending on the clinical context.

8.4.3. Adjuvant radiation therapy: vulva

8.4.3.1. Adjuvant radiotherapy to the vulva and groin is often recommended in the presence of poor prognostic indicators. However, it requires careful consideration as it carries a potential for significant morbidity, which could adversely affect a woman's quality of life.

8.4.3.2. The factors influencing the need for adjuvant radiotherapy are surgical margins and groin node positivity. There is not enough evidence to recommend adjuvant local therapy routinely in patients with close surgical margins. However, some authors also recommend adjuvant radiation for patients with a high risk of local recurrence, which includes those with stage IVA disease, LVSI, and deep invasion (Modesitt & Nakayama, 2017).

8.4.3.3. A substantial clinical benefit of adjuvant radiotherapy has been clearly demonstrated for patients with two or more lymph-node metastases, whereas the role of radiation in patients with a single intracapsular metastasis remains controversial (Homesley, Bundy, Sedlis & Adcock, 1986; Oonk, de Hullu & van der Zee, 2010).

8.4.3.4. The dose of radiation is determined by the initial extent of regional disease and any known residual (Hacker et al., 2015).

- If the groin nodes are positive and meet the requirements for adjuvant radiation, the initial radiation treatment fields should include the pelvis, inguinal nodes, and primary site, which are treated to a total dose of at least 50 Gy.
- If there are multiple positive nodes or if there is evidence of extracapsular extension, doses up to 60 Gy may be given to a reduced volume.
- Gross vulvar disease probably requires 60–70 Gy to achieve local control, although investigators are currently exploring a wide variety of chemoradiation schedules, and the relationship between dose and local control remains somewhat uncertain.
- After a groin dissection with microscopic inguinal metastases, 50 Gy in 1.8–2.0 Gy fractions is usually sufficient.

8.4.3.5. Current recommendations for postoperative radiation treatment of the perineum include close or positive margins, depth of invasion more than 5 mm, lymphovascular invasion, or an infiltrative pattern of growth (Dutta & Coleman, 2017).

8.4.3.6. Postoperative radiation is of benefit for patients with close surgical margins (less than 5 mm), if the margins cannot be re-excised (Hacker et al., 2015).

8.4.3.7. Intensity modulated radiotherapy (IMRT) is not recommended as PMB level of care for both vulvar and vaginal cancer.

8.4.4. <u>Adjuvant (radical) therapy: vaginal cancer</u>

8.4.4.1. Adjuvant radiation (External-beam radiation therapy or EBRT) is recommended in patients with stage I poorly differentiated tumors and deeply invasive lesions (Jang et al., 2012 & Jewell, 2017).

8.4.4.2. External-beam radiation therapy (EBRT) is recommended in patients with stage I poorly differentiated tumors and deeply invasive lesions and in all patients with stage II-IV disease (Jewell, 2017).

8.4.4.3. In stage II, combination radiation therapy with brachytherapy and EBRT is usually employed to deliver a combined dose of 70-80 Gy to the primary tumor volume (Frank, Jhingran, Levenback & Eifel, 2005).

8.4.4.4. Brachytherapy is recommended on motivation on a case by case basis as the technique depends on the location and the depth of the tumor. The dose of brachytherapy is calculated to aim for a total equivalent dose of 70-90Gy.

8.4.4.5. Concurrent cisplatin-based chemotherapy should be considered in conjunction with radiation therapy. (Jewell, 2017).

8.4.4.6. Primary vaginal cancer is a rare entity with very little documentation. Though early stage vaginal cancers have better outcomes treated with surgery or radiotherapy or surgery followed by radiotherapy, radiotherapy alone is the preferred mode of treatment in vaginal cancers (Shrivastava, Agrawal, Mittal & Mishra, 2015).

8.4.4.7. Treatment of vaginal cancer involves a combination of external beam radiotherapy and brachytherapy with surgical resection in a small subset of patients. Despite these treatments, prognosis is poor.

8.4.5. Palliative radiation

8.4.5.1. Palliative radiation of 1-15# is recommended as PMB level of care for both vulvar and vaginal cancer.

8.5. Chemotherapy

Chemotherapy has been used neo–adjuvantly to reduce the extent of surgery, and in the adjuvant setting, postoperatively, alone or concomitantly with radiation in node positive disease, as well as in recurrent and metastatic disease.

8.5.1. Chemotherapy for vulvar cancer

8.5.1.1. Adjuvant chemotherapy for vulvar cancer

Radiation with concurrent cisplatin is recommended as PMB level of care.

8.5.1.2. Definitive chemotherapy for vulvar cancer

Following encouraging results from a series of studies reviewing current literature on clinical management of vulvar carcinoma, it

was concluded that weekly cisplatin should be applied for chemotherapy, although mitomycin C and 5-flurouracil might serve as alternative regimens in the case of contraindications for cisplatin (Tans, Ansink, van Rooij, Kleijnen & Mens, 2011; Woelber et al., 2013).

8.5.1.3. Chemotherapy for metastatic vulvar cancer

8.5.1.3.1. Patients with metastatic disease are eligible for chemotherapy (Rogers & Cuello, 2018; Rogers & Cuello, 2018; Almadrones-Cassidy, 2010).

8.5.1.3.2. Woelber and colleagues (2013), according to their clinical experience with other squamous cell carcinomas, suggest that a platinum-based chemotherapy might be effective in vulvar cancer as well, and it consists of cisplatin and paclitaxel (Woelber et al., 2013).

8.5.1.3.3. Paclitaxel shows moderate activity for local control in advanced vulvar cancer.

8.5.2. Chemotherapy for Vaginal Cancer

Chemotherapy for vaginal cancer can be classified under adjuvant and metastatic.

8.5.2.1. Adjuvant / definitive chemotherapy for vaginal cancer

Miyamoto & Viswanathan (2013), assert that in early vaginal cancer chemoradiotherapy, cisplatin is given as a single drug.

8.5.2.2. Chemotherapy for metastatic vaginal cancer

Cisplatin, 5FU, Carboplatin and paclitaxel are recommended as PMB level of care in the metastatic setting.

*Table 8: PMB level of care for chemotherapy of vulvar and vaginal cancers*

| Indication | Active ingredient/s |
|---|---|
| Adjuvant: vulva | Cisplatin<br>Radiation + concurrent chemotherapy |
| Definitive: Vulva | Cisplatin<br>5FU |
| Metastatic: vulva | Carboplatin<br>Paclitaxel<br>Cisplatin<br>5FU |
| Adjuvant: vaginal | Cisplatin<br>Carboplatin |
| Metastatic: vaginal | Cisplatin<br>5FU<br>Carboplatin<br>Paclitaxel |

## 9. FOLLOW UP CARE

*Table 9: Recommended follow up interventions for vulvovaginal cancer*

| Description | | Comment |
|---|---|---|
| Clinical assessment | Consultations | The following follow up schedule is generally acceptable: 3 monthly for a year, every 4 months for 2 years, 6 monthly for the next 5 years and thereafter annually for 10 years. |
| Pathology | Full Blood Count (FBC) incl. platelets | |
| | Liver function test | |
| | Renal function (U&E) | |
| Imaging | Ultrasound: abdominal / pelvic | |
| | CT abdomen and pelvis | Not routine; unless suspected recurrence |
| | Chest x-ray | |
| Cytology | | |
| Biopsy | | Only for recurrence |

## 10. BEST SUPPORTIVE CARE

CMS developed a PMB definition document on best supportive care for gastrointestinal oncology conditions.(available at https://www.medicalschemes.com/files/PMB%20Definition%20Project/BestSupportivCare%20GIT3103docx.pdf). The document contains some guidance for the management of side effects of chemotherapy, which can be applied across all oncology conditions (management of nausea and vomiting, management of diarrhea and pain management). Other rehabilitation interventions specific to vulvovaginal cancers should be considered for funding when referred by the primary treating provider.

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