

ESTRO/ESGO/SIOPe Guidelines for the management of patients with vaginal cancer

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ABSTRACT

Primary vaginal malignancies are rare, comprising only 2% of all female genital tract malignancies in adults and 4.5% in children. As part of its mission to improve the quality of care for women with gynecological cancers across Europe, 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.

ESTRO/ESGO/SIOPe nominated practicing clinicians who are involved in the management of vaginal cancer patients and have demonstrated leadership through their expertise in clinical care and research, their national and international engagement and profile as well as dedication to the topics addressed to serve on the expert panel (13 experts across Europe comprising the international development group). To ensure that the statements were evidence based, the current literature was reviewed and critically appraised.In the case of absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the international development group. Prior to publication, the guidelines were reviewed by 112 independent international practitionners in cancer care delivery and patient representatives and their comments and input were incorporated and addressed accordingly.

These guidelines cover comprehensively the diagnostic pathways as well as the surgical, radiotherapeutical and systemic management and follow-up of adult patients (including those with rare histological subtypes) and pediatric patients (vaginal rhabdomyosarcoma and germ cell tumours) with vaginal tumours.

INTRODUCTION

Primary vaginal cancer is rare, comprisingonly 2% of all female genital tract malignancies in adults.[1] For this reason, available clinical data aresparse and consist mainly of retrospective, typically relatively small monocentric series, collected over a considerable period of time. Many of the recommendations are therefore extrapolated from the treatment of cervical cancer, with which they share many etio-pathological and anatomical similarities.

It is estimated that only 10% of all vaginal malignancies originateprimarily from the vagina in adults; the remaining being metastatic from other sites (eg, cervix, endometrium, vulva, rectum). To support a diagnosis of primary vaginal cancer, a recent or past (last 5 years) concomitant cancer of the vulva, cervix, endometrium or colorectum needs to be excluded unless this clearly represents a morphologically different tumor type from the original neoplasm.

Vaginal cancers most commonly affect elderly, postmenopausal women. Squamous cell carcinoma (SCC) is the most common histologic type comprizing 80–95% of the cases. However, there are also a variety of unusual morphological tumor types, someoccuring in young children. Most cases of primary vaginal SCC are HPV-associated, explaining why also young women in their 20 s and 30 s are increasingly being affected. Therefore, the risk factors for vaginal SCC are similar to those of cervical cancer: multiple lifetime sexual partners, early age at first intercourse, and smoking. Further risk factors for more rare tumor types include a history of vaginal adenosis (associated or not with diethylstilbesterol (DES)) as a risk factor for some types of adenocarcinoma, previous DES exposure and endometriosis. Rare histological types are described in this article.

A distinct population consists of primary vaginal cancers diagnosed in childhood, with a median age at diagnosis of 2 years.[2] These mainly consist of embryonal rhabdomyosarcoma (RMS) and yolk sac tumor (YST), the latter representing malignant germ cell tumors (GCT) in this age group, each having their unique features and specific management recommendations which are also described.

In adults, postcoital and/or postmenopausal vaginal bleeding is the most common clinical presentation.[3] Less common symptoms apart from a palpable vaginal mass are related to local extension of disease including urinary (eg, frequency, dysuria, hematuria), or gastrointestinal symptoms (constipation, diarrhea/ symptoms related to a fistula). Pelvic pain from extension of disease beyond the vagina is present in 5% of patients. Approximately 20% of women are asymptomatic. Vaginal cancers may be detected as a result of cytologic screening for cervical cancer or may be an incidental finding of a vaginal mass on pelvic examination.

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Anatomically, the vagina connects the cervix at the level of the fornices with the vulva at the level of the vaginal orifice or hymnal ring. The main pattern of lymphatic spread follows the pelvic lymphatic drainage: tumors in the upper two thirds of the vagina drain and spread mainly towards the internal iliac, external iliac and obturator regions; tumors involving the lower third of the vagina may also spread to the inguinal lymph node region; and those involving the posterior vaginal wall and rectovaginal septum are at an increased risk for nodal spread towards the presacral and mesorectal nodes. Distant metastases are most commonly found in para-aortic lymph nodes, lung or bone.

Known prognostic factors for vaginal cancer in adults are stage of the disease, tumor size, tumor location (upper third of the vagina appears to be more favorable), histological type, HPV status and age. The survival of women with vaginal cancer is mostly associated with the stage of the disease; 5 years overall survival being 77%, 52%, 42%, 20% and 13% for stages I, II, III, IVA and IVB, respectively.[4]

As part of its mission to improve the quality of care for women with gynecological cancers across Europe, the European Society of Gynecological 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.These guidelines are intended for use by gynecologic oncologists, general gynecologists, surgeons, pediatricians, radiation oncologists, pathologists, medical and clinical oncologists, radiologists, general practitioners, palliative care teams, and allied health professionals.

RESPONSIBILITIES

These guidelines are intended for use by all health professionals that are involved in the treatment and care of vaginal cancer patients, across all allied disciplines. Even though our aim was to present the highest standard of evidence in an optimal treatment setting of qualified gynecological cancer centers, ESTRO, ESGO and SIOPe acknowledge the fact that there will be broad variability in practices between the various centers worldwide and also significant differences in terms of infrastructure, access to medical, radiation and surgical technology, but also training, medicolegal, financial, and cultural aspects that will affect the implementation of any treatment guidelines. Any clinician applying or consulting these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. These guidelines make no representations or warranties of any kind whatsoever regarding their content, use, or application and disclaim any responsibility for their application or use in any way.

METHODS

The guidelines were developed using a five-step process as defined by the ESGO Guideline Committee (see Figure 1). The strengths of the process include creation of a multidisciplinary international development group, use of scientific evidence and international expert consensus to support the guidelines, and use of an international external review process (physicians and patients). This development process involved one pilot, introductory meeting and three 2 day virtual meetings of the international development group, chaired by Remi Nout (Netherlands, ESTRO), Christina Fotopoulou (United Kingdom, ESGO) and Gabriele Calaminus (Germany, SIOPe).

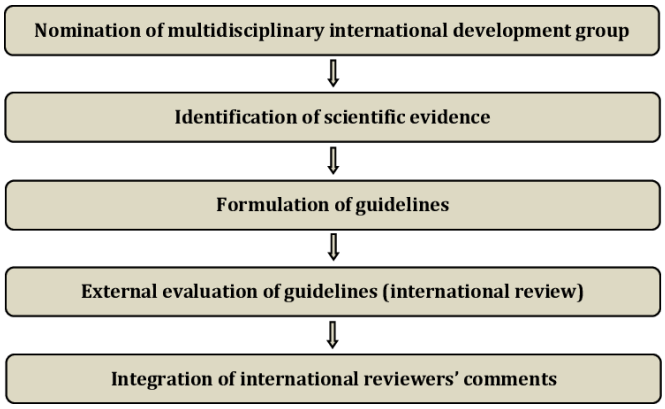


Figure 1 Development process.

The ESTRO/ESGO/SIOPe nominated practicing clinicians who are involved in the management of vaginal cancer patients and have demonstrated leadership through their expertize in clinical care and research, their national and international engagement and profile as well as dedication to the topics addressed to serve on the expert panel. The objective was to assemble a multidisciplinary panel and it was therefore essential to include professionals from all relevant disciplines that is,.gynecological, medical and radiation oncology, as well as pathology and pediatric surgery to contribute to the validity and acceptability of the guidelines.

To ensure that the statements were evidence based, the current literature was reviewed and critically appraised. A systematic, unbiased literature review of relevant studies published between January 2000 and January 2022 was carried out using the MEDLINE and EMBASE databases (see Online Supplemental Appendix 1). The literature search was limited to publications in English. Priority was given to high-quality systematic reviews, meta-analyses, and randomized controlled trials, but studies of lower levels of evidence were also evaluated. The search strategy excluded editorials, letters, and in vitro studies. The reference list of each identified article was reviewed for other potentially relevant articles. The development group was also allowed to consider older significant evidence (if needed).

Based on the collected evidence and clinical expertize, the international development group drafted guidelines for all the topics. The guidelines were retained if they were supported by sufficiently high level of scientific evidence and/or when a large consensus among experts was obtained. An adapted version of the "Infectious Diseases Society of America-United States Public Health Service Grading System" was used to define the level of evidence and grade of recommendation for each of the recommendations[5] (see Table 1). In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the international development group.

The ESTRO/ESGO/SIOPe established a large multidisciplinary panel of practicing clinicians who provide care to patients with vaginal cancer to act as independent reviewers for the guidelines. These reviewers were selected according to their expertize, had

Table 1 Levels of evidence and grades of recommendations

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, experts opinions
Grades of recommendations	
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, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

to be still involved in clinical practice/research, and were from different European and non-European countries to ensure global perspective.

Gynecological cancer patients were also included.The independent reviewers were asked to evaluate each recommendation according to its relevance and feasibility in clinical practice (quantitative evaluations, only physicians). Open comments were encouraged, so that comprehensive quantitative and qualitative evaluations of the guidelines were completed. Patients were asked to evaluate qualitatively each recommendation (according to their experience, personal perceptions, etc.). Evaluations of the external reviewers (n=112) were pooled and discussed by the international development group to finalize the guidelines development. The list of the 112 external reviewers is available in Online Supplemental Appendix 2.

GENERAL RECOMMENDATIONS

Primary vaginal cancer is rare, constituting only 2% of all gynecologic malignancies in adults,[1] and only 4.5% of all gynecologic malignancies in children.[2] Given this low incidence and the complexity of vaginal cancer,care should be centralized in specialized and accredited gynae-oncology cancer centresand referral networks and for children in pediatric oncology centers.Following the principlesof multidisciplinary cancer management, all patients should be dicussed ina dedicated multidisciplinary team that includes relevant specialists in the diagnosis and management of vaginal cancer.This dedicated team of specialists should include as core members gynae-oncologists or pediatric oncologists, radiation (clinical-) and medical oncologists, gynaeco-radiologists, gynaeco-pathologists and clinical nurse specialists. Any other specialists such as general surgeons, plastic surgeons, urology surgeons,palliative care and psychosocial care specialists may complement the core team when necessary.Patients should be carefully counseled on the suggested treatment plan and alternative options. Such counseling should be tailored to the individual patients needs and should include discussion of potential risks and benefits of all treatment options, including the option for second opinion.

Recommendations

- Decision-making regarding treatment, across all stages, should be decided based on objective clinical, radiological and pathologic work-up following discussion in a dedicated multidisciplinary team of specialists in the diagnosis and management of vaginal cancer [V, A].
- Patients should be carefully counseled on the suggested treatment plan and alternative options. Potential risks and benefits of all treatment options, including the option for second opinion, should be discussed and tailored to the individual patients-needs [V, A].
- Centralization of care in specialized centers and referral networks is recommended given the low incidence and complexity of care [V, A].
- Enrolement of patients with vaginal cancer in clinical trials or registries when possible is strongly encouraged [V, A].
- Use of patient reported outcome measures is encouraged [V, B].

DIAGNOSTIC WORK-UP (LOCAL, REGIONAL, DISTANT): CLINICAL EXAMINATION, COLPOSCOPY, HISTOLOGY, IMAGING

Staging is defined using TNM and/or FIGO classifications; following a complete work-up including a clinical examination with biopsies (under general anesthesia), chest imaging and an abdomino-pelvic MRI. Screening for distant metastases can be doneon the basis ofacomputed tomography (CT) or positron emission tomography-computed tomography(PET-CT) imaging. Pelvic MRI is the standard recommended imaging to determine local extent.[6 7] PET-CT is recommended especially in node positive or locally advanced disease; for treatment planning before chemoradiotherapy or exenterative surgery with curative intent, or in evaluation of recurrent disease.[8] PET-CT could also be used directly, that is, not following a CT scan. Colposcopy should be added in early-stage vaginal cancer to map the initial extent of the disease; this is both relevant in case of a potential surgical treatment, as well as for radiotherapy. In

selected cases, lymph node staging surgery, cystoscopy or proctoscopy should be considered.

Prognostic factors are based on tumor size, location, nodal status, histologicaltumour type and presence of lymphovascular space invasion (LVSI). Immunocompromised patients are at higher risk (autoimmune disorders, HIV, etc). Before diagnosing a primary vaginal SCC, a SCC from cervix/vulva, and for adenocarcinoma a metastasis from elsewhere in the female genital tract or GI tract, during the previous 5 years, should be excluded.

Recommendations

Staging and Characterization of Vaginal Cancer, TNM Classification and International Federation of Gynecology and Obstetrics (FIGO)

- Vaginal cancers should be staged according to the TNM classification, and FIGO classification (see Table 2) [IV, A].
- The method used to determine tumor status (T), lymph node status (N), and systemic status (M), that is, clinical (c), including imaging, and/or pathological (p) should be documented [IV, A].

Table 2 TNM and FIGO (2019) classification of cancer of the vagina[71–73]

	AJCC		IUCC	
FIGO 2018	eighth edition		eighth edition	
Stage	Stage	Grouping	Stage	Description
0			Tis	Carcinoma in situ
			N0	
			M0	
I	IA	T1a	T1	The cancer is only in the vagina and is no larger than 2 cm (4/5 inch) (T1a).
		N0	N0	It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
		M0	M0	
	IB	T1b		The cancer is only in the vagina and is larger than 2.0 cm (4/5 inch) (T1b).
		N0		It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
		M0		
II	IIA	T2a	T2	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).
		N0	N0	It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
		M0	M0	
	IIB	T2b		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).
		N0		It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
		M0		
III	III	T3	T3	The cancer is growing into the pelvic wall and/or has blocked the flow of urine (hydronephrosis) which is causing the kidneys to not work. (T3)
		N0	N0	
		M0	M0	OR
		OR	OR	The cancer can be any size and might be growing into the pelvic wall and/or has blocked the flow of urine (hydronephrosis) which is causing the kidneys to not work. (T1 to T3). AND It has also spread to nearby lymph nodes in the pelvis or groin (inguinal) area (N1) but not distant sites (M0)
		T1 to T3	T1 to T3	
		N1	N1	
		M0	M0	
IVA	IVA	T4	IVA	The cancer is growing into the bladder or rectum or is growing out of the pelvis (T4)
		Any N		It might or might not have spread to lymph nodes in the pelvis or groin (inguinal area) (Any N). It has not spread todistant sites (M0)
		M0		
IVB	IVB	Any T	IVB	The cancer has spread to distant organs such as the lungs, liver, or bones. (M1). It can be any size and might or might not have grown into nearby structures or organs (Any T).
		Any N		It might or might not have spread to nearby lymph nodes (Any N).
		M1		

- For RMS in childhood,it is recommended to use the IRS classification in addition to the TNM classification [IV, A].
- Localization (upper, middle, lower third) and maximum sizeof the primary tumor, and of any nodal disease should be specified and documented [V, A].
- Even though these staging systems are designed for epithelial carcinomas of the vagina they may be used for non-epithelial malignancies where specific staging systems are not available [V, B].
- HPV association should be determined for tumor classification [V, A].
- Unusual and rare morphological tumor types should undergo specialist pathology review [V, A].

Initial Clinical and Radiological Diagnostic Work-up

- Pelvic and vaginal examination is the first step in the diagnosis of vaginal cancer [IV, A].
- Examination under general anesthesia may be required to obtain tissue for histological confirmation and to determine the full extent of the disease [IV, C].
- Examination under colposcopicguidance is recommended particularly in stage I disease for exact mapping of any (pre-) invasive disease. Full documentation of the initial extent of the lesions visualized by clinical diagrams and/or photographs is recommended [IV, A].
- MRI is the standard imaging modality to determine local tumor extent [IV, A].
- Expert pelvic ultrasound may be complementary [IV, C].
- CT chest-abdomen-pelvis is recommended as first step in the assessment of nocal and distant disease spread [IV, A]. PET-CT may be considered for provision of additional information, especially in locally advanced disease in adults [IV, C].

PRINCIPLES OF PATHOLOGICAL EVALUATION

The pathology parameters to be included in the report of resection specimens of primary vaginal malignancies are listed below with brief comments and are adapted from the recently published International Collaboration on Cancer Reporting (ICCR) dataset for reporting of carcinomas of the vagina where more details are provided.[9] This ICCR dataset is evidence-based and has been produced by a panel of internationally recognized expert gynecological pathologists and a single clinician in each specific field. The datasets have been subject to international open consultation and are freely available online from the ICCR website for worldwide use (http://www.iccr-cancer.org/datasets/published-datasets/female-reproductive).

Proforma reporting is advised since this ensures capture of all the relevant data elements and facilitates comparison of data between different centers. Proforma reporting helps ensure that data elements are more consistently captured with reduced potential for omission of elements.

Given the rarity of primary vaginal malignancies, there is little published research regarding some of the parameters included and some are "extrapolated" from primary cervical and vulval tumors. Since vaginal malignancies are rare, correct diagnosis of the more unusual morphological types may be faciltated by specialist pathology review. As well as facilitating a correct diagnosis, referral of cases has the added advantage of helping to accrue case series of unusual tumor types.

Recording the location of a primary vaginal carcinoma may be important for several reasons and, if no attached anatomical structures are present, this is facilitated by the specimen being orientated by the surgeon. HPV-associated SCC tend to arise in the upper two-thirds of the vagina, while HPV-independent SCC tend to involve the lower-third.[10] Clear cell carcinomas show a predilection for the upper two-thirds, mesonephric adenocarcinomas are usually located in the lateral walls and mucinous carcinomas of intestinal type typically arise in the lower posterior third.[11]

Tumour Dimensions

Measurement of tumor dimensions is important for staging (only in AJCC version of TNM, but not in UICC version of TNM or in FIGO), patient management and prognostication. The maximum horizontal dimension and the depth of invasion should be reported in mm. While there are no widely used recommendations for measuring depth of invasion, the ICCR recommends that this is taken from the base of the epithelium from which the tumor arises to the deepest point of invasion.[9] The final pathology report should only contain one set of measurements based on a correlation of the gross and microscopic features; in other words, there should not be separate gross and microscopic measurements. In providing the final tumor dimensions, the measurements in a prior specimen, such as an excisional biopsy, may need to be taken into account. It is recommended to add together the maximum horizontal measurement in different specimens when calculating the final horizontal extent, although this may overestimate the maximum horizontal extent. The depth of invasion is taken as the maximum depth of invasion in either specimen.

Histological Tumor Type

Vaginal malignancies should be typed according to the 2020 WHO Classification of Female Genital Tumours.[12] SCCis by far the most common vaginal malignancy but, as discussed earlier,spread from adjacent sites, especially the cervix and vulva should be excluded and a diagnosis of a cervical or vulval SCC in the past 5 years is usually taken as excluding a primary vaginal SCC. As in the cervix and vulva, vaginal SCC is classified into HPV-associated and HPV-independent types.[10 12] HPV-associated SCC are most common and are secondary to persistent infection by oncogenic high-risk HPV (most commonly type 16); they are associated with smoking, immunosuppression and often multifocal HPV-associated lesions in other areas of the lower female genital tract (vulva, cervix) and anal/perianal regions.Since morphology is not reliable in distinguishing between HPV-associated and HPV-independent SCC, ancillary testing is necessary to determine the HPV status. Because of the rarity of these neoplasms within the vagina, evidence is limited compared with the vulva but HPV-independent SCC have worse disease-free and overall survival compared with HPV-associated SCC.[10]Grading of vaginal SCC is not recommended and therefore, not included in the ICCR dataset.

The pathology report should include details as to the operative procedure and the various organs submitted. A vaginectomy specimen may be partial or total.

Exact specimen dimensions are not necessary for staging, clinical management or prognosis but it is recommended that the

specimen dimensions be recorded in the pathology reportsince this gives clinicians an indication as to how radical a resection has been undertaken.

The pathological stage should be provided in the pathology report.

When lymphadenectomy is performed, all identified nodes should be submitted for histological examination, including sections containing perinodal fat to confirm the presence or absence of extracapsular extension.

Primary vaginal adenocarcinomas are extremely rare and there are several morphological types, including HPV-associated, endometrioid, clear cell, mucinous (gastric-type or intestinal-type) and mesonephric.[11 13–18] Skene's gland adenocarcinomas arising from periurethral glands also rarely present as primary vaginal neoplasms.[14] The specific histological type should be specified in the pathology report and given the rarity of these neoplasms referral for a specialist opinion may be useful. These adenocarcinoma types are broadly analagous to those occurring in the cervix and before diagnosing a primary vaginal adenocarcinoma, a metastasis from elsewhere should always be excluded. For example, before diagnosing an HPV-associated adenocarcinoma or a gastric-type adenocarcinoma, a primary in the cervix should be excluded and before diagnosing an intestinal-type adenocarcinoma, a colonicor rectal primary should be ruled out. Some primary vaginal adenocarcinomas, for example HPV-associated gastric and clear cell type may be associated with and arise from adenosis. Endometrioid and clear cell carcinomas may arise from endometriosis. Carcinosarcoma, adenosquamous carcinoma and adenoid basal carcinomaalso rarely occur as primary neoplasms in the vagina. Neuroendocrine neoplasia is classified according to the 2020 WHO Classification (neuroendocrine tumor, small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, mixed neuroendocrine-non-neuroendocrine carcinoma); these are extremely rare primary vaginal neoplasms.[12]

Non-epithelial malignancies rarely arising in the vagina include various sarcomas (including embryonal RMS in young patients), adenosarcoma, malignant melanoma, GCT (in particularYST) and haematopoietic neoplasms.

Lymphovascular Space Involvement

There is a lack of evidence regarding the prognostic significance of LVSI in primary vaginal carcinomas because of the rarity of these neoplasms. Two studies have evaluated LVSI as a prognostic factor in primary vaginal carcinomas; this was not statistically significant in one study and no conclusion was documented in the other.[19 20] However, the presence or absence of LVSI should be included in the pathology report since it may alter clinical management in some cases and also by extrapolation from cervical and vulval carcinomas, many of which are biologically similar to vaginal carcinomas.

Resection Margin Status

Due to the rarity of primary vaginal malignancies, there is little published evidence regarding the optimal cut-off of clear resection margins in predicting recurrence and prognosis. Resection margins should be microscopically clear of disease, but no minimum cut-off is defined and no large negative margins are required. Tumor involvement of a margin or tumourdistance from the margins (nearest peripheral mucosal margin and the deep margin) should be included in the pathology report. The location of the involved or nearest peripheral margin should be specified if possible. Involvement of a peripheral margin by a high-grade precursor lesion (in particular HPV-associated high-grade squamous intraepithelial lesion (HSIL)) should also be recorded and the margin specified if possible.

Lymph Node Status

When lymphadenectomy is performed, all identified nodes should be submitted for histological examination, including sections containing perinodal fat to confirm the presence or absence of extracapsular extension. For nodes which are grossly involved by tumor, representative sampling is acceptable, while nodes which are grossly inconspicious should be submitted in their entirety after sectioning at 2 mm intervals perpendicular to the long axis of the node.

The anatomic location and number of lymph nodes identified, the number containing tumor, the size of the largest tumor deposit and the presence or absence of extracapsular spread should be documented in the pathology report.

Sentinel Lymph Nodes

The use of sentinel lymphadenectomy alone is not yet established in the management of vaginal cancers. Still, when sentinel lymph node (SLN) is performed, the histopathological examination principles are the same as for other neoplasms. Intraoperative assessment of sentinel nodes is a reliable procedure but may miss micrometastases and isolated tumor cells. After frozen section analysis, the tissue needs to be put into a cassette, fixed in liquid fixative (preferably 4% buffered formalin), processed and embedded in paraffin.

Ultrastaging of the paraffin blocks, including immunohistochemistry similar to that for cervical carcinoma is suggested if no metastases are present in the first section. A minimum procedure should include 4serial sections at 150 µm and at least, at two levels an additional section needs to be cut and stained with a broad-spectrum cytokeratin antibody (eg, AE1/AE3). According to the SENTIX study on cervical carcinoma, this procedure allows to detect more than 90% of isolated tumor cells and micrometastases. If the resources of the pathology lab allow, it is recommended to cut serial sections through the whole block (eg, at 100–150 µm) and to perform additional cytokeratin immunostainings (eg, at 0.5 mm interval). Cytokeratin-positive cells should always be correlated with the morphology. Müllerian inclusions (endosalpingiosis, endometriosis) and mesothelial cells may rarely be present in pelvic and para-aortic lymph nodes and are also cytokeratin positive.

Coexistent Pathology/Precursor Lesions

Recording the presence of precursor lesions and coexistent pathology is important for vaginal SCC since this gives insight into the pathogenesis of the tumor, specifically whether it is HPV-associated or HPV-independent. HSIL is the precursor of HPV-associated vaginal SCC; unlike in the vulva, there is currently no recognized precursor lesion of HPV-independent vaginal SCC.

There are also recognized precursor lesions of some primary vaginal adenocarcinomas and these should be recorded on the pathology report; their presence may be useful in helping to

confirm a vaginal primary. Some primary vaginal adenocarcinomas, for example those of gastric, HPV-associated and clear cell type may be associated with and arise from adenosis which is usually sporadic but which may be secondary to in utero exposure to DES.[15–18] Primary vaginal endometrioid and clear cell carcinomas may arise in endometriosis and intestinal-type adenocarcinomas may arise in tubular and tubulovillous adenomas.[11 13] Mesonephric adenocarcinomas arise from benign mesonephric remnants.

Ancillary Studies

Since morphology is not reliable in distinguishing betweenHPV-associated and HPV-independent SCC, ancillary techniques, namely p16 immunohistochemistry and/or HPV molecular testing, are essential to correctly classify vaginal SCC.[10] Given its wide availability and rapid turnaround time, almost all laboratories will perform p16 immunohistochemistry rather than HPV testing. If p16 immunohistochemistry and/or HPV testing has been performed on a diagnostic biopsy, it does not need to be repeated on the resection specimen, although it is useful to record the results in the report of the resection specimen. It is important to stress that only so-called "block-type" p16 staining in a squamous lesion (in situ or malignant) is supportive of an association with oncogenic high-risk HPV.[21] HPV-associated adenocarcinomas also exhibit diffuse block-type p16 immunoreactivity and are HPV positive. It is also stressed that p16 staining should not be reported simply as positive since many HPV-independent premalignant and malignant lesions and non-neoplastic tissues exhibit focal (so-called mosaic) staining. If HPV subtyping is requested molecular technologies need to be used.

Other immunohistochemical markers and ancillary studies may be of value in helping to classify primary vaginal adenocarcinomas. For example, HPV-associated adenocarcinomas exhibit diffuse block-type p16 immunoreactivity and are HPV positive. Intestinal-type adenocarcinomas may be positive with intestinal markers such as CK20 and CDX2, mesonephric carcinomas with GATA3, CD10 and TTF1 and clear cell carcinomas are typically positive with Napsin A. Skene gland adenocarcinomas are usually positive with prostatic markers such as prostate specific antigen, prostatic acid phosphatase and NKX3.1. Embryonal RMS are typically positive with desmin and the specific skeletal muscle markers myogenin and myoD1 while melanomas are positive with melanocytic markers S100, HMB45, melan A and SOX10.

Pathologically Confirmed Distant Metastasis

Documentation of known metastatic disease should be recorded on the pathology report.

Provisional Pathological Staging

The pathological stageshould be provided in the pathology report. The latest version of either FIGO or TNM staging or both can be used depending on local preferences. Although these staging systems are designed for epithelial malignancies, they should also be used for non-epithelial malignancies where specific staging systems are not available. The term "provisional pathological staging" indicates that the stage provided may not represent the final tumor stage which should be determined at the multidisciplinary tumor board meeting where all the pathological, clinical and radiological features are available.

A tumor should be staged following diagnosis using various appropriate modalities (clinical, radiological, pathological). While the original tumor stage should not be altered following treatment, the TNM system allows staging to be performed on a resection specimen following non-surgical treatment; in such cases, if a stage is being provided on the pathology report, it should be prefixed by 'y' to indicate that this is a post-therapy stage.

Block Identification Key

The origin of all tissue blocks should be recorded,ideally in the final pathology report. This is important should the need for internal or external review arise since the reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. Recording the origin of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials.

MANAGEMENT OF STAGE I (T1N0M0) IN ADULT PATIENTS: SURGERY VERSUS (CHEMO) RADIATION THERAPY AND BRACHYTHERAPY

Two strategies for initial management with curative intent could be discussed: surgical resection vs primary (chemo)-radiation therapy. There is no randomized evidence for this comparison, only retrospective series. If surgical resection is considered, this should be only under the premise that a complete tumor resection with microscopically clear margins is feasible without excessive morbidity and that no adjuvant radiation therapy will be required. Extrapolating from the evidence and recommendations in cervical cancer, any combination of radical surgery and radiotherapy for vagina cancer will further increase iatrogenic morbidity and should therefore be avoided.

Surgical strategy includes a lymphnode staging depending on the localization of the primary lesion. As complete tumor removal with free margins is the goal of any curative surgery for vaginal cancer, the surgical route should be pursued only for small size lesions (maximum size up to 2 cm) stage I (T1N0M0) disease, that are not close to urethra or rectum, so that they would require additional urological and/ or GI resections.[20]Any tumor resection would need to be combined with partial or complete colpectomyin order to ensure microscopically free margins.[22]Fertility preserving measures should be discussed and considered in patients of childbearing age.

The extent of dissection for complete tumor removal depends on the patterns of extent of spread of the invasive and pre-invasive vaginal disease (pre-therapeutic colposcopy) to achieve microscopically clear margins.If a total colpectomy is performed or a large part of the vagina are resected in a sexually active patient, reconstructive surgery for restoration of the vaginal function would need to be discussed with the patient.

Extent and site of the lymph node staging at the time of the vaginal resection depends on the location of the tumor in the vagina (upper vs lower part): a pelvic lymph node dissection in accordance to the cervical cancer lymph node staging should be undertaken in tumourslocated inthe upper two thirds of the vagina, while inguinofemoral nodal staging equivalent to the dissection done for the vulva cancers is recommended in tumourslocated inthe lower

third of the vagina.Use of SLN principles alone is not yet established in vaginal cancer. SLN may detect microscopic nodal metastasis and avoid unnescessarypotentiall morbidity of apelvic with or without inguine femoral lymphadenectomy.

Primary chemoradiotherapy includes the combination of external beam radiotherapy (EBRT), brachytherapy and cisplatin-based chemotherapy as the recommended regimen.[23]Concomitant cisplatin-based chemotherapy is recommended.[24]Extrapolating from cervical cancer, whencisplatin is contraindicated, alternative options include carboplatin, or radiotherapy alone. In premenopausal women, ovarian transposition should be discussed up front.

Consideration in the Decision-making of Initial Treatment in Stage I (T1N0M0)

Both strategies (initial surgery or definitive radiation therapy) seem to offer similar survival benefit so it is more about weighing the risks and iatrogenic morbidity that each patient will have from each approach tailired to her needs to decide for the best treatment strategy. The decision for the most appropriate treatment of choice will depend on the operability and location of the tumor but also on patients' wishes. If complete surgical resection would mean to resect large parts of the vagina resulting in a mutilation/loss of function, then surgical approach should not be pursued unless there are contraindications for radiotherapy (eg, previous radiotherapy, inflammatory bowel disease, pelvic kidneys,etc).

High rates of major intra- and grade three postoperative morbidities have been described (16% and 30% respectively) related to the surgical treatment of vaginal cancer.[20] For example, ureteric complications such as hydronephrosis or fistulas seem to occur more commonlyin patients treated surgically for vaginal- compared with cervical cancers.[25] Extrapolating from the evidence and recommendations in cervical cancer, any combination of surgery and radiotherapy for vagina cancer will further increase iatrogenic morbidity and should therefore be avoided.

Almost half of patients treated surgically as initial management of their vaginal cancer, will postoperatively require adjuvant (chemo)-radiation consolidation therapy after all, increasing so overall iatrogenic morbidity.[20 26]

The advantage of initial (chemo)-radiation therapy is to offer the best compromise in terms of local control, organ sparing and grade three iatrogenic morbidities. Outcomes after (chemo) radiotherapy followed by image-guided adaptive brachytherapy (IGABT) for patients with primary vaginal cancer are summarized in Table 3.[27–33]

In selected patients with tumors confined to the vaginal wall and a maximum size up to 2 cm and limited thickness (that can be appropriately covered by intracavitary technique alone, i.e.<7 mm thick), brachytherapy alone can be considered, after comprehensive surgical lymph node staging.[34]

Recommendations

General Recommendations

- A histological diagnosis should be made before undertaking any treatment [V, A].
- The combination of radical surgery and radiotherapy should be as principleavoided in any treatment planning due to the increasedrisk of complications and side-effectsafter combined treatment [IV, A].

Surgery

- The surgical route should be considered only for small size lesions (maximum size up to 2 cm) 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 assessmentdepending 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].
- Use of 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].

Table 3 Study outcomes of IGABT for patients with primary vaginal cancer

	Years of inclusion	N	Median FU (months)	Dose to D90 CTV-T_{HR} (Gy)	2y-LC (%)	2y-DSS (%)	2y-OS (%)	Morbidity (%)
Dimopoulos *et al*[27]	1999–2006	13	43	86	92*	NA	85*	23
Fokdal *et al*[28]	2005–10	9	18	82	92†	59†	74†	4
Huertas *et al*[29]	2004–16	27	40	73	82	75	91	15
Gebhardt *et al*[30]	2011–16	16	39	77	93‡	64‡	67‡	3
Manuel *et al*[31]	1973–2014	47	24	81	93	86	82	2
Lee *et al*[32]	2005–11	10	17	74	86	60	62	13
Westerveld *et al*[33]	2001–16	148	29	80	86	73	79	17

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 EBRT and brachytherapy is recommended in stage I [IV, A].
- Concomitant cisplatin-based chemotherapy is recommended[24] [IV, A].
- Ovarian transposition should be discussed up front in premenopausal women undergoing radiotherapy [IV, B].

MANAGEMENT OF ADULT PATIENTS WITH STAGES T2-T3-T4, N0M0 OR ANY T-STAGE, N1M0

Definitive platinum-based chemoradiotherapy consolidated by a brachytherapy boost is the preferred treatment of choice for the management of patients with locally advanced or node positive vaginal cancer.[23] Outcomes after (chemo)radiotherapy followed by IGABT for patients with primary vaginal cancer are summarized in Table 3. Inprinciple, standard surgicaldebulkingof lymph nodes is not indicated, in very exceptional cases very bulky lymphnodes may be removed, mainly for palliation.

Although chemoradiation is the mainstay treatment approach in locally advanced disease including T4, in selected cases with large necrotic fistulation/cloacke formation between vagina/bladder/rectum at initial presentation or for patients with contraindication for radiotherapy such as previous pelvic radiotherapy, ulcerative bowel conditions or pelvic kidneys, a pelvic exenteration or GI-/GU-diversion before chemoradiation may be considered. Any exenterative surgery for vaginal cancer should be performed under curative intent with the aim of microscopically clear margins. Exenterative surgery should be combined with reconstructive techniques for urinary- and bowel diversions (continent or not continent) with additional consideration of neovaginal formation.

In patients of childbearing age, fertility preserving measures (eg, ovarian transposition) should be discussed and considered.

Recommendations

- 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

Due to the rarity of vaginal cancer high level evidence supporting specific chemotherapy regimens is lacking, and therefore evidence is extrapolated from cervical cancer. Patients with limited distant (oligo-) metastatic disease at presentation should be considered for treatment with curative intent. Treatment for recurrent disease is individualized and rather under a palliative aspect.There is limited evidence on standard treatment options of recurrent vaginal cancer. Recommendations are therefore extrapolated from evidence in cervical cancer and treatment is highly individualized depending on patients' symptoms, performance status, and tumor dissemination pattern.Reirradiation with IGABT for central recurrences is an alternative option for selected patients, especially in patients unfit for or refusing exenteration surgery, which should be restricted to highly specialized centres.[35]

Recommendations

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 dedicatedmultidisciplinary 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 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 shouldbe considered [IV, B].
- Reirradiation with IGABT for central recurrences maybe 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].

RARE HISTOLOGICAL SUBTYPES

Vaginal cancers are uncommon and histological types other than the most common SCC are extremely rare.[2] For that reason, any treatment recommendations for the rarer types of vaginal cancer are extrapolated from the general recommendations of the disease, or from recommendations for the same histological types arising in other organ systems. As discussed previously, referral for a specialist gynecological pathology opinion is advisable.

Rare vaginal cancers include among others: various types of adenocarcinoma, various types of sarcoma, malignant melanoma and neuroendocrine and haematopoetic neoplasms.Registration in rare cancer networks is strongly encouraged which facilitated the accrual of case series with increased opportunities for knowledge and research.[36–38]

Adenocarcinomas

Adenocarcinomas may arise in vaginal adenosis, mesonephric remnants, periurethral glands, and endometriosis. Clear cell carcinoma is the best-known type of adenocarcinoma, primarily because of their occurrence in young women who have been exposed in utero to DES. Clear cell carcinomas usually present as polypoid masses, most commonly involving the anterior vaginal wall. Approximately 70% of patients will present at stage I.

In female fetuses exposed in utero to DES, the actual risk of developing clear cell carcinoma through age 34 is only 1 in 1000, with the highest risk in those who were exposed before 12 weeks of gestation. The median age at diagnosis of DES-related clear cell carcinoma of the vagina is 19 years (range: 7–33 years). DES-related clear cell carcinoma is nowadays very rare. Non-malignant abnormalities including vaginal adenosis and structural abnormalities of the uterus, cervix, or vagina may occur in 25–45% of patients.

Sarcomas

Vaginal sarcomas in adultsare very rare; a variety of sarcoma types have been reported in the literature. Treatment is adapted to each individual histological type with surgical resection as the mainstay of treatment. Pathological and molecular classification of sarcomas in general is a rapidly evolving field with many new entities being defined which may reveal potential therapeutic targets. Embryonal RMS (botryoid sarcoma) is the major type in children.

Melanomas

Primary vaginal malignant melanomas are rare accounting for only 3% of melanomas of the female genital tract and 0.3%–0.8% of all melanomas in women. They are associated with poor survival outcomes with 5 year survival rates of 5%–25% due to their high tendency to metastasize and recur. Clinically, amelanotic melanoma of the vagina may be mistaken for other primary vaginal malignancies. Distinction of primary malignant melanoma from metastatic melanoma to the vagina is crucial for the adequate management.

Despite having a poor prognosis, early detection and treatment may improve prognosis. Caucasian women at a mean age of 60 years represent the typical profile of patients with vaginal melanoma. Vaginal bleeding is the most common presenting symptom. At examination, a dark colored nodule, plaque, or ulceration is seen, most frequently involing the distal one-third of the anterior vaginal wall.Sometimes, melanomas are nonpigmented.

Recommendations

Adenocarcinomas

- Recommendations for women exposed to 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 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 CHILDHOOD AND ADOLESCENTS

Pediatric and adolescent primary vaginal malignancies are rare and represent only 4.5% of all gynecologic malignancies in children.[2] The main histological types are RMS (70%) andGCT/YST (27%); clear cellcarcinomais less common (3%). Vaginal RMS is almost always of embryonal type and represents less than 2% of all RMS while approximately 8% of all YST occur in the vagina.[39] YST is by far the most common GCT and the only relevant malignant GCT occurring in the vagina. Overall, vaginal RMS and YST share some similar clinical characteristics. Presenting symptoms are mainly vaginal bleeding, vaginal mass or vesical obstruction. These tumors arise in very young patients at a median age of 2 years.[40] The vagina is considered a “favorable site” for these neoplasms with favorable prognosis (expected overall survival>90%) and low incidence of nodal or distant tumor spread at diagnosis. RMS and YST are highly chemosensitive. Therefore, a multimodal strategy starting with systemic chemotherapy should be always consideredin the first line. For these neoplasms, no risk factors or specific genetic background is known. This differs from uterine and cervical RMS which may be associated with germline or somatic *DICER1* mutations and DICER1 syndrome). Because of the rarity of these diseases in this age group patients should be treated in experiencedcentres.

Vaginal RMS have frequent favorable risk factors with few regional nodal (<7%) or distant (<5%) tumor spread, frequent small

(59%≤5 cm) and T1 tumors (69%).Vaginal YST is frequently associated with elevated serum AFP (alpha-foetoprotein), which should always be measured at diagnosis and during treatment.

Regarding radiotherapy for vaginal cancer in childhood and adolescents, when necessarybrachytherapy is preferred because of its ability to deliver focally high doses while sparing organs at risk, especially gonadal, urinary, rectal and bone structures. Compared with external radiotherapy, dose to uterus are also lower. In addition, the integral radiation dose to patient body is lower and therefore it is the best irradiation modality to decrease the risk of second neoplasms. In most of the cases, this is an intracavitary brachytherapy procedure, using an intravaginal applicator adapted to patient anatomy and tumor shape. This may be based on a vaginal tumourimpression using a vaginal mouldperformed under general anesthesia.[41] If there are residual polyps, a surgical debulking can be performed, without resection of the vaginal wall, in order to allow the placement of brachytherapy applicator. In case there is extensive parametrial and/or paravaginal extension, interstitial catheters are also used. For patients with involvement of the exocervix and/or of the fornices, it may be necessary to place an intrauterine catheter. Most available literature refers to low dose rate treatments that are becoming less available. Pulse dose rate (PDR) or high dose rate (HDR) brachytherapy procedures are however good alternatives, allowing for better dose distribution through the stepping source technology. Due to high radiosensitivity of normal tissues in children, PDR treatments should be preferred if possible, to exploit the theoretical radiobiological superiority of PDR brachytherapy. Use of 3D imaging is mandatory to guide treatment planning. The target volume is defined by residual tumor sites, as per clinical and radiological assessment. For PDR treatment, irradiation is usually delivered through continuous hourly pulses of 0.42–0.5 Gy per hour, up to a total dose of 50–60 Gy[42–47].

Most of the literature comes from series where a total dose of 60 Gy was prescribed but tumor dose/effect relationships are lacking. For HDR brachytherapy, a total dose of 27.5–36 Gy is delivered in 5 to 12 fractions over 3–10 days. A bilateral ovarian transposition is necessary in most the cases. Feasibility using a temporary transposition, has been confirmed in very young or prepubertal patients.[48 49] Brachytherapy for pediatric RMS should be performed in expert centers with high patient volume. Centralization is encouraged given the rarity of the disease.

Recommendations

Pediatric RMS

Vaginal RMS - Diagnosis

- Full clinical examination including systematic evaluation with vaginoscopy under general anesthesia, as soon as this is feasible, with tumor mapping including detailed description (this can include photographic documentation and vaginal impression) is recommended [V, A].
- Biopsy for histological confirmation should occur [IV, A]; in case of a large polypoid lesion, resection could be performedbut without excision of the vaginal wall [IV, C].
- Histopathological diagnosis including immunohistochemistry and/or molecular analysis (FISH, RT-PCR and/or RNA sequencing) is needed to confirm the diagnosis. In these rare tumors, it is recommended to seek the opinion of a specialist pediatric, gynecological or sarcoma pathologist or reference network [IV, A].
- At diagnosis, initial tumor resection attempt should be avoided due to the high chemo-sensitivity of RMS, and therefore the evaluation of the necessity of any delayed local ablative techniques after neoadjuvant chemotherapy is recommended [IV, A].

Vaginal RMS - Initial Work-up

- Pelvic and abdominal MRI is recommended for the initial work-up of the local tumor extent [IV, A].
- To rule out nodal and systemic metastasis, FDG PET-CT or whole body MRI, and low-dose chest CT are recommended [IV, A].
- Only in case of a radiologicallysuspicious pelvic, inguinal or abdominal nodal involvement, lymph node biopsy for histological orcytological confirmation is recommended [IV, A].

Vaginal RMS - Chemotherapy Schedule

- The chemotherapy schedule should be adapted to risk factors(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 MRI and vaginoscopy after 3 and 6 courses of neoadjuvant chemotherapy. Any suspicious residual vaginal lesionsshould 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 (ie, cyclophosphamide>8 gr/m²) waspart of the neoadjuvant chemotherapy [IV, B]:

- Surgery:
  - 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 associatedvaginal wall resections [IV, B].
  - In case of residual tumor after neoadjuvant therapy:
    - Unifocal small residue: partialvaginectomy (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) isrecommended [IV, A]
    - If the tumor involves more than half of the vagina or is multifocal: brachytherapy should be preferred overtotal 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 upperpart 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 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 caseswith 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].

Pediatric GCT

GCT - Diagnosis

- Full clinical examination including vaginoscopy under general anesthesia is recommended [IV, A].
- Biopsy for histologic confirmation is not mandatory in the presence of high AFP levels, but should be undertaken if the risk of morbidity is low. In very young patients (<2 years) a biopsy should always be obtained for histological confirmation due to the physiological higher serum AFP levels [IV, A].
- At diagnosis, initial tumor resection should always be avoided as vaginal GCT are highly chemo-sensitive [IV, A].
- In case of biopsy, histopathological diagnosis should include immunohistochemical analysis (eg, with antibodies against AFP, PLAP, glypican-3, cytokeratin, etc.). In these rare tumors, it is recommended to strive for confirmation by an expert pathologist or reference network [IV, A].

Gct - Initial Work-up

- Pelvic and abdominal MRI is recommended for local and regional work-up [IV, A].
- Low dose chest CT scan is recommended to exclude lung metastases [IV, A].

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 AFP [IV, A].

GCT - Local Therapy

- Surgery should be reservedfor 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].

- Local therapy for the primary tumor is adapted to the tumor response, assessed by pelvic MRI after at least three courses and clinically with vaginoscopy. In case of a suspicious residual vaginal nodule it is preferable to remove any residual vaginal lesion by a partial resection of the adjacent vaginal wall, even if AFP levels are normal, than to perform a simple biopsy of the nodule that then will require a re-resection to achieve clear margins.If conservative surgery is not feasible, brachytherapy can be proposed as local treatment.If the resected nodule is completed resected; no further chemotherapy is needed even if viable cells present [IV, B].
- In case of complete remission after neoadjuvant chemotherapy confirmed by a negative pelvic MRI and negative vaginoscopy and normal AFP, no local treatmentis indicated if a strict follow-up is possible [IV, C]. Strict follow-up in patients with vaginal GCT after the end of treatment is recommended, consisting of AFP and ultrasound every 3 months during the first 2 years, then every 4 months during the third year, and every 6 months up to 5 years follow-up. In case of rising serum biomarker (AFP) or suspicious findings on ultrasound an abdominal and pelvic MRI and vaginoscopy are recommended [IV, A].
- Adjuvant radiotherapy is individualized and decided within amultidisciplinary team. Radiotherapy is only indicated if no complete response can be achieved by chemotherapy±organ sparing surgery. In case of radiotherapy, vaginal brachytherapy is preferred over EBRT to minimize long term morbidity.If EBRT is needed, proton beam therapy is preferred [IV, B].
- Ovarian transposition is recommended if radiotherapy is part of the treatment plan [IV, B].

NEOVAGINAL RECONSTRUCTIVE SURGERY

Any surgery that includes complete or large partial resection of the vagina should include considerations of reconstructive techniques to avoid significant impairment on patients' quality of life. The indication for neovaginal reconstruction as well as the timing that is, one- vs two- stage procedure will depend on patients age, performance status, oncological profile and treatment journey as well as her wishes.[50–53]

In principle, no neovaginal surgical reconstruction should routinely be performed in small children but this should be delayed when they reach adolescence. The timing of neovaginal reconstruction should be placed before the start of menarche (approx. 8 years) to avoid kryptomenorrhea and uterine obstructive symptoms. Neovaginal reconstruction should be performed by an expert team of adolescent gynaecological- and pediatric- surgeons as well nurse specialists for aftercare and appropriate follow-up.Rare development of secondary malignancies in the neovaginal tissue should be considered and discussed with the patients.[54–57]

The aim of the reconstructive surgery of the vagina is twofold: to restore a vaginal cavity (to give the patient the opportunityhaving sexual activity) and to fulfill the pelvic cavity to decrease the rate of post-operative fluid collection and abscess (to counteract the empty pelvis syndrome). However, primaryreconstructive surgery increases the operative time and peri and post-operative morbidity and therefore indications should be carefully defined weighing the individual risks and benefits and taking into consideration the oncologic history, overall prognosis and patients' comorbidities, wishes and compliance.[50 52 53]

Assessment of patients' compliance is important, since long term side effects such as secondary cancer/dysplasia, prolapse, non-functionality are highly challenging in non-compliant patients.

Surgical techniques include following options[53 58–61]:

- Gastrointestinal tract (small or large bowel).
- Myocutaneous flaps (pedicled or free flaps).
- Different options exist for the flap: abdominal (VRAM, DIEP), gracilis, pudendal, gluteal or exclusively local flap.
- Omental or peritoneal flaps.
- Use of artificial material: split skin/amnion/artificial skin.

Even though neovaginal reconstruction is associated with better functional and quality of life scores, the patients' overall quality of life is still mainly determined by their underlying malignant condition and, thus function scores have been shown to be inferior to those reported by patients having a neovagina due to benign conditions such as vaginal agenesis.[53]

Morbidities of Neovaginas50–63

- Fistula formation.
- Stenosis.
- Long term dilatation necessary/perofations.
- Scar tissue formation.
- Secondary cancer.
- Wound dehiscence (in patients having a reconstruction with an abdominal flap).
- Permanent vaginal discharge with mucosal fluid (in patients having a reconstruction with bowel).
- Odor.
- Prolapse.

Postoperative Care

Adequate postoperative care is crucial for the long-term functionality of the neovagina. A holistic support by clinical nurse specialists and specialized psycho-oncologists is key for success. A systematicprogram involving regulal vaginal dilatation should be defined and planned with the patients. Early involvement of the partner, if available, usually induce functionality and longer term outcomes.

Patients should have regular follow-ups to assess rare risks such as dysplasia or cancer of the neovagina, prolapse or even colitis like symptoms in bowel neovagina.[50–63]

Recommendations

- When considering neovaginal reconstruction the age, performance status, sexual activityandpatients' wishes should be evaluated and discussed. Patients who are sexually active and wish to pursue sexual activity are the optimal surgical candidates. Otherwise, there is a risk of stenosis of neovagina/obliteration [IV, A].
- The standardized questionnaires (such as: female sexual function index scores, quality of life scores, depression scales) in the preoperative screening of patients suitable for neovaginal reconstruction are valuable in order to identify pre-existing sexual function disorders. Preoperative sexual disorders may cause the postoperative and long term use of the neovagina challenging again with the risk of obliteration/stenosis [IV, B].
- The preoperative discussion should include counseling with psychologists and clinical nurse specialists. Partner(s) should ideally be involved, where applicable, in preoperative

counseling. A supportive network for patients is important especially in the immediate postoperative period to keep the neovaginal cavity open and functions (vaginal dilatators, sexual intercourse, etc.) [IV, A].

- The choice between different procedures depends on several major criteria: previous irradiation, type of surgery (colpectomy, anterior, posterior or total pelvic exenteration), anatomy, weight, age, free or pedicled flap, previous history (smoking, cardio-vascular disease), previous abdominal surgery [IV, B].

PRINCIPLES OF RADIOTHERAPY

The section below refers to the principles of radiotherapy for adult patients.

Definitive Chemoradiotherapy and Brachytherapy: General Aspects

Definitive management (without tumor related surgery) consists of concomitant pelvic chemoradiotherapy (platinum based) and brachytherapy. Overall treatment time for the definitive treatment should not exceed 7 to 8 weeks. Delay of treatment and/or treatment interruptions have to be avoided.

Definitive Chemoradiotherapy

EBRT can be applied as concomitant chemoradiotherapy with total dose of 45 to 46 Gy (1.8 to 2.0 Gy per fraction) and single-agentradiosensitizing chemotherapy, preferably cisplatin (weekly 40 mg/m²) so that definitive radiotherapy is not compromised. If cisplatin is not applicable, alternative treatment options are fluorouracil or carboplatin. EBRT may also be applied without concomitant chemotherapy according to treatment selection (ie, patients unfit for any chemotherapy). In such cases, regional hyperthermia may be considered.

Tumor and lymph node - related target volume for intensity modulated radiotherapy (IMRT) includes the primary vaginal tumor, the vagina and the adjacent tissues such as the paravaginal space, parametria, uterine cervix if in situ, and the pelvic lymph nodes (obturator, internal, external and common iliac, presacral). In case of pelvic lymph node involvement indicating an increased risk of para-aortic lymph node spread, EBRT may include the para-aortic region up to the renal vessels (45 Gy). In case of para-aortic lymph node involvement, target volume includes at a minimum the region up to the renal vessels. In case of a primary tumor located in the lower third of the vagina, inguino-femoral lymph nodes are part of the EBRT target volume.

A reduced target volume for EBRT resulting in a small pelvic field not including the common iliac nodes may be considered in selected patients with T1-2 tumors with negative lymph nodes on imaging and no LVSI.

Boost treatment for involved lymph node(s) may be applied as simultaneous integrated boost within the IMRT treatment or as sequential boost. The total dose including the contribution from brachytherapy should be 55 to 60 Gy (equieffective dose to 2 Gy per fraction [EQD2]).

Image-guided radiotherapy is recommended for IMRT to ensure safe dose application in the tumour-related targets, to account for motion uncertainties, to reduce margins, and to achieve reduced doses to organs at risk. Overall treatment time for EBRT should not exceed 5 to 6 weeks.

Definitive Brachytherapy

IGABT is recommended, preferably using MRI at the time of brachytherapy. IGABT is delivered toward the end of or after concomitant chemoradiotherapy. Repeated gynecologic examination is mandatory, and alternative imaging modalities such as CT and ultrasound may be used.

The tumour-related targets for brachytherapy include the residual gross tumor volume (GTV-Tres) after chemo- radiotherapy, the adaptive high-risk clinical target volume (CTV-T_{HR}) including the GTV-Tres and residual adjacent pathologic tissue, and the intermediate-risk clinical target volume (CTV-T_{IR}).

Intravaginal brachytherapy can be performed without anesthesia whereas combined intravaginal/interstitial brachytherapy should be performed under anesthesia. Cylinder-type applicators or individually manufactured applicators (eg, mold, 3D-printed applicators) with central and peripheral source positions should be used for intravaginal brachytherapy. In tumors located in the upper third, when uterus in situ, an intrauterine tandem may be used to ensure optimal contact and fixation. Combined intravaginal/interstitial applicators should be considered for residual tumors with>7 mm thickness or for residual tumors with paravaginal diseasein order to achieve a sufficiently high radiation dose in the whole CTV-T_{HR}. Depending on the applicator type, interstitial needles can be placed (1) intravaginally through the applicator or (2) perineally with or without the use of a template.

In IGABT, the planning aim should be to deliver a brachy- therapy dose of 30 to 40 Gy (EQD2) to reach a total EBRT+brachytherapy dose of equal to or greater than 75 to 85 Gy EQD2 (D90) (assuming 45 Gy through EBRT) to the CTV-T_{HR}. Dose volume and point constraints for rectum, bladder, vagina, sigmoid, and bowel are recommended, and they have to be based on the published clinical evidence.

The lower third of the vagina is more sensitive and this should be taken into account when deciding on the planning aim.Brachytherapy should be delivered in several fractions as high dose rate (usually 3–4) or in 1 to 2 coursesas pulse dose rate brachytherapy. Care should be taken to optimize patient comfort and to avoid applicator movements during (fractionated) brachytherapy; preferably this includes a multidisciplinary approach.

Adjuvant Radiotherapy or Chemoradiotherapy

Adjuvant radiotherapy or chemoradiotherapy follows analog principles for target selection and dose and fractionation as outlined for definitive treatment.The application of IMRT and image-guided radiotherapy is to be considered as treatment-related morbidity may be reduced.

Adjuvant (additional) brachytherapy should be considered only if a well-defined limited area accessible through a brachytherapy technique is at high risk of local recurrence (eg, positive margins in vagina, paracolpiaparametria). Such adjuvant brachytherapy should follow the major principles outlined above for image-guided brachytherapy.

Definitive 3D Conformal EBRT or Chemoradiotherapy- and Radiography-based Brachytherapy

Three-dimensional conformal radiotherapy alone or as definitive concomitant chemoradiotherapy (platinum based) and 2D radiography - based brachytherapy is recommended, if IMRT and/or IGABT are not available. In case of 3D conformal radiotherapy and/

or radiography- based brachytherapy, the recommendations for EBRT and IGABT as outlined above in regard to target, dose, fractionation, and overall treatment time have to be respected as much as possible.A sequential lymph node boost is applied as appropriate after completion of 3D EBRT.

Planning aim for brachytherapy should be based on applicator-related dose points (applicator surface, 5 mm tissue depth), and the use of a system (eg, Paris system) for interstitial approaches. Radiography- based dose point constraints plus 3D dose volume constraints as available for rectum, bladder, vagina, sigmoid, and bowel are recommended, and they have to be based on the published clinical evidence.

FOLLOW-UP OF PATIENTS AFTER TREATMENT OF VAGINAL CANCER

Aims of oncologic follow-up are detection of recurrent disease, and also assessment and prevention of long term sequelae with emphasis on quality of life after treatment. Literature on follow-up after treatment for vaginal cancer is scarce. Some evidence may be extrapolated from cervical cancer management with which it shares many similarities. However, there are several aspects of follow-up associated with vaginal malignancies that deserve specific attention, such as issues related to neovagina, childhood vaginal cancer treatment and profound sexual dysfunction. Given the rarity of the disease, and lack of high-volume experience and evidence, especially in the case of childhood vaginal cancer and neovagina surgery, centralized treatment and follow-up is recommended.

The survival of patients with vaginal cancer is mostly associated with the stage of the disease; 5 years overall survival being 77%, 52%, 42%, 20% and 13% for stages I, II, III, IVA and IVB, respectively.[4] Large retrospective studies show that 70 to 80% of relapses occur within the first 2 years after treatment. Known prognostic factors are stage of the disease, tumor size, tumor location, histological tumourtype and grade and age of the patients. Local recurrence is most common, followed by regional lymph node involvement and distant metastasis.[64 65] Extrapolating from cervical cancer guidelines routine vaginal cytology shows low accuracy for detection of recurrence; interpretation is poor especially after radiation and is not cost effective. Local recurrence is usually symptomatic or detected by clinical examination.[66] Again, since lack of evidence specific to vaginal cancer patients, according to cervical cancer guidelines routine imaging and laboratory tests do not show benefits and are indicated when symptoms or suspicious clinical findings appear.[66] In general, for assessing local recurrence, apart from obtaining histological verification, MRI is the method of choice, whereas CT scan, PET-CT and whole-body MRI are best tools for evaluating distant metastasis.[66] Currently, there is no clear data on vaccination against HPV for women already treated for vaginal cancer.

The most important long term sequelae after treatment of vaginal cancer, either by surgery or chemoradiation, are lymphedema, genito-urinary, gastro-intestinal, and profound sexual dysfunction.[67–69] These should be therefore actively prevented, early detected and treated. Vaginal cancer is generally not a hormone-dependent disease and hormone replacement therapy may be considered according to regular menopausal recommendation.

Furthermore, the neovagina may be associated with the risk of secondary cancers. The neovagina may be constructed by variety of tissues (bowel, skin graft, vulvar skin, rectus abdominis flaps), that are placed to non-physiologic compartment and exposed to new contacts/stresses, consequently tissue dysplasia may occur.[70]

In the light of the rarity of the disease, lack of high volume experience and evidence, centralization of treatment and follow-up is of importance.

Recommendations

- Primary objectives of follow-up for patients with vaginal cancer should include the following [IV, A]:
  - Early detection of recurrent disease.
  - Patient education and support.
  - Cancer rehabilitation with the goal to prevent and reduce psychosocial, physical, social, and existential consequences of cancer and its treatment starts at time of diagnosis. The efforts should optimize physical ability and quality of life of women affected by cervical cancer and include family members/caregivers. Several professions for counseling should be available, for example, psychologist, sex therapist, physiotherapist, and dietitian.
  - Assessment of long-term outcome and iatrogenic toxicity.
  - Quality control of care.
- Data on patient initiated follow-up in primary vaginal cancer are lacking, and therefore can not yet be safely recommended [V, D].
- Follow-up should be composed of the following [IV, A]:
  - Patient history (including elicitation of relevant symptoms).
  - Physical examination (including a speculum examination and bimanual pelvic examination, detailed vulvar examination as well as inguinal lymph node assessment). If uterus has been left in situ screening of cervical cancer,incluing HPV, should continue. After radiotherapy cytology screening is not reliable.
  - Physician assessment of adverse events using validated scales (eg, Common Terminology Criteria for Adverse Events).
  - Prevention and management of cancer- and treatment related adverse effects, for example, sexual dysfunction (eg, counseling, vaginal dilators and lubricants, local estrogen) and lymphedema.
  - In case of the appearance of treatment-related symptoms, a referral to a dedicated specialist (eg, gastroenterologist, urologist/gynecologist) should be considered.
  - Patients should be educated about symptoms of potential recurrence and potential long-term and late effects of treatment. Patients should also be counseled on sexual health, lifestyle adaptation, nutrition, exercise, obesity, and cessation of smoking.
  - Follow-up schemes may be individualized, taking into accountpatients age, prognostic factors, treatment modality, and estimated risk and/or occurrence of adverse effects. Since the majority of relapses occur within the first 2 years after treatment, in general, follow-up intervals of 3 to 4 (6) months for the first 2 years and then 6 to 12 months up to 5 years are recommended.

Follow-up After (Radical) Surgery

- Follow-up should be carried out by physician experienced with follow-up care after surgery following the general recommendations [V, A].
- In patients with a neovagina secondary cancer related to the tissue/organ used may occur and should be anticipated. The neovagina should be examined by a surgeon experienced with the surgical procedure and examination of the neovagina [V, A].

Follow-up After Definitive Chemoradiotherapy

- The same imaging method should be used for evaluation of tumor response as was used at baseline [IV, A].
- Initial evaluation of tumor response, should be performed not earlier than 3 months following completion of treatment [IV, A]. In unclear response, a re-evaluation should not be performed before 8–12 weeks thereafter [IV, D].
- Follow-up should be performed by a physician experienced with follow-up care after radiotherapy [V, A]. Vaginal vault cytology is not recommended in these patients [IV, D].
- Providers should inform and educate on sexual and vaginal health and rehabilitation because of the vaginal and sexual morbidity that may occur as consequence of the cancer and the treatment. Vaginal dilation should be offered, as well as vaginal lubricants and local estrogen [IV, A].

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